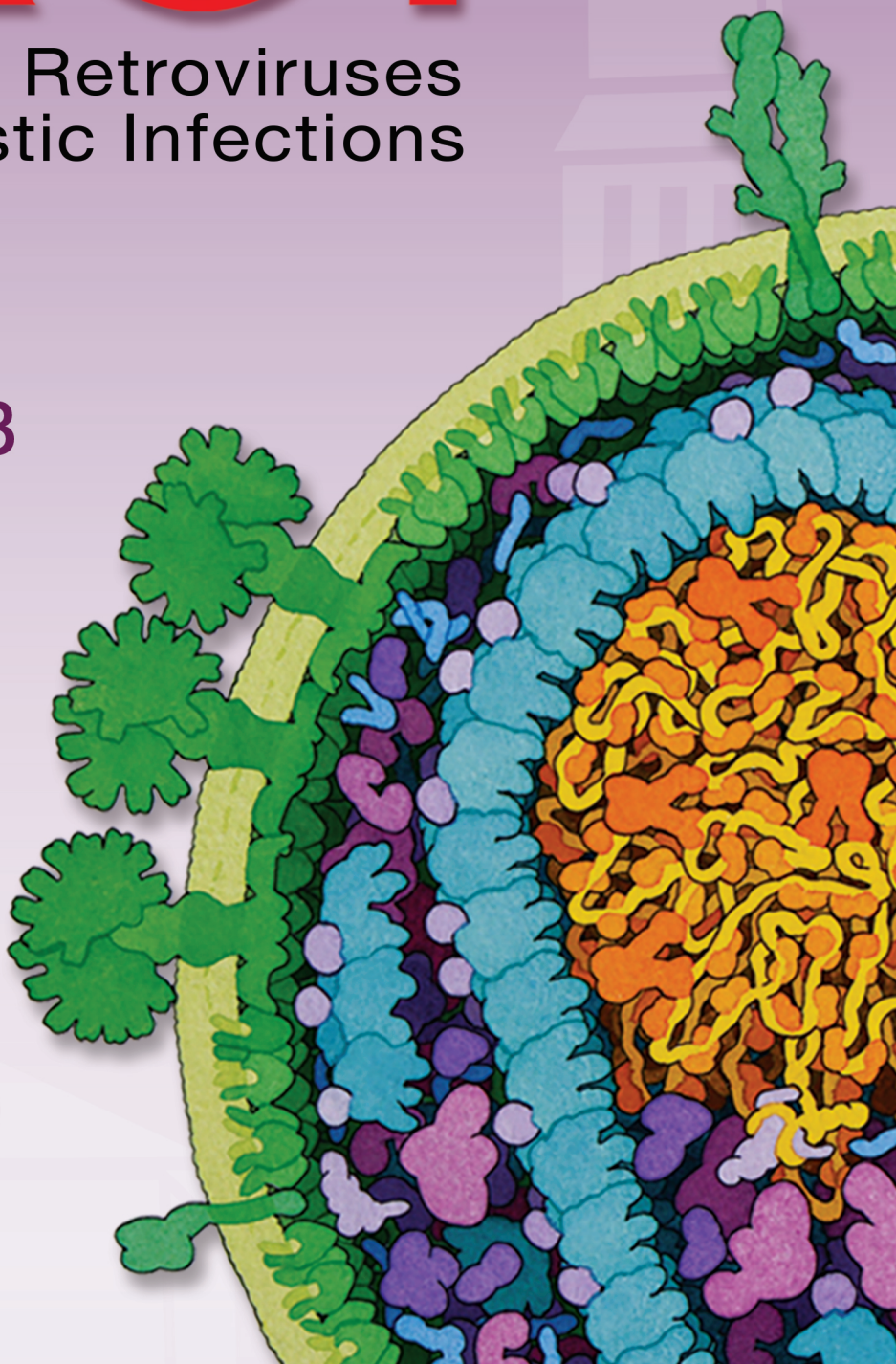
Abstract eBook

25th CROI

Conference on Retroviruses and Opportunistic Infections

Boston
March 4-7, 2018



IAS–USA
International Antiviral Society–USA

CONTENTS

The contents of this electronic abstract book are current as of April 2, 2018. Please note that the contents may be updated periodically.

ISBN #978-1-7320053-1-0

ABSTRACT PROCESS

Scientific Categories

A. Virology
B. Pathogenesis: Human Studies and Animal Models
C. Host Immune Responses to Infection, Vaccines, and Immunotherapy
D. HIV Reservoirs, Latency, and All Curative Strategies Including Therapeutic Vaccines and Gene Therapy
E. Neuropathogenesis and CNS HIV Complications
F. Clinical Pharmacology
G. Antiretroviral Therapy: Pre-Clinical and Randomized Trials
H. Antiretroviral Therapy: Efficacy and Effectiveness Studies
I. HIV Drug Resistance
J. HIV Diagnostics
K. Hepatitis Viruses and Liver Complications
L. Malignancies
M. Cardiovascular Complications of HIV Infection and Antiretroviral Therapy
N. Other Complications of HIV Infection and Antiretroviral Therapy
O. Tuberculosis and Other Opportunistic Infections
P. Maternal and Fetal HIV
Q. Pediatrics and Adolescents
R. Epidemiology
S. Testing
T. Prevention Interventions
U. Contraceptive and Reproductive Health in Women
V. Implementation and Scale-Up of Treatment and Care
W. Population and Cost Modeling

Abstract Content

Author names, institutions, abstract titles, and abstracts in the Program and Abstracts eBook are generally presented as submitted by the corresponding author.

Abstract Review Process

The Program Committee (PC) and a panel of volunteer external reviewers reviewed approximately 2000 submitted abstracts. Each abstract was reviewed by 5 to 10 reviewers selected for each abstract category based upon their individual expertise.

PC members and external experts in the field reviewed the abstracts for the quality and originality of the work and scored them numerically. All reviewers were instructed to abstain from scoring any abstract on which they are an author or coauthor, have a financial or personal conflict of interest, or do not have the appropriate expertise to evaluate. Scores ranged from 1 (definite oral presentation) to 5 (rejected).

Scores for each abstract were averaged and the standard deviation was calculated to assess variability. If variability was high, outlier scores are identified and censored. Abstracts with high variability in scores were discussed individually during a series of conference calls. Abstracts were accepted for oral presentations, for poster presentations, or rejected. Late-breaking abstract reviews included an assessment of the late-breaking nature of the work (versus just being a late submission).

Common Reasons for Abstract Rejection

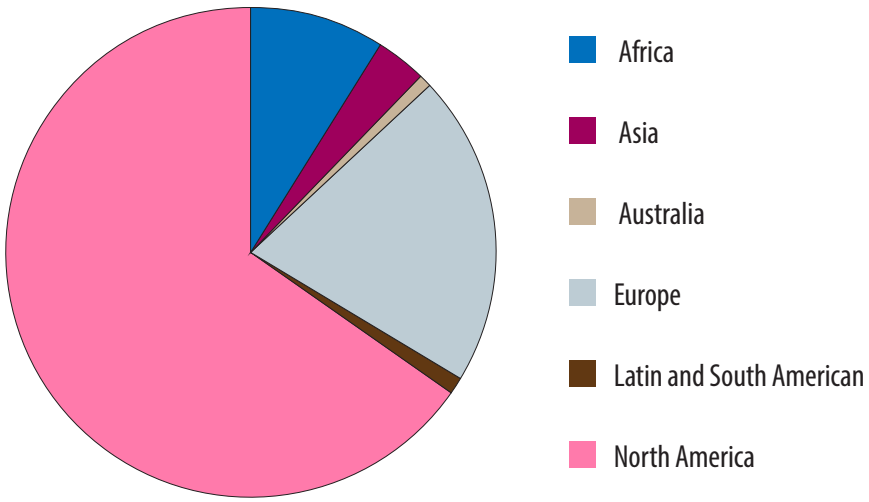
- Information is not new enough
- Methodology is inadequate or insufficient to support conclusions
- Background does not summarize the hypothesis
- Submission is poorly written
- Abstract is duplicative of other submissions
- Abstract is not appropriate for CROI
- Controls are absent or inadequate
- Statistical evaluation is inadequate or absent
- Summary of essential results is inadequate or absent
- Data are inadequate or insufficient to support conclusions
- Submission reports clinical trial and data from unplanned analysis or incomplete or ongoing studies
- Format does not follow guidelines (eg, section[s] missing, more than 1 graphic, table, or figure submitted)

Statistics for Abstracts

General abstract submitted	1960
General abstracts accepted	1061
General oral abstracts	95
General poster abstracts	966
Late-breaking abstracts submitted	203
Late-breaking abstracts accepted	44
Late-breaking oral abstracts	19
Late-breaking poster abstracts	25
Total abstracts submitted	2163
Total abstract accepted	1105

All Authors on Accepted Abstracts

Region	N	Percent
Africa	101	9.1
Asia	35	3.2
Australia	11	1
Europe	226	20.5
Latin and South America	12	1.1
North America	720	65.2



ORAL ABSTRACTS

1 PROGRAM COMMITTEE WORKSHOP FOR NEW INVESTIGATORS AND TRAINEES

Moderators: John W. Mellors[1], **Serena S. Spudich**[2]
[1]*University of Pittsburgh, Pittsburgh, PA, USA,* [2]*Yale University, New Haven, CT, USA*

The Conference for Retroviruses and Opportunistic Infections (CROI) provides a forum for basic, clinical, and epidemiologic investigators to present and discuss discoveries relevant to HIV and other major human pathogens. In this 25th year of CROI, the annual Program Committee Workshop for New Investigators and Trainees again sets the stage for the new science to be presented at the conference, by providing background and perspective in the format of succinct overview talks that provide key updates across a range of basic and clinical topics. This year, the stage will be set by a narrated animation showing an overview of the HIV life cycle of HIV at a molecular scale, presented by **Dr Janet Iwasa**. **Dr Frank Kirchhoff** will then review recent new knowledge in the field of molecular virology, including an update on the function and relevance of HIV-1 accessory factors. **Dr Alexandra Trkola** will report on advances in developing broadly neutralizing antibodies for prevention, therapy and vaccines and provide new insights on HIV-1 interference with immune functions. **Dr Richard Chaisson** will discuss new developments in HIV-related tuberculosis (TB), including next-generation molecular diagnostic tests, progress in improving treatment for multidrug resistant and extensively drug resistant TB, and new findings on TB preventive therapy and its impact on survival. **Dr Wafaa El-Sadr** will review the status of the HIV epidemic with a focus on its evolution and the communities and populations that are bearing the brunt of new infections. She will highlight the evolution of HIV prevention efforts, challenges faced in achieving the desired impact of various interventions and highlight current and future prevention innovations. Finally, **Dr Huldrych Günthard** will give an overview on the current knowledge of the latent HIV reservoir and it's implications for cure strategies. He will discuss different mechanisms of HIV-persistence, potential residual transcription and residual replication on antiretroviral therapy and current and new cure strategies. Speakers will identify areas of controversy or gaps in knowledge that require future investigation, and direct attendees to relevant work to be presented at CROI. Moderated discussion after each talk will provide opportunities for attendees to interact with the speakers and ask questions.

2 MARTIN DELANEY PRESENTATION ON WOMEN IN RESEARCH

Moderator: Lisa Diane White, *SisterLove, Inc, Atlanta, GA, USA*

Embedded notions of women have negatively impacted their representation in research as investigators, research participants and consumers of research products. Stereotypical perceptions about gender also limit the depth of research exploration of disease conditions that may affect men and women differently. There are significant gender differences in the way drugs are metabolized and tolerated, their side effects, and their benefits. Women have been grossly underrepresented in human clinical trials resulting in findings which may not apply to them. Even when both sexes are included, sex-specific analyses are generally not reported. Research 'legislation' on inclusion of women in research has not been effective. The limited number of female researchers and silencing of voices advocating for women's health are barriers to good science. This session will highlight these issues with a focus on necessary and practical solutions. Discussants will highlight the importance of gender mainstreaming in the design and implementation of basic and clinical research, the crucial need to have women as investigators and leaders, and the complementary role of activism for women's issues in research. **Dr Dázon Dixon Diallo** will discuss the role of women as activists in research. **Dr Tonia Poteat** will provide a perspective of women conducting research. **Dr Monica Gandhi** will discuss the importance of mentorship in developing the next generation of investigators.

3 VIRUS-LIKE NANOCARRIER FOR DELIVERY OF BIOMOLECULES BETWEEN CELLS

Joerg Votteler, *University of Utah, Salt Lake City, UT, USA*

Targeted delivery of biomolecules such as proteins, mRNAs, and DNA editing complexes is one of the biggest challenges in realizing the promise of treating many diseases. Emerging research is demonstrating the potential of engineering viral capsids directly as vehicles and/or as inspirations for designing new nanocarrier delivery systems. This approach is attractive because viral capsid proteins have evolved to assemble, package cargoes, exit cells to form extracellular virions, and enter new cells. I will review several natural carrier systems in which increasing structural and biochemical knowledge has provided the opportunity to re-design and improve upon their native properties. I will also review systems in which our increasing understanding of the sophisticated functions of capsid proteins has inspired the de-novo design of self-assembling protein nanocages. These approaches couple symmetric modelling with computational design of new protein–protein interfaces to generate new protein assemblies with atomic level accuracy. The computationally designed nanocages can then be further optimized using directed evolution approaches to optimize their biophysical properties and to incorporate desirable functions that are tailored to specific applications. Following these general principles, we have engineered protein nanocages that direct their own release from human cells inside small membrane enclosed vesicles in a manner that resembles viral assembly and release pathways. Robust enveloped protein nanocage (EPN) biogenesis requires three elements: membrane binding, self-assembly, and recruitment of the cellular ESCRT pathway (endosomal sorting complexes required for transport). When these elements are present, EPNs can be released from cells within small membrane enclosed vesicles that each contain multiple nanocages. We have identified various combinations of membrane binding, self-assembly, and ESCRT recruiting elements that can produce EPNs efficiently, indicating that the strategy is very general. EPNs pseudotyped with viral fusion proteins can enter target cells, thereby transferring their cargos from one cell to another. I will discuss how we are now extending these systems to create new synthetic delivery systems based on the principles of virus assembly and entry.

4 3D AND MULTI-SCALE IMAGING OF HIV-1 SPREAD IN TISSUES

Pamela J. Bjorkman, *California Institute of Technology, Pasadena, CA, USA*

Critical aspects of HIV-1 infection occur in mucosal tissues, which contain large numbers of HIV-1 target cells that are depleted early in infection. We used electron tomography (ET) to image HIV-1 in tissues of HIV-1–infected humanized mice. The resolution and preservation quality of reconstructed tissue volumes allowed identification of budding virions and free virions in both immature and mature states. Three-dimensional imaging of an active infection provided evidence of synchronous virus release and rapid maturation and revealed differences between cultured cell and tissue infection models. More recently, we combined tissue clearing and 3D-immunofluorescence with ET to longitudinally assess early HIV-1 spread in lymphoid tissues. Immunofluorescence revealed peak infection density in gut at 10-12 days post-infection when blood viral loads were low. Human CD4+ T-cells and HIV-1–infected cells localized predominantly to crypts and the lower third of intestinal villi. Free virions and infected cells were not readily detectable by ET at 5-days post-infection, whereas HIV-1–infected cells surrounded by pools of free virions were present in ~10% of intestinal crypts by 10-12 days. ET of spleen revealed thousands of virions released by individual cells and discreet cytoplasmic densities near sites of prolific virus production. These studies highlight the importance of multiscale imaging of HIV-1–infected tissues and are adaptable to other animal models and human patient samples.

5 SINGLE CELL VIRAL AND RECEPTOR BAR CODES: BEYOND THE SINGLE CELL TRANSCRIPTOME

Eli A. Boritz, *NIAID, Bethesda, MD, USA*

By simultaneously determining millions or billions of individual nucleic acid sequences in a single experiment, next-generation sequencing technologies allow the analysis of rare events even in the context of very large populations. Therefore, these technologies can help facilitate study of HIV genetic variants or HIV-infected cells within highly heterogeneous ex vivo samples from HIV-positive individuals. This talk will consider the application of this experimental approach to key questions in basic and translational HIV research. Specific examples to be discussed include the detection of antiviral drug-resistant virus variants in people not yet treated with drug, and the comprehensive characterization of HIV-infected cellular reservoirs in blood and tissues by single-cell whole transcriptome sequencing. The purpose of this discussion is to update the audience on ongoing work in the field and to prompt consideration of other uses for next-generation sequencing in HIV prevention and therapy studies.

6 SEEING THE FOREST THROUGH THE TREES: USING PHYLOGENETICS TO IMPACT THE EPIDEMIC

Susan J. Little, *University of California San Diego, San Diego, CA, USA*

While widespread HIV prevention and treatment approaches have resulted in a reduction in HIV incidence in a small but growing number of countries, HIV incidence continues to increase or remain stable in many populations. These populations or risk networks are often linked by shared structural barriers to care and community-level stigma. Prevention intervention strategies are increasingly turning to more granular approaches to understanding the characteristics of the individuals who continue to transmit and acquire HIV infection in these communities. The identification of risk networks represents an opportunity to better understand the transmission risk parameters that may be shared by groups of HIV infected and at-risk persons. Phylogenetic analyses utilize the increasingly routinely collected HIV genetic sequence data to track and predict HIV transmission dynamics. When paired with traditional epidemiologic determinants of disease, these molecular epidemiologic analyses may be used to better understand the dynamics of regional transmission patterns and to evaluate the impact of prevention interventions. The use of phylogenetics and molecular epidemiology in clinical trials is a new and rapidly growing field of study. This presentation will review phylogenetic outcome measures necessary to evaluate network incidence and clinical trial strategies that utilize these methods to provide more detailed insights into persistent "hotspots" of HIV transmission. These approaches represent a powerful tool in planning more focused prevention interventions to reduce incidence in particular subepidemics. This presentation will also introduce some of the issues surrounding privacy protection related to HIV molecular epidemiological studies.

7 MEASURING THE POPULATION-LEVEL IMPACT OF INTERVENTIONS

Jessica E. Justman, *ICAP at Columbia University, New York, NY, USA*

Population-based assessments of treatment and prevention efforts, whether in the setting of research studies or routine service delivery, are an increasingly important tool to evaluate the impact of interventions and inform future action. This talk will provide an overview of methods for measuring the population-level impact of interventions, including serial population cohorts, community-cluster randomized controlled trials, population-based prospective cohorts, modeling, and population-based household surveys. The latter will include a description of the Population-based HIV Impact Assessment (PHIA) Project, which consists of nationally-representative household-based HIV surveys in 14 countries. For each approach, we will review study design, strengths, limitations, optimal settings and an illustrative example of a relevant study. The talk will focus on examples of HIV interventions but these methods are also suitable for assessing the population-level impact of interventions for a wide range of conditions.

8 PRAGMATIC TRIALS

Alison Grant, *London School of Hygiene & Tropical Medicine, London, UK*

Pragmatic trials aim to evaluate how an intervention will perform in real-world conditions, contrasting with explanatory trials, which aim to determine whether an intervention can work under experimental conditions. The extent to which a trial is pragmatic can be assessed across multiple domains, including whether the study population is highly selected or has broader inclusion criteria; the flexibility of delivery of the intervention; whether the follow-up schedule reflects routine practice; and whether the primary outcome is relevant to patients. Pragmatic trials are not less rigorous than explanatory trials, and may be logistically more challenging to implement. The research question should determine whether a more explanatory or a more pragmatic design is needed. Tools which help assess where a trial lies on the spectrum from explanatory to pragmatic may help investigators ensure that their trial design aligns with the research question.

9 INTERACTIVE CASE-BASED WORKSHOP ON HEPATITIS C

Moderators: Debika Bhattacharya[1], **Arthur Kim**[2]
[1]University of California Los Angeles, Los Angeles, CA, USA, [2]Harvard Medical School, Boston, MA, USA

This interactive case-based session is geared toward clinicians who are involved in HCV treatment. Direct-acting antiviral (DAA) therapies have revolutionized HCV treatment with high sustained virologic response at 12 weeks (SVR12), i.e. HCV cure, in the majority of uncomplicated patients. However, questions remain for several areas of HCV research and clinical care, including the management of HCV in pregnancy, childhood and adolescence, the management of acute HCV infection and DAA failures, and the importance, diagnosis, and management of steatosis before and after HCV treatment. **Dr Ravi Jhaveri** (University of North Carolina Chapel Hill) will discuss the increase in HCV infections in women of child-bearing age, HCV in pregnancy and HCV mother to child transmission. He will also discuss treatment of HCV in childhood and adolescence. **Dr Christoph Boesecke** (University of Bonn) will report on the epidemic of acute HCV infection – particularly among HIV-positive men who have sex with men (MSM), the importance of the treatment of acute HCV, reinfection rates in people who inject drugs (PWID) and the distinction between HCV relapse and reinfection. **Dr Pablo Ryan** (Hospital Universitario Infanta Leonor) will describe clinical cases of HCV DAA failures, the scenarios in which HCV resistance testing should be performed, and review the clinical trials of newly licensed HCV DAAs in the context of re-treatment. Finally, **Dr Kathleen Corey** (Harvard University) will discuss the diagnosis and management of steatosis, in the context of HCV, both before and after HCV treatment.

10 THE POTENTIAL OF INTERNATIONAL COLLABORATIONS FOR HIV PREVENTION: STUDIES OF MOTHER-TO-CHILD TRANSMISSION

Julie Overbaugh, *Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

An interdisciplinary approach is crucial to addressing the enormous challenges of HIV prevention. Prevention of mother-to-child transmission (MTCT) has made great progress, with contributions across disciplines being central to that success. The Nairobi Breastfeeding Clinical Trial (NBT) was one of the early trials to address risk and correlates of breast milk HIV transmission. The NBT also provided unique opportunities to study viral and immune factors that may contribute to infant infection. Studies from the NBT included defining the role of antibodies in the transmission bottleneck and characterizing the contribution of antibodies to infant outcomes. Study of infants in this cohort also showed the surprising result that they developed neutralizing antibody responses more commonly and rapidly than adults, suggesting infants may provide a roadmap for antibody-based HIV vaccine approaches. In addition, the trial has been leveraged by many labs to understand the structure and antigenicity of a canonical HIV envelope protein, BG505. In this lecture, I will use the NBT and the collaborations that emerged from it to illustrate the potential of interdisciplinary, international collaborations to address important questions relevant to HIV prevention research.

11 MICH MAR GENO - THE GIFT OF HOPE

Elizabeth A. Bukusi, *Kenya Medical Research Institute, Nairobi, Kenya*

East and Southern Africa account for over 19 of the 37 million people living with HIV, and contribute up to 43% of new infections globally. With a population of just over 40 million, Kenya has approximately 1.5 million individuals living with HIV with 79% on treatment. Kenya is still not on target to achieve the UNAIDS 90:90:90 goals. In this presentation, 'Mich mar Geno' the gift of hope will be presented through the lens of the 3 C's of Capacity, Collaboration and Community, which have shaped the HIV prevention and treatment landscape. **Capacity:** From a platform of HIV prevention research, building capacity for human resource and infrastructure has contributed to addressing the HIV epidemic both regionally and globally. Training of competent committed

researchers and health care workers has seen Kenyan scientists contribute to major innovations for the HIV prevention and care agenda. Capacity has included bi – directional north -south exchange programs.
Infrastructure expansion and renovation of buildings and with leveraged support from philanthropic donor support has supported new clinical research sites and comprehensive care centers in the regions most affected by HIV.
Community: By mid-2015, the Family AIDS Care Services (FACES) had initiated over 150,000 individuals on HIV treatment and Care, working in 150 clinics. Services provided included HTC, PMTCT, VMMC and cervical cancer screening and treatment.
Collaboration: Both HIV prevention research and HIV care are qualities of the FACES program that impact the community, to reduce stigma and improve health and livelihood outcomes for individuals and their families. Success stories include participation in studies that led to the licensure and roll out of pre-exposure prophylaxis (PrEP); the proof of a 'test and treat strategy which surpassed the UNAIDS 90:90:90 targets'; enhancement of differentiated care models for HIV; a family care model for HIV care, options for integration of family planning and HIV care services, and the ongoing response to the concerns of hormonal contraception and HIV acquisition risk. The challenges of stigma, over reliance on external resources and adolescent friendly services for sexual and reproductive health and HIV care must be comprehensively addressed in order to meet the desired national and global goals.

12 THE EARLY DAYS OF AIDS: LOOKING BACK AND THINKING AHEAD

Harold W. Jaffe, *CDC, Atlanta, GA, USA*

In 1981, AIDS was first recognized in gay men by astute clinicians in Los Angeles. Relatively simple epidemiologic studies pointed to an infectious etiology and established transmission routes before the identification of HIV. Subsequent studies showed the virus posed a risk to healthcare workers through occupational exposure, but was not transmitted by casual contact or mosquito bites, and provided the evidence base for health communication messages. Gay advocacy groups played an important role in expediting the approval of new antiretroviral drugs. Funding from sources such as PEPFAR and the Global Fund provided lifesaving treatment to infected persons in low-income countries. Lessons learned from the early AIDS epidemic will be tested by emerging infectious disease threats. Overall, the world is better prepared to respond to these threats now than it was in 1981. The International Health Regulations and the Global Health Security Agenda provide a framework for global health preparedness. The application of new data analytic tools to electronic health records and social media data can facilitate disease detection, and new genetic techniques help us better understand the spread of infectious diseases. Yet, effective health communication to address public fears of contagion remains a challenge, and human behavior remains difficult to change. Ending the AIDS epidemic as a public health threat will be hard, but is the goal we must pursue.

13 PATHOGENESIS OF TUBERCULOSIS AND VACCINE PREVENTION

JoAnne L. Flynn, *University of Pittsburgh, Pittsburgh, PA, USA*

Tuberculosis (TB) remains a major killer worldwide, with more than 10 million new cases each year, and 1.5 million deaths. TB is also the leading cause of death in HIV+ people throughout the world. Although effective drug treatment exists, the regimen is long (at least 6 months) and the drugs have side effects; there is also a large increase in drug resistant strains of *Mycobacterium tuberculosis*, complicating treatment. In addition, diagnosis of TB is not always timely, leading to transmission and delay of treatment. Although most countries vaccinate newborns with an attenuated mycobacterial strain, BCG, this vaccine has variable efficacy against infection and disease. New vaccines are urgently needed against TB, yet the types of immune responses that will provide durable protection are not clear. Novel technologies and improved animal models have led to new insights into *M. tuberculosis* infection, and provide clues for improved vaccines and interventions. This talk will review new approaches to our understanding of tuberculosis in humans and animal models.

14 IDENTIFICATION OF A NOVEL LOCUS OF HIV REGULATION IN POPULATIONS OF AFRICAN DESCENT

Paul J. McLaren[1], Deepti Gurdassani[2], Manj Sandhu[2], Jacques Fellay[3]
[1]*Public Health Agency of Canada, Winnipeg, MB, Canada,* [2]*Wellcome Trust Sanger Institute, Hinxton, UK,* [3]*École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland*

Background: HIV set point viral load (spVL; $\log_{10}$ RNA copies/ml) strongly correlates with progression and transmission. Genome-wide association studies have shown that ~25% of the variability in spVL is due to host genetics, with the HLA and CCR5 regions being the primary drivers. However, previous studies have focused on individuals of European ancestry, thus assessing only a fraction of human genetic variation. We sought to address this gap by performing a genetic study of spVL in a large sample of individuals of African ancestry.
Methods: A discovery set of 2,517 African American individuals with genome-wide genotyping and spVL data was obtained from four independent studies through the International Collaboration for the Genomics of HIV. As a replication sample, we accessed genome-wide data for 533 individuals from 3 studies in eastern and southern Africa and performed direct genotyping in 117 individuals of African descent living in Switzerland (Ncombined=3,167). Association was tested between spVL and genetic variants by linear regression. Discovery and replication results were combined by meta-analysis. Bioinformatic analysis included variant annotation for modification of protein function and gene expression.
Results: In the discovery sample, we observed a novel association between spVL and rs77029719 ($p=5.7\times10^{-8}$; $\beta=-0.30$) which was confirmed in the replication set (Pcombined=7×10^{-10} ; βcombined=-0.31). The effect of rs77029719 was remarkably consistent across populations, with the G allele associating with lower spVL in all groups (range = -0.2 to -0.5 $\log_{10}$(copies/ml)). This variant being located on chromosome 1, this association cannot be explained by the known effects of HLA (chr6) or CCR5 (chr3). rs77029719 falls within a lincRNA and shows strong linkage ($r2 > 0.6$) with several variants across four genes (CHD1L, FMO5, PDIA3P, PRKAB2). Bioinformatic analysis suggests that rs77029719 plays a role in regulating splicing and expression of CHD1L, which encodes a DNA helicase protein that interacts with PARP1, an enzyme implicated in HIV integration. Interestingly, rs77029719 is only present in populations of African descent, suggesting a population-specific mechanism of HIV control.
Conclusion: We identified an African specific genetic locus that controls HIV replication in vivo with a potential role in modulating HIV integration. These findings suggest a potential new target for anti-HIV drug development and demonstrate the critical need to perform genetic studies in multiple populations.

15 HOST FACTORS ASSOCIATED WITH BNAB DEVELOPMENT IN HIV-1 CONTROLLERS

Enrique Martin-Gayo[1], Hsiao Rong Chen[1], Ce Gao[1], Zhengyu Ouyang[2], Dhohyung Kim[1], Kellie E. Kolb[3], Alex K. Shalek[3], Bruce D. Walker[1], Mathias Lichterfeld[4], Xu G. Yu[1]
[1]*Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA,* [2]*University of California San Diego, La Jolla, CA, USA,* [3]*MIT Institute for Medical Engineering & Science, Cambridge, MA, USA,* [4]*Brigham and Women's Hospital, Boston, MA, USA*

Background: Induction of broadly neutralizing antibodies (bNAbs) is highly desired for a preventive vaccine against HIV-1. Typically, bNAbs develop under high levels of viremia and immune activation; nevertheless, Abs with high neutralizing breadth are also produced in some untreated HIV-1 controllers with low viral loads. However, specific host factors promoting these Ab responses have not been identified yet. Here, we analyzed transcriptional and functional features of primary conventional dendritic cells (cDCs), monocytes (Mo) and B cells from HIV-1 controller groups with different levels of neutralizing Ab breadth against HIV-1.
Methods: RNAseq was performed from sorted circulating cDC, B cells and Mo from HIV-1 controllers with (Neut, n=46) or without (Non Neut, n=15) any detectable neutralizing Ab breadth against 11 tested HIV-1 strains. In addition, the ability of primary cDC to prime allogeneic naïve CD4+ T cells into CXCR5+ PD-1+ Bcl-6+ T follicular helper cells (Tfh) was analyzed in functional in vitro assays.
Results: Transcriptional signatures in cDC from controllers with neutralization breadth exhibited two distinct patterns: one group (Neut1; n=25) overlapping with Non Neuts and a separate subgroup of controllers (Neut2; n=21) characterized by up-regulation of inflammatory genes and activation of pathways supporting Tfh polarization. Consistently, cDC from Neut2 patients displayed superior abilities to prime Tfh-like cells in vitro compared to cDC from Neut1 (p=0.04) or Non Neut (p=0.01). Importantly, transcriptional signatures of cDCs from Neut2 appeared to be predicted by IL-12 as an upstream regulator, while Tfh-priming function of these cells was dependent on signaling through IL-12R (p=0.02) and could be enhanced in vitro by the addition of IL-12 to

ordinary cDC obtained from healthy donors. Notably, circulating Mo from Neut2 neutralizers were de-enriched for the inflammatory CD16+ subset (p=0.002), but differentially transcribed genes involved in IL-12 production (p=0.034) compared to Non Neuts. Finally, B cells from Neut2 patients differentially transcribed genes involved in BCR signaling (p= 0.003) and Ig-class switching (p= 0.004) and were more enriched in memory IgD- IgM+ B cells (p<0.0001) compared to Non Neuts.

Conclusion: cDC function is associated with distinct Mo and B cells phenotypical patterns in a subgroup of controllers that develop neutralizing Ab breadth. IL-12 represents a promising adjuvant for vaccine-mediated induction of Tfh responses and bNAb.

16LB INTERDOMAIN STABILIZATION IMPAIRS CD4 BINDING AND IMPROVES IMMUNOGENICITY OF SOSIPS

Peng Zhang[1], Jason Gorman[1], Hui Geng[1], Yin Lin[1], Yaroslavl Tsybovsky[2], Huiyi Miao[1], Qingbo Liu[1], Tsion Andine[1], Alice Kwon[1], Ferzan Uddin[1], Mit Patel[1], Christina Guzzo[1], John R. Mascola[1], Peter D. Kwong[1], Paolo Lusso[1]
[1]NIH, Bethesda, MD, USA, [2]NIH, Frederick, MD, USA

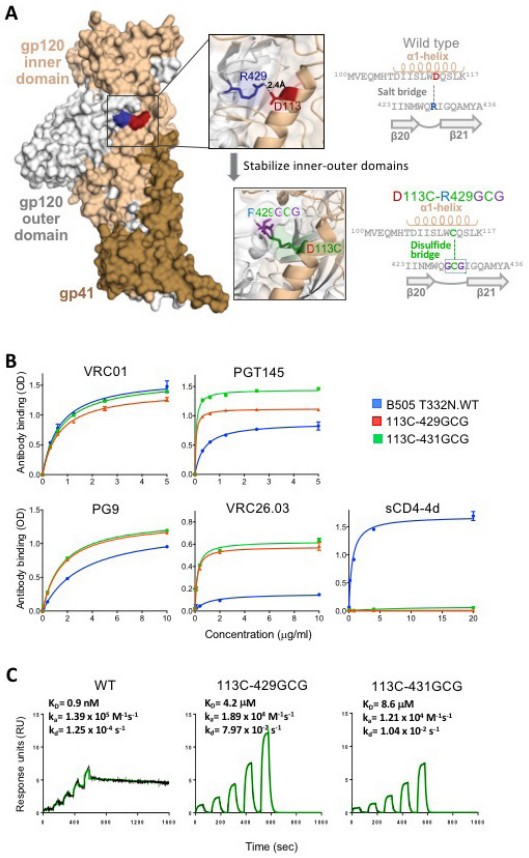
Background: The remarkable structural flexibility of the HIV-1 envelope (Env) and the susceptibility to antigenic remodeling upon CD4 binding represent key obstacles to the development of a protective vaccine. Here, we fixed the HIV-1 Env in pre-fusion configuration with impaired CD4-binding capacity via structure-guided introduction of a neo-disulfide bond bridging the outer and inner domains of gp120. This design was successfully applied to both soluble trimers and native full-length gp160 from diverse HIV-1 strains. Interdomain-locked trimers displayed increased thermal stability, restricted antigenic profile with enhanced binding to trimer-preferring broadly neutralizing antibodies (bNAbs) and lack of recognition by non-neutralizing antibodies. Crystallization of a locked BG505 SOSIP.664 trimer provided a structural basis for the loss of CD4 interaction. In rabbit immunization studies, stabilized trimers elicited the production of neutralizing antibodies against tier-2 autologous viruses with intact glycan shields, irrespective of complexing with a CD4 mimic.

Methods: Mutagenesis, Protein Expression and Purification Negative-staining Electron Microscopy Crystal Structure Expression of Full-length HIV-1 gp160 Flow Cytometry Surface Plasmon Resonance Analysis Rabbit Immunization Pseudovirus Preparation, Infectivity and Neutralization Assays

Results: We stabilized the HIV-1 Env trimer in native pre-fusion configuration using a novel structure-guided strategy bridging two cardinal structural elements, the inner and outer domains, of the gp120 glycoprotein. We designed and characterized interdomain-locked trimers that are selectively and efficiently targeted by potent bNAbs, are poorly, if at all, recognized by weakly- and non-neutralizing antibodies, and are unable to physiologically interact with human CD4. Stabilized trimers derived from two different HIV-1 strains showed improved immunogenicity in rabbits, eliciting the production of potent neutralizing antibodies against tier-2 autologous viruses with intact glycan shield independently of pre-complexing with a CD4-mimetic miniprotein.

Conclusion: The present study provides a new strategy to stabilize the HIV-1 Env trimer and thereby reduce access to epitopes for non-neutralizing antibodies and abrogate CD4 binding. The lack of CD4 binding ensures that Env-based immunogens would not undergo unwanted antigenic modifications or be lost by CD4+ T-cell sequestration after injection into human vaccines.

Figure 1



17 EQUAL DISTRIBUTION OF SIV DNA IN MEMORY T HELPER CELL SUBSETS OF RHESUS MACAQUES

Stephen Lai[1], Joseph Mudd[2], Jason Brenchley[1]
[1]NIAID, Bethesda, MD, USA, [2]NIAID, Baltimore, MD, USA

Background: Interleukin-17 (IL-17) producing T helper cells (Th) are critical to maintaining gut barrier integrity and host response against extracellular bacterial and fungal infections. During the course of Simian Immunodeficiency Virus (SIV) infection, Th17 cells that express C-C chemokine receptor 6 (CCR6) are rapidly and preferentially depleted from mucosal tissues. It has been proposed that CCR6+ Th17 cells are more permissive to SIV, and are thus, preferentially infected.

Methods: Lymphocytes from Peripheral Blood Mononuclear Cells (PBMC), spleen, and Mesenteric Lymph Nodes (MLN) of SIV+, viremic rhesus macaques were isolated and simulated for 6 hours with PMA and ionomycin in the presence of Brefeldin A. CD28+ memory CD4 T cells were studied and CCR6+/IL-17+ and IL-17- CD4 T cells (Th17 cells), CCR4-/IFNg+ and IFNg- CD4 T cells (Th1 cells), CCR4+/IFNg-/IL-17- CD4 T cells (Th2 cells) and FoxP3+ CD4 T cells (Tregs) were then flow cytometrically isolated, and the proportions of cells harboring SIV DNA were then assessed through qPCR.

Results: Viral DNA was detected in all subsets of memory CD4 T cells (irrespective of functionality, phenotype, or anatomic location). However, irrespective of anatomic site studied, we found that no one population of isolated memory, CD28+, CD4 T cells harbored more (or less) viral DNA than any other population of memory CD4 T cells.

Conclusion: Loss of CD4 T cells is a hallmark of progressive HIV/SIV infection and several studies have shown that Th17 cells are preferentially loss from mucosal tissues and lymph nodes that drain mucosal tissues. From our data it is unlikely that preferential loss of Th17 cells is attributed to preferential infection by the virus, itself.

18 KINETICS OF GASTROINTESTINAL DYSFUNCTION IN ACUTE SIV INFECTION OF MACAQUES

Tiffany Hensley-McBain[1], Alicia Berard[2], Charlene J. Miller[1], Jennifer A. Manuzak[1], Alexander S. Zevin[1], Patricia Polacino[3], Brian Agricola[3], Mark Cameron[4], R. Keith Reeves[5], Jeremy Smedley[6], Shiu-Lok Hu[3], Brandon Keele[7], Adam Burgener[8], Nichole Klatt[1]

[1]University of Washington, Seattle, WA, USA, [2]University of Manitoba, Winnipeg, MB, Canada, [3]Washington National Primate Research Center, Seattle, WA, USA, [4]Case Western Reserve University, Cleveland, OH, USA, [5]Beth Israel Deaconess Medical Center, Boston, MA, USA, [6]Oregon Health and Sciences University, Portland, OR, USA, [7]Frederick National Laboratory for Cancer Research, Frederick, MD, USA, [8]Public Health Agency of Canada, Winnipeg, MB, Canada

Background: HIV and pathogenic SIV infection are characterized by gastrointestinal (GI) damage and immune dysfunction resulting in microbial translocation and immune activation, which are major contributors to non-infectious comorbidities and mortality. GI dysfunction includes damage to the epithelial barrier, loss of Th17 cells, neutrophil accumulation, microbial translocation and mucosal and systemic inflammation. However, it is unclear how and when these contributing factors occur relative to one another. Therapeutically targeting GI dysfunction requires elucidating the kinetics of these events to determine if any of these features initiates the cycle of damage.

Methods: We longitudinally evaluated mucosal and systemic T cell activation, microbial translocation, immunity, and the mucosal proteome during acute SIV infection in 6 rhesus macaques challenged intrarectally with 100,000 TCID50 of SIVmac239X. Samples were collected pre-SIV and 3, 7, 14, 21, 28, 49 and 63 days post-SIV. Flow cytometry was used to assess T cell and neutrophil frequencies and activation. LPS binding protein (LBP) was measured as a marker of microbial translocation in plasma by ELISA. The colon proteome was assessed using shotgun mass spectrometry.

Results: We observed early GI immune activation as evidenced by increased CD4+ T cell activation (HLA-DR) beginning 3 days post-SIV in the rectum ($p=0.0312$) and CD8+ T cell activation beginning 14 days post-SIV in the rectum ($p=0.0312$) and colon ($p=0.0312$). We also observed increased T cell proliferation (Ki67) 14 days post-SIV in GI tissues, and a trending increase in LBP beginning 14 days post-SIV ($p=0.0625$). The onset of GI dysfunction preceded peripheral and GI Th17 loss, which occurred 14-28 days post-SIV, and gut neutrophil accumulation was not observed. Proteomic analysis identified 292 proteins that were differentially regulated post-SIV, with 5% FDR for at least one time point. Hierarchical clustering of these proteins demonstrated that proteins involved in epithelial structure were downregulated 3 days post-SIV followed by an upregulation of immune proteins 14 days post-SIV.

Conclusion: Overall, these data demonstrate that immune perturbations such as Th17 loss and neutrophil accumulation occur after alterations to epithelial structural protein pathways, microbial translocation, and GI T cell activation, suggesting epithelial damage and GI dysfunction occurs prior to widespread immune dysfunction.

19 PROGRESSIVE LYMPH NODE DYSFUNCTION DURING SIV INFECTION IS NOT REVERSED WITH ART

Claire Deleage[1], Ismail B. Turkbey[2], Peter L. Choyke[2], Yanling Liu[3], Gregory Q. Del Prete[3], Brandon Keele[3], Jeffrey D. Lifson[3], Jacob D. Estes[3]

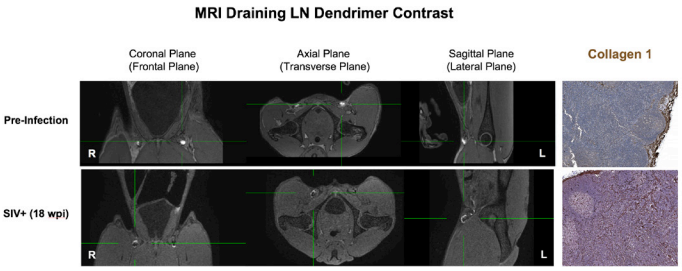
[1]AIDS and Cancer Virus Program, Frederick, MD, USA, [2]National Cancer Institute, Bethesda, MD, USA, [3]Frederick National Laboratory for Cancer Research, Frederick, MD, USA

Background: Initiation and maintenance of effective immune responses depends on the structural and functional integrity of secondary lymphoid tissues, particularly lymph nodes (LN). Among the fundamental biological functions of LN is the filtration of lymph and the capture of particulate antigens. To evaluate the functional consequences of progressive fibrotic damage to lymphoid tissue seen in HIV/SIV infection, we used longitudinal magnetic resonance imaging (MRI) to study uptake of a simulated particulate antigen by draining lymph nodes in SIV infected rhesus macaques (RM), and correlated these findings with histopathological analysis. We also evaluated the impact of combination antiretroviral therapy (cART) and adjunctive anti-fibrotic intervention.

Methods: Four RM were infected (IV) with SIVmac239M, placed on cART (TDF/FTC/DTG) starting at 36 weeks post infection (wpi), and then treated with the anti-fibrotic drug pirfenidone started at 50 wpi continuing through 82 wpi. Longitudinal dynamic MRI scans were used to monitor and quantify lymphatic drainage and inguinal lymph node uptake of gadolinium G5-DOTA dendrimer (~8 nm diameter simulated particulate antigen) after intradermal injection into the anterior portion of the feet. MRI was performed prior to SIV infection and at multiple time points following infection. Correlative analysis of axillary LN fibrotic damage and inflammation were performed using immunohistochemistry and quantitative image analysis.

Results: We observed the rapid onset (beginning 2 weeks post infection) of LN dysfunction manifested by restricted uptake of dendrimer by inguinal LN. Persistent impaired inguinal LN dendrimer uptake correlated with histopathologic evidence of fibrotic damage in axillary LN. cART for 46 weeks, combined with 28 weeks of pirfenidone did not restore dendrimer uptake into the draining lymph nodes, and suggests that fibrotic impairment of LN function may persist for long periods of time.

Conclusion: SIV, and likely HIV, infection is associated with a profound impairment of LN function due to collagen deposition, which may affect the ability to mount effective immune responses. Fibrosis may also impact tissue bioavailability of anti-viral drugs in affected sites.



20 P38 MAPK IN VIVO INHIBITION IMPACTS SIV-MEDIATED IMMUNE ACTIVATION & CD4 T-CELL LOSS

Omkar Chaudhary[1], Felipe Lelis[1], Ronald Veazey[2], **Anna Aldovini**[1]

[1]Boston Children's Hospital, Boston, MA, USA, [2]Tulane National Primate Research Center, Covington, LA, USA

Background: Persistent immune activation is the hallmark of lentiviral infection in AIDS-susceptible species. p38 MAPK, activated in HIV and SIV infection, is key to induction of Interferon-stimulated genes (ISG) and inflammatory cytokines and is associated with some of the pathology produced by HIV and SIV infection in AIDS-susceptible primates. As small molecule p38 MAPK inhibitors are currently tested in human trials for other inflammatory diseases, we evaluated the effects of treating SIV-infected macaques with a p38 inhibitor, PH-797804, in conjunction with ART.

Methods: Rhesus macaques were infected with SIVmac251 and divided in 6 groups: Group 1, had no treatment, Group 2, p38 inhibitor alone, Groups 3 and 5 initiated ART at week 6 or 1 after infection, Group 4 and 6 initiated ART + PH797804 at week 6 or 1 after infection. ART efficacy was evaluated by measuring viral loads and reservoirs. As primary endpoints for PH-797804 efficacy, we evaluated protein levels of selected ISG and differences in expression of surface and intracellular molecules linked to immune activation and inflammatory cytokines plasma levels. As secondary endpoints, we evaluated effects of treatment on viral loads, reservoirs, and immune system preservation.

Results: ART treatment reduces viremia to very low or undetectable levels. PH797804 had no side effects, did not further reduced the viremia, and did not affect immune responses to SIV. Administered alone, it had no significant effect on immune activation. When combined with ART, numerous immune activation markers were significantly reduced compared to ART alone treatment. CD38/HLA-DR and Ki-67 percentages in blood, lymph node and rectal CD4+ and CD8+ T cells and plasma levels of IFN-, IL-6, IL-8, and IP-10 were all significantly reduced. IRF7, pSTAT1 and IP-10 protein accumulation was also reduced. Significant preservation of CD4+/IL22+, CD4+ CM T-cells and improved ratio of Th17+/ Treg+ /CD4+ T cell was observed. After ART interruption, viremia rebounded in a similar fashion in the groups that received ART, with or without the inhibitor.

Conclusion: The p38 MAPK inhibitor used here, already in clinical trials for other inflammatory diseases, significantly reduced immune activation during ART and further reduced SIV-mediated immune system deterioration. However, suppression was not complete and was approximately 65% of that of untreated animals. Residual SIV replication in tissues during ART is under investigation.

21 INTRON–CONTAINING HIV-1 RNA ACTIVATES TYPE I INTERFERON AND INFLAMMATORY CYTOKINES

Sean McCauley, Kyusik Kim, Anetta Nowosielska, Ann Dauphin, William E. Diehl, Jeremy Luban
University of Massachusetts, Worcester, MA, USA

Background: HIV-1-infected people who take antiviral drugs that render viremia undetectable have ongoing inflammation of unknown etiology. The HIV-1 provirus, a permanent genetic element in long-lived cells of the immune system, is not eliminated by antiviral drugs. Most HIV-1 proviruses in infected people are replication defective but many are transcriptionally active. Therefore, a possible contributor to this chronic inflammation may be continual HIV-1 transcription in the absence of productive viral production.

Methods: CD4+ T cells and monocytes were isolated from healthy blood donors. Dendritic cells and macrophages were generated through cytokine differentiation of monocytes. All viruses were defective to a single round of infection and produced through HEK293 transfection of 2 or 3 part viral plasmids.

Results: We found that the HIV-1 provirus activated innate immune signaling in dendritic cells, macrophages, and CD4+ T cells. Immune activation required HIV-1 provirus transcription and expression of CRM1-dependent, Rev-dependent, RRE-containing, unspliced HIV-1 RNA. If rev was provided in trans, all HIV-1 coding sequences were dispensable except those cis-acting sequences required for replication or splicing.

Conclusion: These results indicate that Rev-dependent, intron-containing, HIV-1 RNA is detected by the innate immune system, and that drugs which inhibit HIV-1 transcription or Rev-dependent, HIV-1 RNA metabolism, would add qualitative benefit to current antiviral drug regimens.

22 SWITCH TO BICTEGRAVIR/F/TAF FROM DTG AND ABC/3TC

Jean-Michel Molina[1], Douglas Ward[2], Indira Brar[3], Anthony Mills[4], Hans-Jurgen Stellbrink[5], Luis López-Cortés[6], Peter Ruane[7], Daniel Podzamczer[8], Cynthia Brinson[9], Joseph M. Custodio[10], Hui Liu[10], Kristen Andreatta[10], Hal Martin[10], Andrew Cheng[10], Erin Quirk[10]
[1]St. Louis Hospital, Paris, France, [2]Dupont Circle Physicians Group, Washington, DC, USA, [3]Henry Ford Hospital, Detroit, MI, USA, [4]Southern California Men's Medical Group, Los Angeles, CA, USA, [5]ICH Study Center, Hamburg, Germany, [6]Hospital Universitario Virgen del Rocio, Sevilla, Spain, [7]Peter J Ruane, MD Inc, Los Angeles, CA, USA, [8]Hospital Universitario de Bellvitge, Barcelona, Spain, [9]Central Texas Clinical Research, Austin, TX, USA, [10]Gilead Sciences, Inc, Foster City, CA, USA

Background: Bictegravir, a novel, unboosted INSTI with a high barrier to resistance and low potential for drug interactions, has been coformulated with the recommended NRTI backbone of emtricitabine and tenofovir alafenamide (B/F/TAF) as a fixed-dose combination (FDC). We report the primary Week (W) 48 efficacy and safety Phase 3 results of switching to B/F/TAF from dolutegravir plus abacavir/lamivudine (DTG+ABC/3TC) or FDC of DTG/ABC/3TC.

Methods: HIV-infected adults virologically suppressed on DTG/ABC/3TC or DTG plus ABC/3TC (DTG/ABC/3TC group), with estimated glomerular filtration rate (eGFR) ≥50 mL/min were randomized 1:1 to switch to B/F/TAF (50/200/25 mg) once daily or continue current regimen as DTG/ABC/3TC through week 48 in a double-blinded fashion. Primary endpoint was proportion with HIV-1 RNA ≥50 copies/mL (c/mL) at W48 (FDA snapshot). Noninferiority was assessed through 95.002% confidence intervals (CI) using a margin of 4%. Secondary endpoints were proportion with HIV-1 RNA <50 copies/mL and safety (adverse events [AEs], laboratory results, bone mineral density [BMD], and renal biomarkers).

Results: 563 participants were randomized and treated (B/F/TAF n=282, DTG/ABC/3TC n=281): 11% women, 22% Black, median age 46 yrs (range 20-71). At W48, 1.1% switching to B/F/TAF and 0.4% continuing DTG/ABC/3TC had HIV-1 RNA ≥50 c/mL (difference 0.7%; 95%CI -1.0% to 2.8%, p=0.62), demonstrating noninferiority. At W48, proportion with HIV-1 RNA <50 c/mL was 93.6% on B/F/TAF and 95.0% on DTG/ABC/3TC. No participant developed resistance to any study drug. The most common AEs were upper respiratory tract infection (10% B/F/TAF, 10% DTG/ABC/3TC), diarrhea (9%, 5%), nasopharyngitis (7%, 8%) and headache (7%, 7%). Few participants (6 [2%], 2 [1%]) had AEs leading to premature study drug discontinuation. Mean BMD increased similarly in both groups. Percentage changes from baseline in renal biomarkers were similar between treatment groups (Table). Lipid parameters were similar between groups with the exception of a small decrease in triglycerides seen in the B/F/TAF group.

Conclusion: Switching to B/F/TAF was noninferior to continuing DTG/ABC/3TC with low rates of W48 virologic failure, high rates of maintained virologic suppression, and no resistance. B/F/TAF was well tolerated, with a similar bone and urine protein safety profile to DTG/ABC/3TC.

- None

Table.

Change from baseline at Week 48	B/F/TAF (n=284)	DTG/ABC/3TC (n=283)	P value
Median % changes in Renal Biomarkers, median			
Urine Albumin: Creatinine Ratio	+14%	+9%	0.74
Urine Retinol Binding Protein: Creatinine Ratio	+20%	+29%	0.31
Urine Beta-2-Microglobulin: Creatinine Ratio	+21%	+17%	0.53
Median change in eGFR (mL/min)	+1.0	-1.8	<0.001
Mean % changes in BMD, mean			
Spine	+0.69	+0.42	0.33
Hip	+0.16	+0..30	0.47
Median change in Lipid parameters			
Total cholesterol (mg/dL)	0	+2	0.77
LDL cholesterol (mg/dL)	+1	+2	0.42
HDL cholesterol (mg/dL)	-1	0	0.13
Total Cholesterol:HDL ratio	0.0	0.0	0.56
Triglycerides (mg/dL)	-5	+3	0.028

^ p-values were from the 2-sided Wilcoxon rand sum test to compare the 2 treatment groups.
* p-values were from the ANOVA model including treatment as a fixed effect.

23 IMPACT OF RALTEGRAVIR INTENSIFICATION OF FIRST-LINE ART ON IRIS IN THE REALITY TRIAL

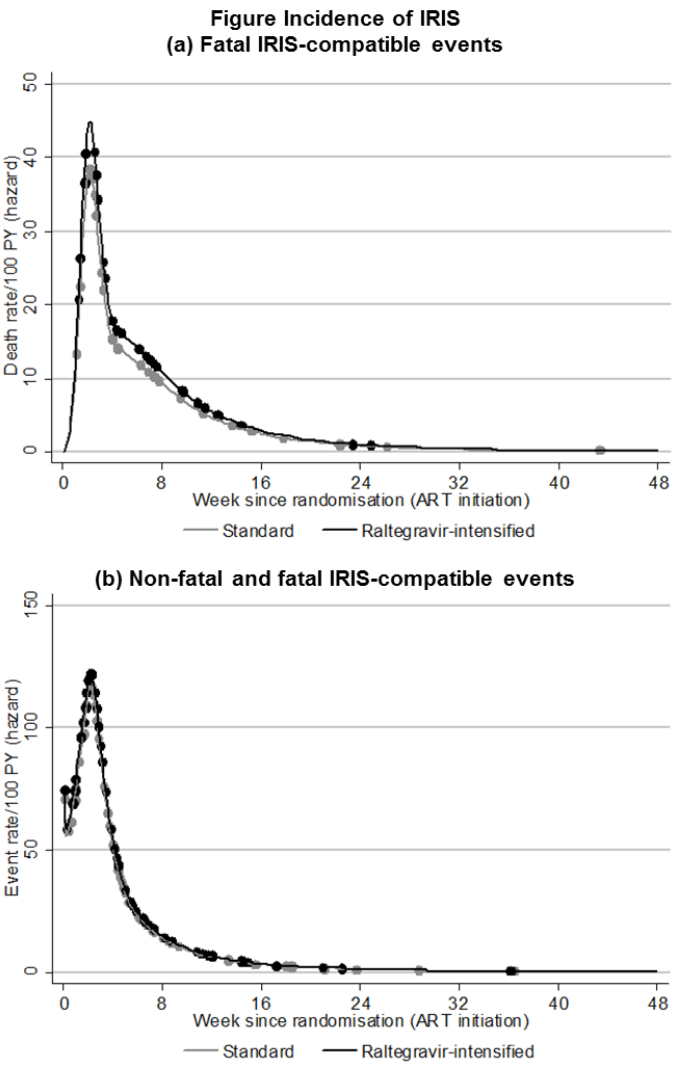
Diana Gibb[1], Alexander J. Szubert[1], Ennie Chidziva[2], Abbas Lugemwa[3], Shalton Mwaringa[4], Abraham Siika[5], Jane E. Mallewa[6], Mutsa Bwakura-Dangarembizi[2], Sheila Kabahenda[3], Andrew Reid[2], Keith Baleeta[3], Sarah Walker[1], Sarah Pett[1]
[1]MRC Clinical Trials Unit at UCL, London, UK, [2]University of Zimbabwe, Harare, Zimbabwe, [3]Joint Clinical Research Centre, Lubowa, Uganda, [4]KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya, [5]Moi University, Eldoret, Kenya, [6]Malawi–Liverpool–Wellcome Trust Clinical Rsr Prog, Blantyre, Malawi

Background: Among HIV-infected adults/children with CD4<100 cells/ul initiating ART in sub-Saharan Africa, the REALITY trial (ISRCTN43622374) showed that 12-week raltegravir (RAL)-intensified quadruple therapy resulted in significantly faster VL declines through 24 weeks, but did not reduce overall mortality or WHO 3/4 events compared to standard triple-drug ART. Integrase inhibitors may replace NNRTIs in first-line ART; there is concern that more rapid VL declines may lead to higher rates of serious IRIS in severely immunocompromised individuals starting ART.

Methods: ART-naïve HIV-infected adults/children ≥5y with CD4<100 cells/ul were randomized to initiate ART (2NRTI+NNRTI) with 12 weeks RAL (Std+RAL) or without (Std). Events, causes of death, and compatibility with IRIS were adjudicated by an endpoint review committee blind to randomization. Predictors of time to first fatal/non-fatal IRIS-compatible event were identified using backwards elimination treating death from other causes as a competing risk.

Results: 1805 patients with median baseline CD4 37 cells/ul and VL 249770 c/ml (74.0%≥100,000c/ml) were randomized to Std+RAL (n=902) vs Std (n=903). Mean change in $\log_{10}$ VL at week 4 was –3.4(SE 0.03) in Std+RAL vs -2.7(0.03) in Std (p<0.001; 42.8% vs 14.5% <50 c/ml respectively). In total 67(29.8%) of 225 deaths were adjudicated as IRIS-compatible, occurring a median 4.4(IQR2.6-9.4) weeks after ART initiation; a further 113 non-fatal IRIS-compatible events occurred after median 3.4(2.0-6.3) weeks on ART (figure). Fatal/non-fatal IRIS-compatible events occurred in 89(9.9%) Std+RAL vs 86(9.5%) Std patients (p=0.79). TB-IRIS occurred in 53(5.9%) vs 54(6.0%) respectively (p=1.00), cryptococcal-IRIS in 15(1.7%) vs 16(1.8%) (p=1.00), other IRIS events of known aetiology in 17(1.9%) vs 14(1.6%) (p=0.59) (Kaposi's sarcoma (8 vs 4), viral hepatitis (1 vs 3), CNS event unknown pathogen (3 vs 1), CMV (2 vs 1), toxoplasmosis (1 vs 1), PCP (0 vs 2), lung event unknown pathogen (0 vs 2), and other (3 vs 0)), and IRIS events of unknown aetiology in 4(0.4%) vs 2(0.2%) respectively. Risks of non-fatal/fatal IRIS were independently higher in those with lower pre-ART CD4 (p<0.001), older individuals (p=0.004) and those with TB at ART initiation (p=0.01).

Conclusion: Despite significantly more rapid declines in HIV VL, there was no evidence that 12 weeks' RAL intensification impacted incidence or case-fatality of IRIS in severely immunocompromised individuals initiating ART.



24 HAIR ANTIRETROVIRAL LEVELS STRONGLY PREDICT VIROLOGIC OUTCOMES IN ACTG'S A5257 TRIAL

Monica Gandhi[1], Igho Ofotokun[2], Peter Bacchetti[1], Chengshi Jin[1], Heather Ribaudo[3], David Haas[4], Anandi N. Sheth[2], Howard Horng[1], Nhi Phung[1], Karen Kuncze[1], Alexander Louie[1], Hideaki Okochi[1], Raphael J. Landovitz[5], Jeffrey J. Lennox[2], Judith S. Currier[5]

[1]University of California San Francisco, San Francisco, CA, USA, [2]Emory University, Atlanta, GA, USA, [3]Harvard University, Cambridge, MA, USA, [4]Vanderbilt University, Nashville, TN, USA, [5]University of California Los Angeles, Los Angeles, CA, USA

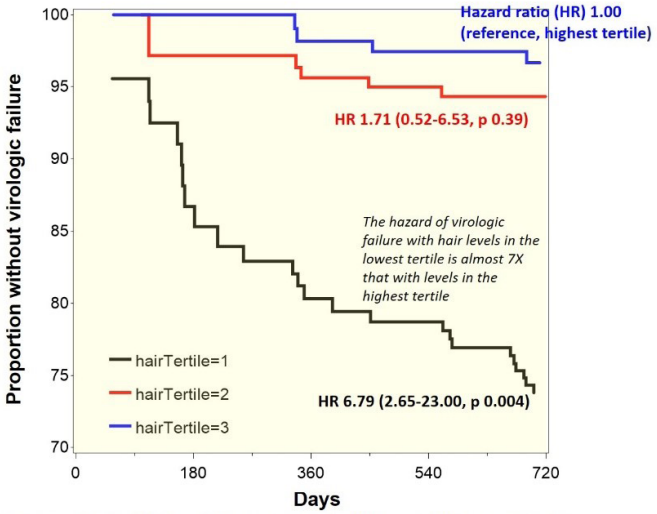
Background: AIDS Clinical Trials Group (ACTG) A5257 was a three-arm study comparing atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r) and raltegravir (RAL)-based regimens in naïve patients. The study showed similar rates of virologic success in all three arms, with RAL regimens better tolerated than protease inhibitor-regimens. Hair antiretroviral (ARV) levels reflect long-term exposure and have been associated with virologic outcomes in cohorts, but have never been evaluated in a treatment trial.

Methods: Hair samples were collected at weeks 4, 8, 16, and then quarterly; concentrations of ATV, DRV and RAL were measured by LC-MS/MS using methods approved by the NIH DAIDS Clinical Pharmacology and Quality Assurance (CPQA) Program. Self-reported adherence was assessed using visual-analog scales. The primary endpoint of A5257 was virologic failure (VF). Proportional hazards regression models estimated the association of ARVs in hair with VF. A time-varying predictor defined as the logarithm of the most recently measured hair level divided by the within-arm median enabled modeling a common hair level effect across arms.

Results: Hair and viral load data were available for 2192 person-visits among 599 participants followed for a median of 217 weeks. Rates of virologic failure by two years were 26%, 6%, and 3% for those with hair levels in the lowest, middle and highest tertiles, respectively. Lower hair ARV levels strongly predicted higher risk of VF [HR 1.69 (95% CI 1.43-2.04, p<0.001) for every 2-fold decrease in hair level], which remained consistent for each drug individually and when adjusting for self-reported adherence and other factors. The hazard of VF with hair ARV levels in the lowest tertile was 6.8 times that with levels in the highest tertile (Figure). Self-reported adherence (median 100% in each arm) and hair ARV levels were weakly correlated (Pearson's ρ 0.15, 0.15, 0.01 for ATV, DRV, RAL, respectively).

Conclusion: We show for the first time that higher long-term ARV exposure as assessed by hair levels predicted a significantly decreased risk of virologic failure in a randomized treatment trial. The risk of virologic failure was high following a low hair ARV level. Correlations between self-reported adherence and hair levels were poor, likely revealing limitations to self-report. Further study is warranted on whether early monitoring of hair ARV levels followed by targeted adherence interventions based on this metric will be able to reduce subsequent VF rates on HIV treatment.

Figure: Kaplan-Meier plot showing time to virologic failure by tertile of hair concentration in A5257



706 person-visits for ATV arm; 776 person-visits for DRV arm; 710 person-visits for RAL arm. Curves estimated for hypothetical persons remaining in the given tertile throughout follow-up. Tertiles of the actual participants could change over time

25 TENOFOVIR DIPHOSPHATE IN DRIED BLOOD SPOTS IS A STRONG PREDICTOR OF VIRAL SUPPRESSION

Jose R. Castillo-Mancilla[1], Mary Morrow[1], Ryan P. Coyle[1], Stacey Coleman[1], Edward M. Gardner[2], Jia-Hua Zheng[1], Lucas Ellison[1], Lane R. Bushman[1], Jennifer J. Kiser[1], Samantha MaWhinney[1], Peter L. Anderson[1]

[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [2]Denver Health and Hospital Authority, Denver, CO, USA

Background: Tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) is a marker of cumulative tenofovir disoproxil fumarate (TDF) exposure and a predictor of PrEP efficacy. However, the predictive value of TFV-DP in HIV infection has not been evaluated.

Methods: DBS for TFV-DP were prospectively obtained from a clinical cohort of HIV-infected individuals on TDF-based therapy (any duration of time) using convenience sampling at the time of their clinic visits, for up to 3 visits over 48-weeks. Log-transformed baseline TFV-DP comparisons utilized t-tests or ANOVA, and are presented as geometric mean [95% CI] fmol/punch. Generalized estimating equations with a logit link, which accounted for repeated measures, were used to estimate the adjusted odds ratio (aOR) of viral suppression (<20 copies/mL) based on the TFV-DP concentration at the time of the study visit. TFV-DP was categorized by the expected number of doses/wk according to a previously completed directly-observed dosing study in HIV negative adults.

Results: A total of 1,198 person-visits from 532 participants (76 female, 79 Black, 106 Hispanic) were analyzed. Among the virologically-suppressed

participants at baseline (n=347), TFV-DP was lower in Blacks (1428 [1251,1630]) vs. Whites (1793 [1678,1916], P=0.002), and vs. Hispanics (1752 [1557,1972], P=0.02); in non-boosted (1614 [1508,1727]) vs. boosted (1884 [1745,2033], P=0.003) regimens, and; in NNRTI-based (1563 [1432,1707]) vs. PI-based (1890 [1704,2095], P=0.006), and vs. multiclass-based (1927 [1650,2252], P=0.02) regimens. The aOR of virologic suppression, after adjusting for age, gender, race, body mas index, serum creatinine, CD4+ T cell count, antiretroviral drug class, duration of therapy and dosing category was 76.5 (95% CI; 26.6-220.5) for a TFV-DP concentration ≥1850 fmol/punch (75th percentile of daily dosing) compared to <350 fmol/punch (<2 doses/wk), as shown in the Figure. The median HIV viral load decreased with higher TFV-DP concentrations; most HIV viral loads were <200 copies/mL in the highest TFV-DP categories.

Conclusion: TFV-DP in DBS is a powerful predictor of virologic suppression in HIV-infected individuals on TDF-based therapy, after controlling for clinically-relevant covariates, and a promising adherence tool in this population. TFV-DP showed slight differences across subgroups. Additional research is required to assess the contributions of antiretroviral adherence versus biology/pharmacology on TFV-DP concentrations among these subgroups.

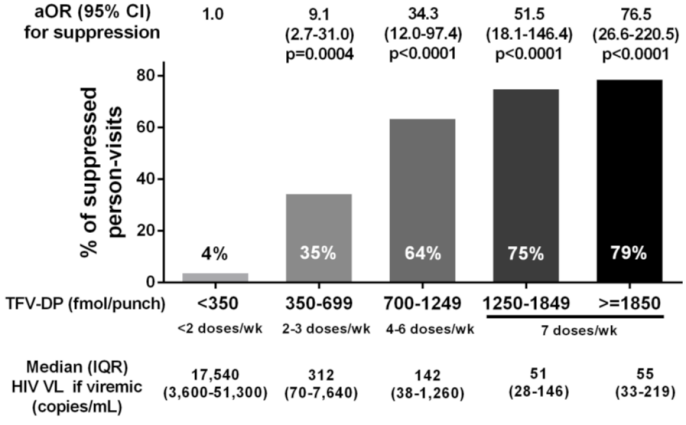


Figure. Percent of person-visits with virologic suppression (<20 copies/mL) and adjusted odds ratio (aOR) of virologic suppression according to TFV-DP concentration and TDF dosing categories.

26 MULTIPLE DAILY DOSES OF MK-8591 AS LOW AS 0.25 MG ARE EXPECTED TO SUPPRESS HIV

Randolph P. Matthews[1], Deanne J. Rudd[1], Vanessa Levine[1], Sandra Zhang[1], Laura Sterling[2], Jay Grobler[1], Ryan Vargo[1], S. Aubrey Stoch[1], Marian Iwamoto[1]
[1]Merck & Co, Inc, Kenilworth, NJ, USA, [2]Celerion, Lincoln, NE, USA

Background: MK-8591 is a nucleoside reverse transcriptase translocation inhibitor (NRTTI) in clinical development for the treatment of HIV-1 infection. MK-8591-triphosphate (MK-8591-TP), the active phosphorylated anabolite of MK-8591, exhibits a half-life of ~78-128 hours in human peripheral blood mononuclear cell (PBMCs). MK-8591 has been assessed in a monotherapy pharmacodynamic (PD) trial in treatment-naïve HIV-1-infected subjects, where single oral doses of MK-8591 from 0.5 mg – 30 mg demonstrated robust viral load lowering after 7-10 days. Here we present pharmacokinetic (PK) data from a clinical trial examining daily administration of MK-8591 in healthy subjects, and the relationship of these data with data from the antiviral efficacy trial in HIV-1 infected subjects.

Methods: In a double-blind, placebo-controlled, three-panel trial, healthy subjects were administered daily placebo or MK-8591 at 5 mg for six weeks, 0.25 mg for four weeks, or 0.75 mg for four weeks (12 active and 4 placebo in each panel). Blood samples were collected for MK-8591 and PBMC MK-8591-TP PK at prespecified times. Vaginal (5 mg, 0.75 mg) or rectal (all three dose levels) biopsies were performed in a subset of subjects to obtain tissue for PK analysis.

Results: All doses were generally well tolerated, with a limited number of mild/moderate adverse experiences reported. Intracellular concentrations of MK-8591-TP that exceeded the EC_{50} were noted following the first dose of 0.25 mg MK-8591. After 2-3 weeks of dosing, steady-state levels of intracellular MK-8591-TP exceeded 1.0 pmol/million cells on average, comparable to levels seen after dosing 10 mg weekly. In the limited assessment of tissue PK, steady-state levels of active MK-8591-TP at all examined dose levels were comparable to reported levels of tenofovir diphosphate observed in rectal tissue following single doses of emtricitabine/tenofovir.

Conclusion: MK-8591 would be expected to lead to HIV suppression after multiple daily doses as low as 0.25 mg.

		MK-8591 Dose								
		0.25 mg MK-8591			0.75 mg MK-8591			5 mg MK-8591		
PBMC MK-8591-TP Pharmacokinetic Parameters	Day	N	GM	GCV or 90% CI	N	GM	GCV or 90% CI	N	GM	GCV or 90% CI
AUC0-24 (pmol/10^6 cells•hr)	1	9	2.36	20.1	9	7.72	31.9	9	57.3	21.5
	28	9	27.3	40.4	9	72.0	24.4	9	520	12.5
	42	NA	NA	NA	NA	NA	NA	9	626	27.3
Cmax (pmol/10^6 cells)	1	9	0.124	26.3	9	0.478	41.3	9	3.11	31.2
	28	9	1.80	44.1	9	6.87	58.5	9	30.5	15.8
	42	NA	NA	NA	NA	NA	NA	9	40.7	24.7
C24 (pmol/10^6 cells)	1	9	0.115	(0.10, 0.13)	9	0.393	(0.34, 0.45)	9	2.69	(2.35, 3.08)
	28	9	0.831	(0.73, 0.95)	9	3.32	(2.90, 3.79)	9	20.9	(18.30, 23.92)
	42	NA	NA	NA	NA	NA	NA	9	21.0	(18.39, 24.04)
Apparent terminal t½ (hr)	28	8	186	16.4	8	177	18.3	NA	NA	NA
	42	NA	NA	NA	NA	NA	NA	9	209	11.4
Plasma MK-8591 Pharmacokinetic Parameters	**Day**	**N**	**GM**	**GCV**	**N**	**GM**	**GCV**	**N**	**GM**	**GCV**
AUC0-24 (nM•hr)	1	9	17.5	14.4	9	53.4	21.4	9	395	20.7
	28	9	32.0	12.5	9	87.2	19.9	9	622	13.8
	42	NA	NA	NA	NA	NA	NA	9	675	14.8
Cmax (nM)	1	9	7.81	27.7	9	18.4	34.1	9	124	32.5
	28	9	8.51	20.5	9	18.4	33.2	9	138	28.0
	42	NA	NA	NA	NA	NA	NA	9	141	26.2
Apparent terminal t½ (hr)	1	9	2.07	11.0	9	5.19	87.7	9	9.38	12.1
	28	9	86.9	89.5	9	122	23.1	9	25.4	21.5
	42	NA	NA	NA	NA	NA	NA	9	230	10.2
Tissue MK-8591-TP + -DP	**Day**	**N**	**AM**	**SD**	**N**	**AM**	**SD**	**N**	**AM**	**SD**
Rectal (fmol/g tissue)	29	8	52100	20700	4	167000	48000	NA	NA	NA
	43	NA	NA	NA	NA	NA	NA	3	662000	17000
Vaginal (fmol/g tissue)	29	0	NA	NA	3	50400	35700	NA	NA	NA
	43	NA	NA	NA				1	191000	NA
Tissue MK-8591	**Day**	**N**	**AM**	**SD**	**N**	**AM**	**SD**	**N**	**AM**	**SD**
Rectal (ng/g tissue)	29	8	17.2	3.84	4	42.8	25.7	NA	NA	NA
	43	NA	NA	NA	NA	NA	NA	3	390	117
Vaginal (ng/g tissue)	29	0	NA	NA	3	32.3	5.4	NA	NA	NA
	43	NA	NA	NA				1	159	NA

NA = Not applicable.
GM = Geometric mean; GCV = Geometric coefficient of variation; AM = Arithmetic mean; SD = Standard deviation
90% confidence interval (CI) (min,max) reported for C24

27 COMPARATIVE LYMPHOID TISSUE PHARMACOKINETICS (PK) OF INTEGRASE INHIBITORS (INSTI)

Courtney V. Fletcher[1], Ann Thorkelson[2], Lee Winchester[3], Timothy Mykris[3], Jon Weinhold[3], Kayla Campbell[3], Jodi Anderson[2], Jacob Zulk[2], Puleng Moshele[2], Timothy Schacker[2]
[1]University of Nebraska Medical Center, Omaha, NE, USA, [2]University of Minnesota, Minneapolis, MN, USA, [3]University of Nebraska, Omaha, NE, USA

Background: The secondary lymphoid tissues (LT), lymph nodes (LN) and gut-associated lymphoid tissue (GALT), are the primary sites of HIV replication and where the latent pool of virus is maintained. In HIV-infected persons with undetectable plasma HIV-RNA, an association has been reported between low concentrations of antiretroviral drugs (ARVs) in LT and measures of persistent viral production. None of those individuals, however, were receiving an INSTI-based regimen. The objective of this work was to compare the LT PK of the INSTIs, dolutegravir (DTG), elvitegravir EVG) and raltegravir (RAL).

Methods: Study participants were HIV-infected persons receiving DTG, EVG (with cobicistat), or RAL, with other ARVs. PBMCs and mononuclear cells (MNCs) from LN, ileum and rectal tissues were obtained, and intracellular concentrations of INSTIs were quantified by LC-MS/MS. Inhibitory quotients (IQ) as the ratio of intracellular concentrations to the protein-binding corrected 90 or 95% inhibitory concentration (IC90-95) of the respective INSTIs were determined. Summary statistics were calculated.

Results: PK data were obtained from a total of 27 persons: DTG, n=10; EVG, n=11; RAL, n=6. NRTIs were: TDF/FTC, n=20; ABC/3TC, n=4; ABC/3TC/TDF, n=1; TDF/3TC, n=1; and TAF/FTC, n=1. Median (and interquartile range) IQ values for the INSTIs in PBMCs, LN, ileum and rectum are given in the Table.

Conclusion: In PBMCs, the median IQ values for DTG, EVG and RAL were 5-fold or more above the IC90-95. This is consistent with clinical trial results showing these INSTIs produce rapid and potent decreases in plasma HIV RNA. In LT, however, all median IQ values were lower than those in PMBCs, except for EVG in the ileum and rectum, which were greater or equivalent, respectively. Only EVG had a median IQ value in the LN (1.85) above the IC90-95. As shown for other ARVs, these INSTIs achieved lower concentrations particularly in the LN, than in peripheral blood. Plasma concentrations of DTG, EVG and RAL have been linked with virologic response; the standard doses of these INSTIs achieve plasma IQ values of 8 or greater. Pharmacodynamic evaluations are needed to determine whether the low concentrations observed in LT create conditions in LT that allow persistent viral production.

Drug	Inhibitory Quotient (intracellular concentration/protein binding corrected IC_{90-95}) Median and Interquartile Range		
	DTG	EVG	RAL
PBMC	5.24 (3.32, 13.23	16.46 (10.76, 25.93)	6.08 (0.94, 14.14)
LN	0.44 (0.26, 0.66)	1.85 (1.51, 2.15)	0.28 (0.26, 0.48)
Ileum	0.43 (0.35, 9.95)	39.88 (7.28, 105.41)	Not done
Rectum	0.41 (0.33, 0.99)	16.97 (7.87, 39.83)	2.71 (2.62, 5.91)

28LB RIFAMPIN EFFECT ON TENOFOVIR ALAFENAMIDE (TAF) PLASMA/ INTRACELLULAR PHARMACOKINETICS

Maddalena Cerrone[1], Omamah Alfarisi[2], Megan Neary[3], Mark A. Marzinke[2], Teresa Parsons[2], Andrew Owen[3], Gary Maartens[4], Anton Pozniak[1], Charles W. Flexner[2], Marta Boffito[1]

[1]Chelsea and Westminster Hospital, London, UK, [2]The Johns Hopkins University, Baltimore, MD, USA, [3]University of Liverpool, Liverpool, UK, [4]University of Cape Town, Cape Town, South Africa

Background: TAF produces lower plasma and higher intracellular (IC) tenofovir (TFV) concentrations than tenofovir disoproxil fumarate (TDF), but is a substrate of drug transporters (e.g. BCRP; ABCG2; ABCB1) and therefore a potential victim of drug interactions, especially with inducers like rifampin (RIF) that act via nuclear receptors such as PXR (NR1I2) and CAR (NR1I3).

Methods: This study is the first to measure the pharmacokinetics (PK) of TAF once-daily (OD) with RIF and compare it directly to TDF. Healthy volunteers aged 18-65 years received TAF/ FTC 25/200mg OD (28 days) with food, followed by TAF/FTC+RIF 600mg OD (28 days, RIF on empty stomach followed by TAF/ FTC with meal after 30 mins), followed by TDF 300mg OD (28 days) with food. Intensive PK sampling occurred on days 28 (TAF/FTC), 56 (TAF/FTC+RIF) and 84 (TDF), and plasma TAF, TFV, FTC and IC TFV-diphosphate (TFV-DP) and FTC-triphosphate (FTC-TP) concentrations were measured by validated LC-MS methods. Subjects were genotyped for polymorphisms in NR1I2 (rs2472677), NR1I3 (rs2307424), CYP3A4 (rs35599367), and ABCG2 (rs2231142).

Results: 17 subjects completed all PK phases (14 females). Plasma TAF and TFV geometric mean ratios (GMR, TAF+RIF vs TAF) and 90% confidence intervals (CI) for the main PK parameters calculated are illustrated in the Table, as well as IC TFV-DP GMR (90%CI). Mean TFV-DP AUC was 122,920 on PK2 versus 24,247 h*fmol/million-cells on PK3. Plasma TFV/IC TFV-DP AUC ratio was unchanged by RIF co-administration (0.001), suggesting that RIF mainly affects TAF absorption and not clearance. FTC-TP PK parameters were not affected by RIF. All polymorphisms were in Hardy-Weinberg equilibrium, and no consistent associations were observed after correction for multiple comparisons.

Conclusion: Relative to TAF 25mg OD, following administration of TAF OD with RIF, plasma TAF Cmax and AUC were decreased by 45% and 47%, respectively, while IC TFV-DP concentrations were decreased by 40%. However, IC TFV-DP concentrations were still 82% higher on average than those achieved by standard dose TDF. These data support further study of TAF when co-administered with RIF in patients with HIV and tuberculosis.

PK Parameter	TAF/FTC+RIF vs TAF GMR (90% CI)	TDF vs TAF/FTC+RIF GMR (90% CI)
Plasma TAF		
C_{max}	0.55 (0.43-0.71)	
AUC	0.53 (0.36 -0.79)	
Plasma TFV		
C_{max}	0.33 (0.26-0.41)	
AUC	0.43 (0.40-0.46)	
C_{24h}	0.45 (0.40-0.51)	
Intracellular TFV-DP		
C_{max}	0.60 (0.48-0.65	0.19 (0.14-0.26)
AUC	0.59 (0.52-0.68)	0.18 (0.14-0.25)
C_{24h}	0.60 (0.47-0.77)	0.19 (0.14-0.26)

29LB SYSTEMATIC VS TEST-GUIDED TUBERCULOSIS TREATMENT: DATA OF THE STATIS RANDOMIZED TRIAL

François-Xavier Blanc[1], Anani D. Badje[2], Maryline Bonnet[3], Delphine Gabillard[2], Eugène Messou[4], Conrad Muzoora[5], Sovannarith Samreth[6], Duc Bang Nguyen[7], Laurence Borand[8], Anaïs Domergue[7], Naome Natukunda[9], Serge Eholie[10], Serge Domoua[10], Xavier Anglaret[2], Didier Laureillard[11]

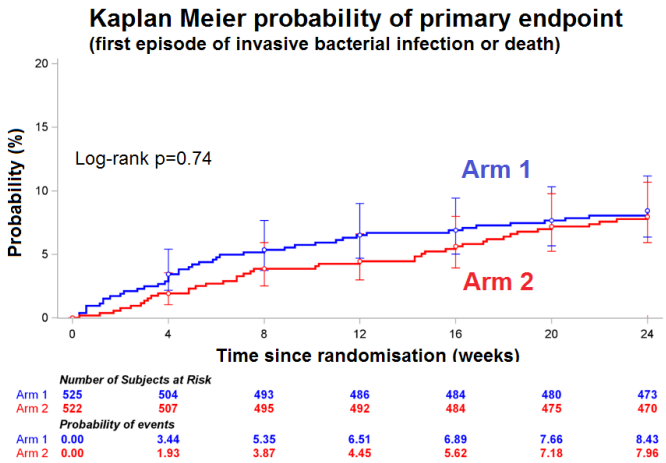
[1]CHU de Nantes, Nantes, France, [2]INSERM, Bordeaux, France, [3]IRD, Montpellier, France, [4]INSERM, Abidjan, Côte d'Ivoire, [5]Mbarara University of Science and Technology, Mbarara, Uganda, [6]National Centre for HIV/AIDS Dermatology and STDs, Phnom Penh, Cambodia, [7]Pham Ngoc Thach Hospital, Ho Chi Minh City, Vietnam, [8]Pasteur Institute in Cambodia, Phnom Penh, Cambodia, [9]Epicentre, Mbarara, Uganda, [10]Université Félix Houphouët-Boigny, Abidjan, Côte d'Ivoire, [11]CHU de Nimes, Nimes, France

Background: Despite increasing access to antiretroviral therapy (ART), many HIV+ adults still present for care with severe immunosuppression. In such late presenters, mortality following ART initiation is high, curable diseases like tuberculosis (TB) or invasive bacterial diseases (IBD) being major causes of mortality. Here, we report the results of the STATIS open-label randomized controlled trial (ANRS 12290, NCT02057796) that compared the efficacy and safety of 2 strategies aiming at decreasing mortality and IBD in late presenters.

Methods: The trial was conducted in Côte d'Ivoire, Uganda, Cambodia and Vietnam. ART-naïve HIV-1 infected adults with CD4<100 cells/µl ready to start ART were randomly assigned to either ART + extensive TB screening (arm 1) or ART + systematic empirical TB treatment (4HRZE/2HR) (arm 2). In arm 1, extensive TB screening included Xpert MTB/RIF on sputum, urine lipoarabinomannan (LAM) and chest X-ray at baseline and at any time during follow-up in case of TB symptoms. ART was initiated immediately in patients who did not start TB treatment at baseline (arm 1 patients with negative TB screening) and 2 weeks after starting TB treatment in others (arm 1 patients with positive TB screening and arm 2 patients). The primary outcome was the occurrence of death or IBD at week 24 (W24). Total follow-up lasted 48 weeks. We used Cox models to compare the probability of outcomes between arms, adjusting for randomization stratification variables (country and CD4 level).

Results: Between Sep. 2014 and May 2017, 1047 participants were included (arm 1: 525; arm 2: 522; 56% from Africa; 44% from South-East Asia). The last one reached W24 in Nov. 2017. Baseline characteristics were: 58% male, mean (SD) age 36 (9) years, body mass index 20.1 (3.5) kg/m2, hemoglobin 11.6 (2.3) g/dl, CD4 36 (27) cells/µl, plasma HIV RNA 5.4 (0.6) $\log_{10}$ copies/ml, with no difference between arms. At W24, 39 patients (3.8%) were lost to follow-up (arm 1: 21; arm 2: 18), while there were 69 deaths (arm 1: 36; arm 2: 33) and 29 IBD (arm 1: 14; arm 2: 15) (Figure). The W24 hazard ratio of events between arm 2 vs. arm 1 was 0.93 (95%CI 0.61-1.42) for death or IBD, 0.92 (0.57-1.48) for death alone, 1.14 (0.54-2.40) for IBD alone and 2.70 (1.80-4.04) for grade 3-4 drug-related toxicity.

Conclusion: Systematic TB treatment is not superior to extensive TB screening using Xpert MTB/RIF and urine LAM and targeted TB treatment to decrease the risk of mortality or IBD in ART-naïve adults ready to start ART with CD4<100/µl.



30LB RESULTS OF ACTG A5288: A STRATEGY STUDY IN RLS FOR 3RD-LINE ART CANDIDATES

Beatriz Grinsztejn[1], Michael D. Hughes[2], Justin Ritz[2], Robert Salata[3], Peter Mugyenyi[4], Evelyn Hogg[5], Linda Wieclaw[6], Robert Gross[7], Catherine Godfrey[8], Nagalingeswaran Kumarasamy[9], Cecilia Kanyama[10], John W. Mellors[11], Carole Wallis[12], Ann Collier[13]

[1]Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro. Brazil, [2]Harvard University, Boston, MA, USA, [3]Case Western Reserve University, Cleveland, OH, USA, [4]Joint Clinical Research Centre, Kampala, Uganda, [5]Social & Scientific Systems, Silver Spring, MD, USA, [6]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [7]University of Pennsylvania, Philadelphia, PA, USA, [8]NIAID, Bethesda, MD, USA, [9]YR Gaitonde Center for AIDS Research and Education, Chennai, India, [10]University of North Carolina Project–Malawi, Lilongwe, Malawi, [11]University of Pittsburgh, Pittsburgh, PA, USA, [12]Lancet Labs and BARC SA, Johannesburg, South Africa, [13]University of Washington, Seattle, WA, USA

Background: Individuals presenting for 3rd line ART are a challenge in resource limited settings (RLS) because of uncertain ARV susceptibility and limited data on virologic responses to remaining available ARV regimens.

Methods: A5288 is an open-label strategy study in RLS in HIV-1 infected individuals presenting with confirmed plasma HIV RNA (VL) ≥ 1000 copies after > 24 weeks of protease-based (PI) 2nd line ART. Primary objective was to use novel antiretrovirals and contemporary management tools, including standard genotyping to select an appropriate 3rd-line regimen, interventions to improve adherence, and VL monitoring, to achieve virologic suppression in ≥65% at 48 weeks of follow-up. Review of prior ART, combined with real-time standard genotype, determined Cohort A-D assignment (Table). An exploratory randomized comparison in Cohort B of NRTIs+DRV/r+RAL (B1) versus ETR+DRV/r+RAL (B2) among HBV Ab- participants was performed; HBV Ab+ participants in B received DRV/r + RAL + TDF/FTC or TDF+3TC (B3). Suppression of VL ≤200 copies/mL at 48 weeks and virologic failure (VF, two consecutive ≥1000 copies/mL ≥ 24 weeks) were 1o and 2o endpoints.

Results: From 2013-2015, 545 participants in 10 countries in Africa, Asia, South America and the Caribbean enrolled: 47% females; median age 41 years, median CD4 count 175 cells/mm^3. At enrollment, drug resistance (moderate or high-level) to 0, 1, 2, and 3 ARV classes was identified in 22%, 20%, 30% and 27% of participants, respectively. Overall, 64% (95% CI 60, 68%) had VL ≤ 200 copies/mL at week 48. Viral suppression and VF differed across cohorts (Table). By week 48, Cohort A had the most Grade ≥ 3 adverse events (39%) and regimen discontinuations (13%). No differences in VL ≤ 200 copies/mL at week 48 or VF ≥ 24 weeks were observed in the randomized comparison of B1 & B2 cohorts.

Conclusion: Regimens containing DRV/r and RAL with or without ETR were highly effective for participants with LPV/r resistance who presented for 3rd line ART. More than half of participants without LPV/r resistance and who remained on 2nd line ART did not achieve viral suppression at week 48. This subgroup requires additional interventions to achieve viral suppression. Targeted real-time genotyping to select regimens for 3rd line ART can appropriately allocate more costly ARVs to those with greater resistance.

Table

Cohort Information				Results	
Cohort	**Definition**	**Regimen Summary**	**# (%)**	**# (%) ≤ 200 copies/mL at Wk 48**	**# (%) confirmed virologic failure**
A	**No LPV/r resistance Susceptible to ≥1 NRTI**	**Continue 2nd line ART**	**287 (53%)**	**125 (44%)**	**145 (51%)**
B1	**Resistant to LPV/r, susceptible to DRV/r & ETR**	**Best available NRTIs + DRV/r + RAL**	**74 (14%)**	**65 (88%)**	**6 (8%)**
B2		**DRV/r + RAL + ETR**	**72 (13%)**	**63 (88%)**	**4 (6%)**
B3	***B3 HBV Ag +**	**DRV/r + RAL + TDF/FTC or TDF+3TC**	**8 (1%)**	**8 (100%)**	**0 (0%)**
C	**Resistant to LPV/r & ETR but susceptible to DRV/r; no prior RAL**	**Best available NRTIs + DRV/r + RAL**	**70 (13%)**	**63 (90%)**	**5 (7%)**
D	**Not eligible for Cohorts A, B, or C**	**Best available local & study supplied ARVs**	**34 (6%)**	**25 (74%)**	**6 (18%)**

31 EFFECT OF TB SCREENING AND RETENTION INTERVENTIONS ON EARLY ART MORTALITY IN BOTSWANA

Andrew F. Auld[1], Tefera Agizew[2], Anikie Mathoma[2], Rosanna Boyd[2], Anand Date[1], Sherri Pals[1], Christopher Serumola[2], Unami Mathebula[2], Heather Alexander[1], Tedd V. Ellerbrock[1], Goabaone Rankgoane-Pono[3], Pontsho Pono[3], Katherine Fielding[4], Alison Grant[4], Alyssa Finlay[2]

[1]CDC, Atlanta, GA, USA, [2]CDC Botswana, Gaborone, Botswana, [3]Ministry of Health, Gaborone, Botswana, [4]London School of Hygiene & Tropical Medicine, London, UK

Background: In 2012, at 22 antiretroviral therapy (ART) clinics, Botswana implemented a phased rollout of the Xpert package of interventions, with 3 components: (1) additional nurses and mentoring to support intensified tuberculosis (TB) case finding (ICF) activities, (2) intensified tracing for patients missing clinic appointments, and (3) Xpert MTB/RIF (Xpert) replacing smear microscopy. We evaluated effect of the Xpert package on early (6- and 12-month) ART mortality in the XPRES trial (ClinicalTrials.gov: NCT02538952).

Methods: At 22 ART clinics, all adult patients (>12 years old) starting ART were enrolled in three phases: (1) a retrospective standard of care (SOC) phase, (2) a prospective enhanced care (EC) phase, and (3) a prospective EC plus Xpert (EC+X) phase. EC and EC+X phases were enrolled as a stepped-wedge trial. Adults enrolled in the EC phase received SOC plus components 1 (TB ICF) and 2 (intensified tracing) of the Xpert package. Adults enrolled in the EC+X phase received SOC plus all 3 components of the Xpert package. All-cause 6-month ART mortality was the primary outcome. An adjusted analysis, appropriate for study design, controlled for baseline differences in individual-level factors and intra-facility correlation. Trial outcome results are final.

Results: 14,963 eligible patients were enrolled; 8,980 in the SOC, 1,768 in the EC, and 4,215 in the EC+X phases. Median age of ART enrollees was 35 years, 64% were female, median weight was 58.4 kg, and median hemoglobin 11.7 g/dL. These characteristics were similar across phases. Pregnancy among females was less common in the SOC than subsequent phases (16% in SOC, 23% in EC, and 32% in EC+X). Median CD4 count at ART initiation was lower in SOC than subsequent phases (184/µL in SOC, 241/µL in EC, and 246/µL in EC+X). In adjusted analysis, compared with the SOC phase, 6-month ART mortality was significantly lower in the EC+X phase, while 12-month ART mortality was significantly lower in both the EC and EC+X phases (Table). When compared with the EC phase, 6- and 12-month mortality rates were not significantly different in the EC+X phase.

Conclusion: In Botswana, interventions to strengthen TB ICF and active tracing were associated with lower early ART mortality and should be considered for scale-up. No additional mortality benefit of replacing smear microscopy with Xpert was observed.

Table: Crude and Adjusted Hazard Ratios Estimating Effect of Enhanced TB Case Finding and Retention Interventions on 6- and 12-month ART Mortality in Botswana

	6-month Mortality Rate/100PY	Crude HR	(95% CI)	p	AHR*	(95% CI)	p
Study Phase							
Standard of Care (N=8,980)	11.4	1.00	--	--	1.00	--	--
Enhanced Care (N=1,768)	6.5	**0.59**	**(0.45-0.79)**	**<0.001**	0.79	(0.57-1.09)	0.151
Enhanced Care + Xpert (N=4,215)	6.3	**0.59**	**(0.48-0.72)**	**<0.001**	**0.77**	**(0.61-0.98)**	**0.031**
	12-month Mortality Rate/100PY	**Crude HR**	**(95% CI)**	**P**	**AHR***	**(95% CI)**	**p**
Study Phase							
Standard of Care (N=8,980)	7.3	1.00	--	--	1.00	--	--
Enhanced Care (N=1,768)	4.0	**0.56**	**(0.43-0.73)**	**<0.001**	**0.72**	**(0.54-0.97)**	**0.033**
Enhanced Care + Xpert (N=4,215)	4.6	**0.58**	**(0.48-0.70)**	**<0.001**	**0.76**	**(0.61-0.95)**	**0.015**

Abbreviations: PY, person-years; HR, hazard ratio; CI, confidence interval; AHR, adjusted hazard ratio; ART, antiretroviral therapy.
*Adjusted for age, sex, pregnancy status, weight, CD4 count at ART initiation, hemoglobin level, and ART regimen.

32 A CLUSTER-RANDOMIZED TRIAL OF SYMPTOM VS TST SCREENING TO IMPROVE CHILD IPT UPTAKE

Nicole Salazar-Austin[1], Silvia Cohn[1], Grace Barnes[1], Molefi Tladi[2], Katlego Matlhaoleng[2], Catharina Swanepoel[3], Zarina Motala[3], Ebrahim Variava[4], Neil A. Martinson[2], Richard E. Chaisson[1]

[1]Johns Hopkins Hospital, Baltimore, MD, USA, [2]Perinatal HIV Research Unit, Soweto, South Africa, [3]Matlosana Department of Health, Klerksdorp, South Africa, [4]Klerksdorp Tshepong Hospital Complex, Jouberton, South Africa

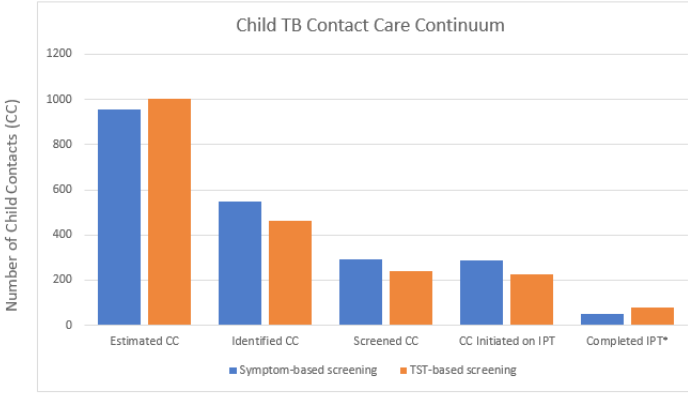
Background: HIV and tuberculosis (TB) disproportionately affect women of reproductive age in sub-Saharan Africa, resulting in increased household TB exposure of HIV-infected and HIV-exposed children. Isoniazid preventive therapy (IPT) is highly-effective at preventing tuberculosis (TB) disease in children < 5 years. IPT implementation has been hampered by health system, provider and patient challenges. In 2006, the WHO recommended symptom-

based screening as a replacement for TST-based screening. There is little data on the effectiveness of this recommendation.

Methods: A cluster-randomized trial was conducted to determine whether symptom-based screening improved the proportion of identified child contacts < 5 years who initiated IPT compared to TST-based screening clinics. From October 2015 through February 2017 in the Matlosana sub-district of North West Province, 16 clinics were randomized to conduct child contact evaluations with either symptom-based or TST- based screening. Training and customized child contact management files were provided to all clinics. Outcome data were abstracted from clinical records. Cluster adjusted results are shown.

Results: Clinic-based tracing identified 547 and 464 children <5 from 1440 and 1597 TB index patients in the symptom-based and TST-based testing clinics, respectively (0.37 vs 0.28 per case; p=0.17). Of these identified contacts, 52% and 57% initiated IPT from the symptom and TST-based screening groups, (p=0.53) and 31% and 40% of children who started IPT more than 7 months previously completed therapy (p=0.36). Three (0.8%) children were not diagnosed with TB by symptom-based screening, requiring a change from IPT to TB treatment. There were no child deaths. Based on an historic average of 0.7 child contacts per index case in Matlosana, we estimate 30% and 25% IPT coverage among child contacts exposed to TB by symptom-based and TST-based screening respectively (p=0.54).

Conclusion: TB nurses in decentralized clinics appropriately initiated IPT using symptom-based screening. However, symptom- based screening did not improve the proportion of identified child contacts initiated on IPT when compared to TST-based screening. Further research is needed to identify bottlenecks and evaluate interventions to ensure all TB-exposed children <5 receive TB preventive therapy.



*Includes only those CC who could have completed IPT by the time the analysis was performed

33 SAFETY AND EFFICACY OF DOLUTEGRAVIR-BASED ART IN TB/HIV COINFECTED ADULTS AT WEEK 24

Kelly Dooley[1], Richard Kaplan[2], Noluthando Mwelase[3], Beatriz Grinsztejn[4], Eduardo Ticona[5], Marcus Lacerda[6], Pedro Cahn[7], Elena Belonosova[8], Mounir Ait-Khaled[9], Kostas Angelis[10], Dannae Brown[9], Rajendra P. Singh[11], Christine Talarico[12], Allan-Raymond Tenorio[12], Michael Aboud[9]

[1]Johns Hopkins University, Baltimore, MD, USA, [2]Desmond Tutu HIV Foundation, Cape Town, South Africa, [3]Clinical HIV Research Unit, Johannesburg, South Africa, [4]Oswaldo Cruz Foundation - Fiocruz, Rio de Janeiro, Brazil, [5]Hospital Nacional Dos de Mayo, Lima, Peru, [6]Fiocruz, Manaus, Brazil, [7]Fundación Huésped, Buenos Aires, Argentina, [8]Orel Regional Center for Prevention and Treatment of AIDS and Infectious Diseases, Orel, Russian Federation, [9]ViiV Healthcare, Brentford, UK, [10]GlaxoSmithKline, Uxbridge, UK, [11]GlaxoSmithKline, King of Prussia, PA, USA, [12]ViiV Healthcare, Research Triangle Park, NC, USA

Background: Concurrent treatment of TB and HIV is compounded by drug interactions, overlapping toxicities, and immune reconstitution inflammatory syndrome (IRIS). The efficacy and safety of dolutegravir (DTG) in antiretroviral treatment (ART) naïve adults with HIV/TB co-infection was assessed.

Methods: INSPIRING (NCT02178592) is a Phase 3b, non-comparative, active control, randomised, open-label study in HIV-1 infected ART-naïve adults (CD4+ ≥50 cells/μL) with drug-sensitive TB. Participants on rifampin-based TB treatment for up to 8 weeks were randomised (3:2) to receive DTG (50mg twice daily during and for 2 weeks post-TB therapy, followed by 50mg once daily [OD]) or EFV (600mg OD), with 2 investigator-selected NRTIs for 52 weeks. For this Week 24 interim analysis, the proportion of subjects with plasma HIV-1-RNA <50 c/mL was derived using the FDA Snapshot algorithm in the intent to treat exposed (ITT-E) population. Safety was assessed in all subjects who received study drug. An independent committee adjudicated IRIS episodes. The study was not powered to show a difference between study arms; no formal statistical hypothesis was tested.

Results: Of 113 subjects enrolled, 69 were randomised to DTG and 44 to EFV. Median baseline HIV-1 RNA and CD4+ cell counts were 5.10 $\log_{10}$ c/mL and 208 cells/μL in the DTG arm and 5.24 $\log_{10}$ c/mL and 202 cells/μL in the EFV arm; 40% were women. The proportions of subjects with HIV-1-RNA <50 c/mL at Week 24 were 56/69 (81%) (95% CI: 72%, 90%) in the DTG arm and 39/44 (89%) (95% CI: 79%, 98%) in the EFV arm. The lower DTG response rate was driven by non-treatment related snapshot failures: five participants (7%) in DTG arm and none in EFV arm discontinued due to non-treatment-related reasons (loss to follow-up/protocol deviations). Median CD4+ cell increases at Week 24 were 146 cells/μL (IQR: 71, 214) for DTG and 93 cells/μL (IQR: 47, 178) for EFV. Two subjects discontinued study treatment due to AEs (both on EFV). TB-Associated IRIS rates (adjudicated and investigator reported) were low (DTG, n=4 [6%]; EFV, n=4 [9%]). No subjects discontinued due to IRIS or liver events.

Conclusion: Interim Week 24 results from this ongoing study show that DTG 50 mg twice daily appears to be effective and well-tolerated in HIV/TB co-infected adults receiving RIF-based TB therapy. Rates of IRIS were low. There were no new toxicity signals for DTG and no discontinuations due to liver events. These data support the use of DTG based regimen in HIV/TB co-infection.

34 PHARMACOKINETICS OF BICTEGRAVIR ADMINISTERED TWICE DAILY IN COMBINATION WITH RIFAMPIN

Joseph M. Custodio, Steve K. West, Sean Collins, Amanda Vu, Deqing Xiao, Hal Martin, Erin Quirk, Brian P. Kearney, Anita Mathias

Gilead Sciences, Inc, Foster City, CA, USA

Background: Bictegravir (BIC; B) is a potent, once-daily, unboosted HIV integrase strand transfer inhibitor (INSTI) with a high barrier to resistance. BIC is coformulated with the NRTI backbone of emtricitabine/tenofovir alafenamide (F/TAF) into the single-tablet regimen, B/F/TAF for treatment of HIV-1 infection. BIC is primarily hepatically eliminated, with similar contributions by the drug metabolizing enzymes CYP3A and UGT1A1. Rifampin (RIF), a component of tuberculosis (TB) treatment, is a potent inducer of metabolizing enzymes. A previous study evaluating the coadministration of RIF with once-daily BIC showed a marked reduction in BIC concentrations. The present study evaluated the pharmacokinetics (PK) of BIC administered twice daily (BID) in combination with RIF.

Methods: Healthy subjects were enrolled into one of two cohorts (N=26/cohort). Cohort 1 subjects received B/F/TAF (50/200/25 mg) QD, 2 hours postprandial, for 28 days. Cohort 2 subjects received B/F/TAF BID plus RIF 600 mg QD, 2 hours postprandial, for 28 days. Intensive plasma sampling was conducted on Day 28 for determination of BIC primary PK parameters ($AUC_{0\text{-}24h}$, C_{max}, C_{trough}). Statistical comparisons for BIC were performed using geometric least squares mean (GLSM) ratios and associated 90% confidence intervals (CI) with B/F/TAF BID plus RIF in Cohort 2 as the test treatment and B/F/TAF QD in Cohort 1 as the reference treatment. Safety was assessed throughout the study and follow up.

Results: Following coadministration of B/F/TAF BID plus RIF for 28 days, the BIC $AUC_{0\text{-}24h}$ and C_{max} were decreased approximately 61% and approximately 47%, respectively, as compared with B/F/TAF QD administration alone (Table 1). Although the observed BIC C_{trough} in all subjects was above the protein adjusted 95% effective concentration ($paEC_{95}$) (162 ng/mL) following B/F/TAF BID plus RIF in Cohort 2, the resulting geometric least squares mean BIC C_{trough} was approximately 80% lower, as compared with that observed following B/F/TAF QD in Cohort 1 (Table 1). All treatments were well tolerated and all subjects completed the study.

Conclusion: The present study results confirm the drug drug interaction between RIF and BIC. These findings show that twice daily administration of B/F/TAF with RIF does not mitigate the induction effect sufficiently to yield BIC C_{trough} concentrations associated with the B/F/TAF registrational Phase 3 studies.

Table 1. BIC PK Parameter Summary

PK Parameter	B/F/TAF BID plus RIF (n=26) Mean (%CV)	B/F/TAF QD (n=26) Mean (%CV)	GLSM Ratio (%) (90% CI)
$AUC_{0\text{-}24h}$ (ng•h/mL)	45600 (23)	115000 (21)	39.5 (35.7, 43.7)
C_{max} (ng/mL)	4560 (19)	8530 (16)	53.2 (49.1, 57.6)
C_{trough} (ng/mL)	608 (30)	3070 (28)	19.7 (17.2, 22.7)

35 HIGHER HIGH DOSE FLUCONAZOLE FOR THE TREATMENT OF CRYPTOCOCCAL MENINGITIS

Umesh G. Lalloo[1], Richard Larsen[2], Judith Aberg[3], Evelyn Hogg[4], Lauren Komarow[5], David B. Clifford[6], Sandy Pillay[1], Deborah Langat[7], Agrey Bukuru[8], Vidya Mave[9], Khuanchai Supparatpinyo[10], **Wadzanai Samaneka**[11]
[1]Durban University of Technology, Durban, South Africa, [2]USDA, Davis, CA, USA, [3]Icahn School of Medicine at Mt Sinai, New York City, NY, USA, [4]Social &Scientific Systems, Silver Spring, MD, USA, [5]Harvard University, Cambridge, MA, USA, [6]Washington University St Louis, St Louis, MO, USA, [7]KEMRI/Walter Reed Proj, Kericho, Kenya, [8]Joint Clinical Research Centre, Kampala, Uganda, [9]BJGMC Clinical Trials Unit, Pune, India, [10]Chiang Mai University, Chiang Mai, Thailand, [11]University of Zimbabwe, Harare, Zimbabwe

Background: The WHO recommends high dose 1200 mg fluconazole (FLU) if amphotericin B (AmB) is not available or not feasible to use in persons with AIDS associated cryptococcal meningitis (CM) in resource limited settings. We report the safety and efficacy of high dose (1200-2000mg/d) oral FLU for the initial treatment of AIDS-associated CM in an AmB-controlled 2-stage dose escalation study.

Methods: HIV-infected adults (18years and older) with acute CM were randomized 3:1(Stage 1) or 2:1 (Stage 2) to high dose oral FLU or AmB. Stage 1 was a dose-finding escalation study of FLU (1200, 1600 and 2000 mg/d for up to 10 weeks) compared with AmB (0.7 mg/kg daily for 2 wks followed by low-dose fluconazole). Stage 2 enrolled simultaneous cohorts of the safe and effective FLU (1600 and 2000 mg/d) vs. AMB for safety and efficacy. Quantitative CSF cultures were evaluated every 2 wks until negative or wk 10 (therapeutic efficacy). After wk 10, all participants took 200 mg of FLU through wk 24 (protocol completion). Antiretroviral therapy (ART) was deferred for 4 wks if ART naïve and in Stage 2, ART was also permitted if initiated before enrollment. FLU dose adjustments were for weight and concomitant rifampin. The 1200mg FLU dose showed inferior efficacy and was excluded from Stage 2. The participants from Stage 1 and Stage 2 were combined in the analysis.

Results: A total of 48, 22, 50 and 48 patients were in the safety analysis in the AmB, 1200mg FLU, 1600mg FLU and the 2000mg FLU groups respectively. There were 46, 20, 45 and 43 in the efficacy analysis. The groups were matched for demographic, clinical and laboratory characteristics. The clearance of crypto (KM prop: 90% CI) was 81%:71-90; 45%:29-65; 56%:45-69; and 60%:49-73. The mortality (KM% over 24 weeks) was 24, 41, 30 and 36% respectively. Log10 baseline CSF crypto CFUs and baseline GCS (below 15) were significant independent determinants of efficacy: $p<0.009$ and $p<0.0043$ respectively. In the safety population baseline $\log_{10}$ HIV viral load, Log_{10} baseline CFUs, and baseline GCS (less than 15) were significant independent determinants: $p<0.020$, $p<0.003$ and $p<0.022$ respectively.

Conclusion: These results suggest that the WHO recommendation of FLU 1200 mg may be too low. It appears that weight based1600mg oral FLU is the most effective dose and safer than 2000mg and may be preferable to use over 1200 mg in conditions where AmB is unavailable. Overall, higher dose FLU was found to safe and well tolerated but less effective than AMB across all doses.

36 ADJUNCTIVE SERTRALINE IN HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS

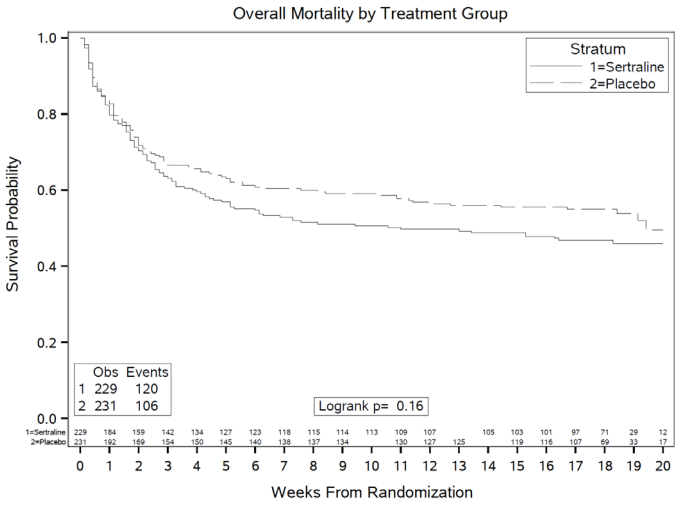
Joshua Rhein[1], Kathy Huppler Hullsiek[1], Lillian Tugume[2], Edwin Nuwagira[3], Edward Mpoza[2], Reuben Kiggundu[2], Kenneth Ssebambulidde[2], Darlisha A. Williams[2], Ananta Bangdiwala[1], Mahsa Abassi[1], Abdu Musubire[2], Conrad Muzoora[3], David Meya[2], David R. Boulware[1]
[1]University of Minnesota, Minneapolis, MN, USA, [2]Infectious Disease Institute, Kampala, Uganda, [3]Mbarara University of Science and Technology, Mbarara, Uganda

Background: Identifying new antifungals effective for cryptococcal meningitis (CM) remains a priority given the high costs, toxicity, and limited availability of current first line therapy. Sertraline has previously demonstrated in vitro and in vivo activity against Cryptococcus. We evaluated the efficacy of adjunctive sertraline for cryptococcal meningitis in a double-blind, randomized, placebo-controlled clinical trial.

Methods: We assessed 18-week survival among HIV-infected adults with cryptococcal meningitis from March 2015 to May 2017. Participants were recruited in Kampala and Mbarara, Uganda and randomly assigned to receive standard therapy (7-14 days of amphotericin + fluconazole starting at 800 mg daily) with either adjunctive sertraline or placebo. Sertraline was administered at a dose of 400 mg/day for 2 weeks, followed by 200 mg/day for an additional 10 weeks prior to tapering. Secondary outcomes included the rate of fungal clearance from cerebral spinal fluid (CSF), adverse events, incidence of relapse, quantitative neurocognitive performance and depression scores.

Results: The trial was stopped for futility after enrolling 460 of a planned 550 patients. The 18-week mortality was 52% in the sertraline group and 46% in the placebo group (hazard ratio for sertraline, 1.21; 95% CI, 0.93-1.57; p=0.16) (Figure). The rate of fungal clearance from CSF was similar between groups (-0.33 (95% CI, -0.36 to -0.30) vs -0.32 (95% CI, -0.35 to -0.30) $\log_{10}$ CFU/mL CSF/day; p=0.37), as was incidence of grade ≥ 4 adverse events (24% vs 26%; p=0.63). While there was no difference in overall neurocognitive performance between groups among survivors at day 14, there was a trend towards improved depression scores among those receiving sertraline (CES-D score of 14 (95% CI, 11-16) vs 17 (95% CI, 14-20) for those receiving placebo; p=0.06). Incidence of relapse (1% in each group) and re-hospitalizations (13% in each group) were similar. Despite the use of high dose sertraline, no cases of serotonin syndrome were observed in the trial. Mortality was similar among antiretroviral naïve and antiretroviral experienced patients.

Conclusion: Sertraline did not reduce mortality among patients with HIV-associated cryptococcal meningitis at tested doses. Investigations are currently underway to better understand the reasons for sertraline inactivity, which may be multifactorial and possibly related to inadequate drug concentrations, drug-drug interactions, or unknown immune effects.



37LB ONE MONTH OF RIFAPENTINE/ISONIAZID TO PREVENT TB IN PEOPLE WITH HIV: BRIEF-TB/A5279

Susan Swindells[1], Ritesh Ramchandani[2], Amita Gupta[3], Constance A. Benson[4], Jorge T. Leon-Cruz[2], Ayotunde Omoz-Oarhe[5], Marc Antoine Jean Juste[6], Javier R. Lama[7], Javier A. Valencia[7], Sharlaa Badal-Faesen[8], Laura E. Moran[9], Courtney V. Fletcher[1], Eric Nuermberger[10], **Richard E. Chaisson**[10]
[1]University of Nebraska Medical Center, Omaha, NE, USA, [2]Harvard University, Boston, MA, USA, [3]Johns Hopkins Hospital, Baltimore, MD, USA, [4]University of California San Diego, San Diego, CA, USA, [5]Molepolole Clinical Research Site, Molepolole, Botswana, [6]GHESKIO, Port-au-Prince, Haiti, [7]Barranco Clinical Research Site, Lima, Peru, [8]University of the Witwatersrand, Johannesburg, South Africa, [9]Social & Scientific Systems, Silver Spring, MD, USA, [10]Johns Hopkins University, Baltimore, MD, USA

Background: Tuberculosis (TB) is the leading killer of people with HIV infection. Preventive therapy is effective but current regimens are limited by toxicity and low completion rates. We hypothesized that an ultra-short course

of isoniazid (H)/ rifapentine (P) would be non-inferior to 9 months H in people with HIV infection.

Methods: This multicenter, randomized, open-label, phase 3 trial enrolled HIV-infected individuals >13 y living in high TB-burden areas or who were TB skin test (TST)/Interferon-ϒ release assay (IGRA) positive. Antiretroviral therapy (ART) with efavirenz or nevirapine was permitted. Participants (pts) were stratified by ART status and CD4 count, randomized 1:1 to 1 month of daily H 300 mg plus P 450-600 mg (1HP) or 9 months daily H 300 mg (9H), and followed until 3 y after the last enrollment. The primary objective was to compare incidence rates (IR) of active TB, TB death, or death from an unknown cause. TB diagnoses and deaths were reviewed independently. A non-inferiority margin of 1.25/100 PY was based on an assumed IR of 2.0/100 PY in the 9H arm.

Results: 3000 pts were recruited by 45 sites in 10 countries from 5/2012-11/2014 and data are current as of 12/20/2017. 1614 (54%) were women, median age was 35 y (IQR 28-43), 1983 (66%) were Black, 730 (24%) Hispanic, and median BMI was 23.5 (IQR 20.9-27.1). Median CD4 count was 470 cells/mm^3 (IQR 346-635) and 50% were on ART at entry. 634 (21%) had positive TST or IGRA. The primary endpoint occurred in 34 pts in the 1HP arm and 35 in the 9H arm, for incidence rates of 0.69/100 PY for 1HP and 0.72/100 PY for 9H (IR difference = -0.025, upper 95% CI: 0.31, Table). Rates were higher for pts not on ART at entry and those with a positive TST/IGRA, with no difference between treatments. For those with baseline CD4 counts <250 cells/mm^3, incidence was higher in the 1HP arm, but the difference was not statistically significant (p=0.12). Serious adverse events occurred in 5.6% of 1HP pts and 7.1% of 9H pts (p=0.1). The incidence of targeted safety events was 3.3/100 PY with 1HP and 5.1/100 PY with 9H (P=0.03); treatment completion was higher in the 1HP arm than 9H (97% vs. 90%, P<0.01). There was 1 case of rifampin-resistant TB in each arm and 1 case of H-resistant TB in the 9H arm.

Conclusion: Once daily 1HP was non-inferior to 9H, had fewer adverse events, and was more likely to be completed in HIV-infected adults and adolescents. This ultra-short course TB preventive therapy could be an important tool to control HIV-related TB.

Characteristic	1HP Events/PY Rate/100 PY	9H Events/PY Rate/100 PY	Incidence Rate Difference (1HP – 9H)
All participants	34/4923	35/4884	
	0.69	0.72	-0.025
			95% CI: (-0.36, 0.31)
Baseline ART			
Yes	14/2378	14/2397	
	0.59	0.58	0.005 (-0.43, 0.44)
No	20/2545	21/2487	
	0.79	0.84	-0.059 (-0.55, 0.44)
TST/IGRA Status			
Positive	11/1107	12/1133	
	0.99	1.06	-0.066 (-0.90, 0.77)
Negative/Unknown	23/3816	23/3751	
	0.60	0.61	-0.01 (-0.36, 0.34)
Baseline CD4 Count			
≤250 cells/mm^3	14/619	7/627	
	2.26	1.12	1.15 (-0.30, 2.59)
>250 cells/mm^3	20/4304	28/4256	
	0.46	0.66	-0.19 (-0.51, 0.12)
Sex			
Male	12/2300	17/2285	
	0.52	0.74	-0.22 (-0.68, 0.24)
Female	22/2622	18/2599	
	0.84	0.69	0.15 (-0.33, 0.62)

38LB URINE-BASED SCREENING FOR TUBERCULOSIS: A RANDOMIZED TRIAL IN HIV-POSITIVE INPATIENTS

Ankur Gupta-Wright[1], Elizabeth L. Corbett[1], Joep J. van Oosterhout[2], Doug K. Wilson[3], Daniel Grint[1], Melanie Alufandika-Moyo[2], Jurgens A. Peters[1], Lingstone Chiume[4], Stephen D. Lawn[1], Katherine Fielding[1]

[1]London School of Hygiene & Tropical Medicine, London, UK, [2]Dignitas International, Zomba, Malawi, [3]Edendale Hospital, Pietermaritzburg, South Africa, [4]Malawi–Liverpool–Wellcome Trust Clinical Rsr Prog, Blantyre, Malawi

Background: Tuberculosis (TB) is the major cause of death in people living with HIV (PLHIV), in part due to suboptimal diagnosis. Urine is easily obtained, and urine diagnostics are rapid, complementary to sputum, have good yield, and reflect often-fatal disseminated TB. Urine screening may therefore reduce death and missed TB diagnosis in severely ill PLHIV.

Methods: The STAMP trial was a pragmatic, individually randomized controlled trial recruiting consecutive, unselected PLHIV admitted to medical wards in Edendale, South Africa, and Zomba, Malawi. HIV testing was offered if status was unknown. Randomization was stratified by site. Consenting eligible patients (≥18years, not on TB treatment) were allocated to either standard of care (SOC) screening (sputum Xpert MTB/RIF) or intervention arms (SOC plus Determine TB-LAM on neat urine and Xpert MTB/RIF on centrifuged urine) regardless of symptoms. Results were reported as TB screen positive or negative to routine clinicians who managed patients masked to study arm. Mortality (primary outcome) and TB events (secondary) were ascertained at 56 days.

Results: We screened 4788 PLHIV and randomised 2600 (1300/arm) from Oct-2015 to Sep-2017. 26 were excluded, leaving 2574 PLHIV for final analysis, of whom 996 (38.7%) had TB suspected and 1861 (72.3%) were on antiretroviral therapy (ART) at admission. Median CD4 was 227 cells/μL. Baseline characteristics did not differ by arm. 27 (1.0%) were lost to follow-up. By 56 days, 272 (21.1%) and 235 (18.3%) patients had died in SOC and intervention arms respectively (risk difference [RD] -2.8%, 95% confidence interval [CI] -5.8 to 0.3, p=0.07; odds ratio 0.83, 95% CI 0.7 to 1.0). Intervention arm mortality was significantly lower than SOC in pre-specified subgroups: CD4<100 cells/μL (RD -7.1%, 95% CI -13.7 to -0.4); haemoglobin <8g/dl (RD -9.0%, 95% CI -16.6 to -1.3); and TB clinically suspected at admission (RD -5.7%, 95% CI -11.0 to -0.5) (Table). TB diagnosis was significantly more likely in intervention (21.9%) than SOC (14.9%) arm (RD 7.3%, 95% CI 4.4 to 10.2%, p<0.001). Differences in TB diagnosis between arms were not confined to any particular subgroups.

Conclusion: Systematic urine screening of hospitalised PLHIV increased overall TB diagnosis and treatment, and reduced mortality in key subgroups despite high ART coverage. Early mortality differences were minimal outside of these subgroups, although reducing missed TB diagnoses is likely to be of wider value.

Trial registration: ISRCTN71603869

		Mortality Risk SOC n/N (%)	Mortality Risk Intervention n/N (%)	Risk difference [Intervention – SOC], %, adjusted for site (95% CI)	p-value	Interaction p-value
Overall		272/1287 (21.1)	235/1287 (18.3)	-2.78 (-5.82, 0.26)	0.074	
Subgroup analyses:						
Site	Malawi	161/660 (24.4)	137/656 (20.9)	-3.51 (-8.03, 1.01)	0.13	0.67
	South Africa	111/627 (17.7)	98/621 (15.5)	-2.17 (-6.30, 1.94)	0.30	
Baseline CD4 cell count, cells/mm^3	< 100	133/373 (35.7)	107/371 (28.8)	-7.09 (-13.71, -0.43)	0.036	0.063
	≥ 100	131/897 (14.6)	127/904 (14.0)	-0.08 (-3.28, 3.11)	0.96	
Baseline haemoglobin, g/dl	< 8	116/298 (38.9)	86/289 (29.8)	-8.97 (-16.58, -1.30)	0.021	0.056
	≥ 8	156/987 (15.8)	149/995 (15.0)	-0.89 (-4.05, 2.26)	0.58	
TB clinically suspected at admission	Yes	136/495 (27.5)	106/501 (21.2)	-5.70 (-10.95, -0.47)	0.033	0.11
	No	136/790 (17.2)	128/779 (16.4)	-0.76 (-4.41, 2.89)	0.68	

39LB A RANDOMIZED CONTROLLED TRIAL OF HIGH-DOSE RIFAMPIN FOR PULMONARY TUBERCULOSIS

Gustavo E. Velásquez[1], Meredith B. Brooks[2], Julia M. Coit[2], Dante Vargas Vásquez[3], Epifanio Sánchez Garavito[4], Roger I. Calderón[5], Judith Jiménez[5], Karen Tintaya[5], Charles A. Peloquin[6], Elna Osso[2], Dylan B. Tierney[1], Kwonjune J. Seung[1], Leonid Lecca[5], Geraint R. Davies[7], Carole D. Mitnick[2]
[1]Brigham and Women's Hospital, Boston, MA, USA, [2]Harvard University, Boston, MA, USA, [3]Hospital Nacional Hipólito Unanue, Lima, Peru, [4]Hospital Nacional Sergio Bernales, Lima, Peru, [5]Partners in Health, Lima, Peru, [6]University of Florida, Gainesville, FL, USA, [7]University of Liverpool, Liverpool, UK

Background: The standard of care for patients with pulmonary tuberculosis is a 6-month, 4-drug regimen that includes rifampin throughout. This blinded, randomized, controlled Phase II clinical trial (ClinicalTrials.gov NCT01408914) systematically examined the concept that increased rifampin doses could shorten standard therapy for tuberculosis and improve treatment outcomes without increased toxicity.

Methods: We randomized 180 adults with new, smear-positive, drug-susceptible pulmonary tuberculosis in equal numbers to receive 10, 15, or 20 mg/kg/day of rifampin during the 8-week intensive phase. The primary endpoints were: [1] change in elimination rate of *M. tuberculosis* $\log_{10}$ colony forming units ($\log_{10}$CFU) on 7H11 Middlebrook medium during the first 8 weeks of treatment (efficacy); and [2] frequency of grade 2 or higher rifampin-related adverse events occurring up to 4 weeks after intensive phase completion (safety). Safety was evaluated in the intention-to-treat (ITT, participants who received at least one dose of study medication) population. Efficacy was evaluated in the modified intention-to-treat (mITT, participants whose CFU data permitted sputum sterilization modeling) and per-protocol (PP, participants whose intensive phase rifampin dose was not altered by a protocol-defined study halt) populations.

Results: The ITT, mITT, and PP analyses included 180 (100%), 174 (96.7%), and 132 (73.3%) participants, respectively. Each 5 mg/kg/day increase in rifampin dose resulted in differences of -0.011 (95% confidence interval [CI], -0.025 – +0.002; P=0.230) and -0.022 (95% CI, -0.046 – -0.002; P=0.022) $\log_{10}$CFU/mL/day in the mITT and PP analyses, respectively. Faster count declines with rifampin AUC_{0-6} (P=0.011) were borderline significant with $AUC_{0-6}/MIC_{99.9}$ (P=0.053). The frequency of grade 2 or higher rifampin-related adverse events was similar across the three treatment arms: 26 (43.3%), 31 (51.7%), and 23 (38.3%) participants had at least one event (P=0.7092). The frequency of rifampin-related serious adverse events was also similar across arms: 1 (1.7%), 1 (1.7%), and 2 (3.3%) participants had at least one event (P=0.2679).

Conclusion: This is the first controlled study to show both dose- and exposure-response of rifampin on sputum culture sterilization. Rifampin doses of up to 20 mg/kg/day were safe compared to the standard dose of 10 mg/kg/day, with similar frequencies of rifampin-related adverse events.

Table 1. Decrease in viable CFU counts of *M. tuberculosis* by treatment arm or pharmacokinetic exposure to rifampin in an unadjusted NONMEM model.

Variable	*N*	$\Delta\log_{10}$ CFU/mL/day	95% CI*	*P* value
5 mg/kg increase in rifampin dose (mITT)	174	-0.011	-0.025 to 0.002	0.230
5 mg/kg increase in rifampin dose (PP)	132	-0.022	-0.046 to -0.002	0.022
1 log increase in rifampin AUC_{0-6} (PP)	126	-0.017	-0.029 to -0.007	0.011
1 log increase in rifampin $AUC_{0-6}/MIC_{99.9}$ (PP)	126	-0.010	-0.021 to 0.000	0.053

Definition of abbreviations: AUC, area under the plasma concentration-time curve; CFU, colony forming units; CI, confidence interval; mITT, modified intention-to-treat; MIC, minimum inhibitory concentration; PP; per-protocol.
* 95% CI were obtained using the sandwich estimator.

40 RAPIDLY GROWING HIV TRANSMISSION CLUSTERS IN THE UNITED STATES, 2013–2016

Anne Marie France[1], Nivedha Panneer[1], Cheryl B. Ocfemia[1], Neeraja Saduvala[2], Ellsworth Campbell[1], William M. Switzer[1], Joel O. Wertheim[3], Alexandra M. Oster[1]
[1]CDC, Atlanta, GA, USA, [2]ICF International, Atlanta, GA, USA, [3]University of California San Diego, San Diego, CA, USA

Background: In early 2016, CDC began routinely analyzing molecular sequence data reported to the National HIV Surveillance System (NHSS) to identify transmission clusters suggestive of recent and rapid growth in the United States. An assessment of the initial 13 clusters identified demonstrated transmission rates greater than the 4/100 person-years (py) estimated for the entire United States. Here, we assessed transmission rates, characteristics, and geographic distribution of all rapidly growing clusters identified during the first 15 months of implementation.

Methods: At quarterly intervals during December 31, 2015– December 31, 2016, we analyzed partial HIV-1 pol sequences reported to the NHSS for persons with HIV diagnosed during the 3 years prior. We calculated genetic distance for each pair of sequences and inferred clusters using a pairwise threshold of 0.005 substitutions/site. Rapidly growing clusters were defined as those with ≥ 5 diagnoses during the most recent 12-month period. We used node ages inferred by molecular clock phylogenetic analysis to estimate HIV transmission rates for these clusters and compared demographic characteristics and transmission category of persons in these clusters to other persons with HIV diagnosed during January 1, 2013 – December 31, 2016 who had sequences available. The Rao-Scott correction to the Pearson Chi-Square test was used to account for correlation between cases in the same cluster.

Results: Among 51,750 persons with sequences analyzed, 60 rapidly growing transmission clusters were identified. Rapidly growing clusters were 5–42 persons in size, with transmission rates ranging from 21–132 transmission events/100 py (median: 44 per 100 py). Compared with the 50,847 persons not in rapidly growing clusters, the 903 persons in rapidly growing clusters were disproportionately young men who have sex with men (MSM) (61% vs 32% p<.0001), and particularly young Hispanic/Latino MSM (26% vs 10%, p<.0001). Clusters were identified in all regions of the country and involved 20 states.

Conclusion: Routine surveillance for rapidly growing clusters consistently identifies clusters across the United States with transmission rates far exceeding the estimated national rate. These findings suggest rapid transmission in networks involving young MSM, especially young Hispanic MSM. Prioritizing these clusters for public health intervention may have increased potential to reduce future infections.

41 CLUSTER ANALYSIS REVEALS IMPORTANT SHIFT OF DRIVERS OF THE HIV EPIDEMIC IN SWISS MSM

Nadine Bachmann[1], Claus Kadelka[2], Teja Turk[1], Katharina Kusejko[1], Jürg Böni[2], Vincent Aubert[3], Sabine Yerly[4], Thomas Klimkait[5], Huldrych F. Günthard[1], Roger Kouyos[1]
[1]University Hospital Zurich, Zurich, Switzerland, [2]University of Zurich, Zurich, Switzerland, [3]Lausanne University Hospital, Lausanne, Switzerland, [4]University Hospitals of Geneva, Geneva, Switzerland, [5]University of Basel, Basel, Switzerland

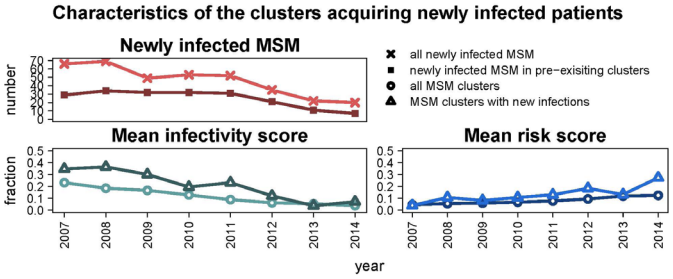
Background: Transmission clusters in phylogenetic trees constructed from densely sampled HIV-1 sequencing data reflect recent or ongoing transmission and can be used to identify local outbreaks. In this study, we aimed to illustrate methods to identify those phylogenetic clusters relevant for targeted prevention in a real-world clinical setting. We hypothesized that cluster growth in high-risk HIV-1 subpopulations can be predicted using a combination of phylogenetic methods, clinical and behavioral data.

Methods: We used HIV-1 pol sequence data from the Swiss HIV Cohort Study (SHCS) and Los Alamos background sequences to construct eight phylogenetic trees including all patients enrolled in the SHCS by the end of the years 2007 to 2014. The SHCS is highly representative of the HIV epidemic in Switzerland and contains sequences for approximately 60% of all ~19'000 patients ever enrolled. We identified HIV-1 transmission clusters of Swiss MSM in eight consecutive years, assigned annual per-cluster infectivity scores as the fraction of cluster members who had a viral load measurement above 1'000 copies/ml and annual per-cluster risk scores as the fraction who reported condom-less sex with occasional partners, and then studied the cluster growth in the subsequent years.

Results: Our analysis revealed that, over the course of the study, the infectivity score became less predictive of new infections within MSM clusters, while the risk score gained predictive power. We quantified the fraction of new infections within pre-existing transmission clusters and compared cluster characteristics of growing and non-growing clusters (Figure). Between 2008 and 2014, 35-65% of the newly infected MSM appeared within pre-existing MSM transmission clusters (p for linear trend=0.6). Uni- and multivariate Poisson regressions with per capita growth as outcome and infectivity and risk scores as dependent variables exhibited that infectivity significantly predicted the per capita growth of a cluster from 2007 to 2012, while the risk behavior was only a significant predictor in 2011, 2012 and 2014.

Conclusion: Our results demonstrate the effectiveness of treatment as prevention but also highlight that in recent years there was an epidemiologically important shift from the diagnosed to the undiagnosed population as the driver

of the HIV epidemic in Swiss MSM. To achieve a further decrease in infection rates, phylogenetic clusters could be used to identify social networks, in which one should intensify HIV-1 testing.



A. Incidence of newly infected MSM in pre−existing MSM transmission clusters compared to the overall incidence. B and C. Comparison of cluster characteristics in growing and non−growing clusters.

42 PHYLOGENETIC PATTERNS OF HIV TRANSMISSION AMONG TRANSGENDER WOMEN IN LOS ANGELES

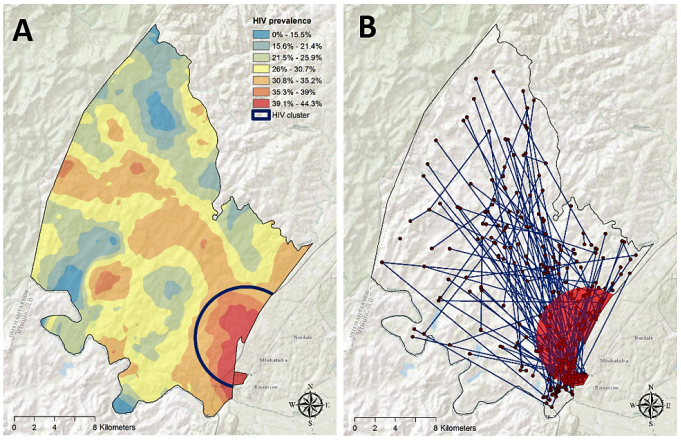
Manon Ragonnet-Cronin[1], Yunyin W. Hu[2], Sheldon Morris[1], Zhijuan Sheng[2], Kathleen Poortinga[2], Joel O. Wertheim[1]
[1]University of California San Diego, San Diego, CA, USA, [2]Los Angeles County Department of Health Services, Los Angeles, CA, USA

Background: Transgender women (TGW) are among the groups at highest risk for HIV infection, with a prevalence of 22% in the US. Despite this high risk, TGW have documented a high rate of undiagnosed HIV infection. We propose that this disparity can be addressed by characterizing TGW in a molecular transmission network to inform a targeted public health response.
Methods: Since 2005, Los Angeles County (LAC) has collected HIV pol sequences from drug resistance testing along with demographics and transmission risk factor data (including transgender status). We reconstructed a molecular transmission network using HIV-TRACE (pairwise genetic distance threshold of 0.015 substitutions/site) from the earliest pol sequences of 22,398 unique individuals in LAC, including 412 (2%) self-identified TGW. We examined the epidemiological predictors of clustering (a proxy for transmission risk) in the network using multivariate logistic regression (diagnosis age, race/ethnicity, transmission risk factor, gender, and country of birth were included as covariates) and calculated assortativity-the tendency for nodes to link to other nodes with the same attributes-for each transmission risk group.
Results: We found 1,722 molecular transmissions clusters, and 36% of individuals (8,133/22,398) clustered in the network. TGW who indicated a sexual risk factor were the most likely to cluster in the network: 147/345 (42.6%) linked to at least one other person (AOR 2.20, $p<0.001$, reference group: cis-men reporting IDU). MSM also had high clustering odds (AOR 2.05, $p<0.001$); TGW who reported IDU did not have significantly elevated odds of clustering. Both MSM and TGF were highly assortative in the network (0.17 and 0.08, respectively; $p<0.001$), indicating that MSM and TGW tended to cluster with members of their own risk groups. TGW were distributed across 126 clusters, and the presence of one TGW in a cluster increased the odds of there being another TGW in the same cluster 9-fold.
Conclusion: TGW in LAC were more likely to cluster than other risk groups, suggesting high transmission rates-despite low representation of TGW in the database. TGW tended to be part of the same clusters, indicating shared risk activities (i.e. linked directly or through shared partners). This assortativity demonstrates the potential to use molecular epidemiology to both identify transmission clusters likely to include undiagnosed or undisclosed HIV-infected TGW and improve the targeting of public health prevention and treatment activities to TGW.

43 ASSESSING THE ROLE OF GEOGRAPHICAL HIV HOT-SPOTS IN THE SPREAD OF THE EPIDEMIC

Diego F. Cuadros[1], Tiago Graf[2], Tulio de Oliveira[2], Till Bärnighausen[3], Frank Tanser[2]
[1]University of Cincinnati, Cincinnati, OH, USA, [2]University of KwaZulu-Natal, Durban, South Africa, [3]Harvard University, Cambridge, MA, USA

Background: In the last few years, a radical shift in thinking about geographical targeted interventions has prompted several international stakeholders (UNAIDS, PEPFAR, GFATM) to include geographical prioritization as a key component of their overall HIV intervention strategy. However, there are some critical unexplored issues that need to be addressed to quantify the real impact of geographically targeted interventions on the epidemic. The spatial connectivity of the transmission network of an entire community has never been studied before, and the contribution of geographical clusters of HIV infections, or 'hot-spots' on the spread of the infection in the entire population is virtually unknown. To address these issues, a spatially explicit transmission network and the transmission intensity from an HIV hot-spot were analyzed.
Methods: We examined a sample of 18,294 individuals located in a hyper-endemic rural community in South Africa, from which 5,624 (4,279 females and 1,345 males) tested positive for HIV. We identified a geographical cluster with high numbers of HIV infections (HIV 'hot-spot') using spatial statistical analysis. Additionally, we genetically sequenced and geo-located 1,222 HIV-positive individuals, identified phylogenetic transmission clusters, and estimated the number of transmission links (individuals grouped in these transmission clusters) that arose from the HIV hot-spot.
Results: From the 351 transmission links identified, 254 links (72.4%) included at least one individual located within the HIV hot-spot (Figure 1). The average distance between individuals genetically linked was 6.4 km. Results from microsimulation models indicated that the observed HIV transmission link configuration does not follow a random pattern, and the probability of transmission link formation is negatively affected by the distance between individuals and the HIV hot-spot.
Conclusion: To our knowledge, this is the first time a geographical transmission network of an entire community was studied. We observed intense transmission dynamics between the HIV hot-spot and the rest of the community located outside this high HIV burden area. These results suggest that geographical hot-spots could have a similar role as behavioral core groups in transmission networks of concentrated epidemics. Targeting these geographical core groups, would not only impact HIV incidence within the hot-spot, but could also disrupt the transmission network of the entire community.



44 USING SUCCESSIVE SURVEYS TO CALCULATE INCIDENCE AMONG AT-RISK POPULATIONS IN THE US

Janet C. Burnett, Qian An, Dita Broz, Cyprian Wejnert
CDC, Atlanta, GA, USA

Background: Although high prevalence of HIV has been documented, very few incidence estimates exist among persons at high risk for HIV infection in the United States. Given the limitations in estimating HIV incidence, various methods should be triangulated to provide a well-supported estimate in a population of interest. National HIV Behavioral Surveillance (NHBS) conducts cross-sectional surveys every 3 years among men who have sex with men (MSM), persons who inject drugs (PWID) and sexually active heterosexuals of low socioeconomic status at increased risk for HIV infection (HET) for 20 cities with high prevalence of HIV. We propose using successive cross-sectional surveys to estimate a pooled HIV incidence for each population through a nested cohort comprised of participants with at least one repeat observation across three surveillance cycles (MSM: 2008-2014; PWID: 2009-2015; HET: 2010-2016).
Methods: For each cycle, venue-based sampling (MSM) and respondent-driven sampling (PWID and HET) were used to recruit participants ≥18 years for interview and HIV testing. Repeat participants were identified using a combination of date of birth, race/ethnicity, city and gender, if applicable.

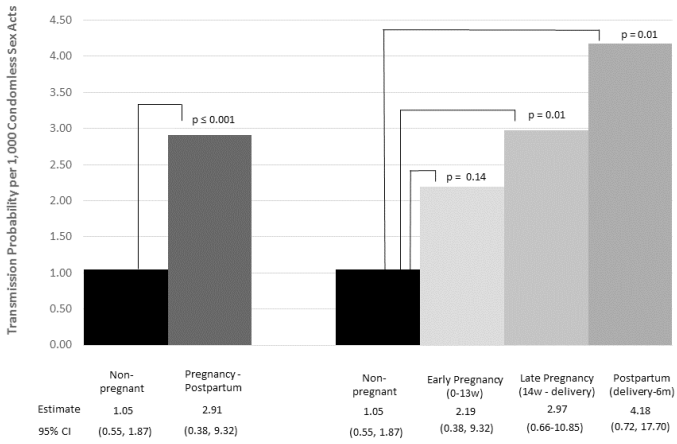
We assumed HIV-negative participants were at-risk during the entire period between cycles. Participants who tested positive for HIV infection at their first NHBS interview were excluded. We calculated person-years at risk from the individual time between cycles and used the total number of seroconversions to estimate incidence and a binomial distribution to approximate variance.
Results: Successive surveys recaptured nested cohorts of 1,110 MSM, contributing 5080 person-years, 2,548 PWID, contributing 12,283 person-years and 855 heterosexuals at high risk, contributing 3,941 person-years. We observed 127 seroconversions or an incidence rate of 2.5 per 100 person-years (95% confidence interval [CI]: 2.1 to 3.0 per 100 person-years) among MSM; 73 seroconversions or an incidence rate of 0.6 per 100 person-years (95% CI: 0.5 to 0.7 per 100 person-years) among PWID; 17 seroconversions or an incidence rate of 0.4 per 100 person-years (95% CI: 0.2-0.6 per 100 person-years) among HET.
Conclusion: These estimates are consistent with previously published incidence estimates among these populations. Measuring incidence can be challenging. Using repeat cross-sectional surveys to simulate a cohort, may serve as another strategy in estimating HIV incidence.

45 FEMALE HIV ACQUISITION PER SEX ACT IS ELEVATED IN LATE PREGNANCY AND POSTPARTUM

Kerry A. Thomson[1], James P. Hughes[1], Jared Baeten[1], Grace John-Stewart[1], Connie L. Celum[1], Craig R. Cohen[2], Nelly R. Mugo[1], James Kiarie[1], **Renee Heffron**[1]
[1]University of Washington, Seattle, WA, USA, [2]University of California San Francisco, San Francisco, CA, USA

Background: In many settings with high HIV prevalence, fertility rates are also high and women spend a significant proportion of their reproductive years pregnant, postpartum, or breastfeeding. Some, but not all, studies have demonstrated significantly higher HIV incidence during pregnancy. Per sex act analyses contribute an understanding of the absolute and relative risks of HIV transmission, and can provide insight into whether increased risk during pregnancy and postpartum is attributable to biological or sexual behavior changes. These data are critical to inform the delivery of HIV prevention interventions for women.
Methods: 2,751 African HIV serodiscordant couples with HIV uninfected female partners were followed prospectively for ≤48 months in two HIV prevention studies. Sexual frequency and condom use was reported monthly. HIV and pregnancy testing occurred monthly or quarterly depending on the study. Study time was categorized by reproductive stage as early pregnancy, late pregnancy, up to 6 months postpartum, or non-pregnant. HIV events that could not be linked between study partners by genetic sequencing were excluded. We used a complementary log-log model to compare the probability of male-to-female HIV transmission per sex act by reproductive stage. The reference case for HIV transmission probability is a condomless sex act between a 25 year old woman not using PrEP and a male partner with HIV RNA of 10,000 copies/ml.
Results: Pregnancy incidence was 12.50 per 100 woman-years (95% CI: 11.52-13.55) and 82 HIV transmission events occurred. The HIV transmission probability was 1.05 per 1,000 sex acts when women were not pregnant, 2.19 in early pregnancy, 2.97 in late pregnancy, and 4.18 in postpartum women (Figure). After adjustment for condom use, age, use of PrEP, and HIV viral load, the probability of HIV transmission per sex act was significantly higher in late pregnancy (aRR 2.82, p=0.01) and postpartum (aRR 3.97, p=0.01) compared to non-pregnant time.
Conclusion: The risk of HIV transmission per sex act steadily increased through pregnancy and was highest during postpartum, even after accounting for sexual behavior, PrEP, and HIV viral load, suggesting that biological changes during these periods increase HIV risk. While further research is needed to better understand biological susceptibility, scale-up of HIV prevention and testing in antenatal and postpartum care in high HIV prevalence settings is warranted to prevent sexual transmission and identify acute maternal HIV infections.

Figure: Male to Female HIV Transmission Probabilities by Reproductive Stage



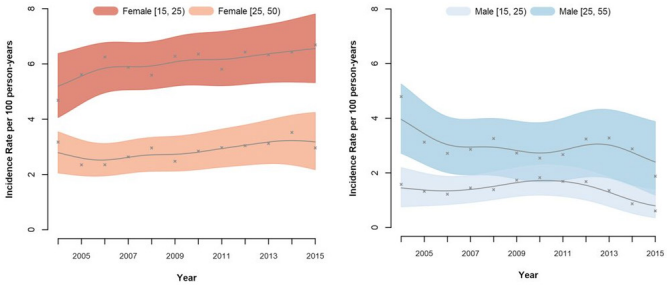
Adjusted absolute male-to-female HIV transmission-probabilities represent condomless sex with an HIV-1 infected partner with viral load of 10,000 copies/ml for a 25 year old female not taking pre-exposure prophylaxis (PrEP).

46 SHARP DECLINE IN MALE HIV INCIDENCE IN A RURAL SOUTH AFRICAN POPULATION (2004–2015)

Alain Vandormael[1], Adam N. Akullian[2], Adrian Dobra[2], Tulio de Oliveira[3], Frank Tanser[1]
[1]Africa Health Research Institute, Mtubatuba, South Africa, [2]University of Washington, Seattle, WA, USA, [3]University of KwaZulu-Natal, Durban, South Africa

Background: The extraordinary scale-up of antiretroviral therapy (ART) is expected to reduce the rate of new HIV infections at the population level. In this study, we calculated the incidence of HIV for males and females using data from a complete South African population.
Methods: The Africa Health Research Institute (AHRI) maintains an annual HIV surveillance system in the Umkhanyakude district of the KwaZulu-Natal province. Between 2004 and 2015, we followed 6,287 males (aged 15–54 years) and 8,661 females (aged 15–49 years) from their earliest HIV-negative test date until their latest HIV-negative or earliest HIV-positive test date. In addition, we obtained viral load measurements from all HIV-positive participants in 2011, 2012, and 2014 and included ART initiation data from the 17 health-care clinics in the AHRI surveillance area.
Results: The HIV incidence rate declined among males aged 15–25 years between 2012 and 2015, from 1.70 (95% CI: 1.13–2.26) to 0.60 (95% CI: 0.00–1.29) events/100 person-years, as well as for males aged 25–54 years, from 3.28 (95% CI: 1.97–4.55) to 1.87 (95% CI: 0.60–3.56) events/100 person-years. For females aged 15–25 years, however, the HIV incidence rate increased from 6.32 (95% CI: 5.34–7.32) to 6.67 (95% CI: 5.25–8.16) events/100 person-years between 2013 and 2015. Throughout the study period, the HIV incidence rate was flat for females aged 25–49 years, ranging from 4.14 (95% CI: 3.35–5.01) to 5.00 (95% CI: 4.37–5.69) events/100 person-years. ART coverage was significantly higher in woman, increasing from 28.3% to 43.6% between 2010 and 2013, when compared with men, which increased from 26.7% to 32.3%. Among woman aged 15–25 years, the virologic suppression level increased from 20.8% (95% CI: 16.5–25.2%) in 2011 to 40% (95% CI: 34.4-45.7%) in 2014. During this period, the virologic suppression level increased only slightly for men of the same age group, from 15.2% (95% CI: 5.8–24.7%) to 18.5% (95% CI: 7.8–29.2%).
Conclusion: The HIV incidence rate declined for all men aged 15–54 years between 2012 and 2015 but increased among young woman aged 15–25 years. We hypothesize that the more conscientious treatment-and-care behaviors of woman-i.e., higher ART uptake and higher rates of virologic suppression-has begun to protect men from acquiring HIV.

Figure 1: HIV incidence by age and sex, 2004–2015.



47LB ONGOING HIV MICROEPIDEMICS IN RURAL SOUTH AFRICA: THE NEED FOR FLEXIBLE INTERVENTIONS

Cordelia Coltart[1], Maryam Shahmanesh[1], Stephane Hue[2], Janet Seeley[2], Till Bärnighausen[3], Benn Sartorius[4], Tulio de Oliveira[4], Thembelihle Zuma[5], Natsayi Chimbindi[5], Anne Johnson[1], Deenan Pillay[5], Frank Tanser[5]
[1]University College London, London, UK, [2]London School of Hygiene & Tropical Medicine, London, UK, [3]Heidelberg University, Heidelberg, Germany, [4]University of KwaZulu-Natal, Durban, South Africa, [5]Africa Health Research Institute, Mtubatuba, South Africa

Background: Using one of Africa's largest HIV seronegative cohorts in KwaZulu-Natal, South Africa, we recently identified remarkable space-time variations in HIV incidence (2004-14) with the rapid emergence of a rural cluster (incidence >10% per year), near a recent coal mine development. We have undertaken a phylogenetic, epidemiological and social science investigation to understand the drivers, and guide optimal intervention, for this microepidemic.
Methods: HIV incidence was measured through population-based annual surveillance. A phylogeny of 2179 HIV-1 subtype C partial pol sequences -1376 local sequences (2010-14, 15% of HIV positive population) and 803 publically available South African control sequences (2000-14) -was reconstructed by maximum likelihood inference. A dated phylogeny was inferred using Beast 2. We geo-located individuals to their residences and conducted a rapid ethnographic assessment of the HIV risk and prevention landscape in adolescents and young adults during 2017.
Results: Phylogenetic reconstruction revealed a distinct monophyletic cluster (75 local sequences). The dated phylogeny suggests this emerged from a common source, with two bursts of infection (2012, 2014) and was expanding at the time of last sampling (2014). There were more males (57 vs. 43%, $p<0.01$) and higher employment (proportion in full-time employment: 45 vs. 18%, $p<0.01$) in this cluster compared to the population. Geospatial analyses revealed over 40% resided within a rural area adjacent to a mine. Another 40% of cases were located in the peri-urban area, adjacent to the main highway, previously identified as a high incidence area. The ethnographic survey found that local economic development brought money to this poor rural area, but at the cost of moving homes and bringing young men and truck drivers to the area. Whilst this did not appear to have resulted in visible sex work around the mine area, the residents described a rise in opportunities for transactional sex and access to alcohol and "places of risk" in a nearby urban area.
Conclusion: Our findings highlight the continued emergence of concentrated microepidemics within an existing hyperendemic region, with the potential to fuel ongoing transmission. Rapid socioeconomic changes, such as those induced by mines and other industrial developments, that bring people and money to poor areas may have unintended health consequences. We propose that flexible HIV prevention and sexual health services are required to rapidly respond to such events.

48 MECHANISMS OF EARLY CD8+ T CELL CONTROL

Jonah Sacha, *Oregon Health and Sciences University, Portland, OR, USA*

HIV has proved a daunting target for vaccine development, foiling efforts to generate cellular and humoral responses capable of targeting viral vulnerabilities. While decades of research have demonstrated the critical role of CD8+ T cells in containing viral infections, the ability to elicit HIV-protective T cell responses with conventional approaches has remained frustratingly elusive. Nearly all T cell-based vaccine regimens tested to date have used non-persistent vectors, which engender predominantly central memory T cell (T_{CM}) responses. In the case of HIV infection, vaccine-induced T_{CM} CD8+ T cell responses are at a kinetic disadvantage to the rapid pace of viral replication, thus giving rise to a scenario of an anamnestic immune response that arrives at the site of infection "too late" with "too little" magnitude to prevent irreversible establishment of the persistent viral reservoir. In contrast, accumulating evidence supports a protective role for effector memory T cell (T_{EM}) responses, which are fully differentiated memory T cells located directly at portals of pathogen entry, able to respond to pathogens orders of magnitude more quickly than T_{CM} responses. Here, we present evidence for the early vulnerability of HIV to cellular immunity and discuss the rationale for inclusion of CD8+ T_{EM} responses in prophylactic HIV vaccine design.

49 EARLY BROADLY NEUTRALIZING ANTIBODY TREATMENT LEADING TO T-CELL CONTROL

Malcolm Martin, *NIAID, Bethesda, MD, USA*

Background: Highly potent and broadly neutralizing anti-HIV 1 antibodies (bNAbs) have been used to prevent and treat lentivirus infections in humanized mice, macaques and humans. To determine whether the administration of a combination of bNAbs during the acute SHIV infection of rhesus macaques might lead to long-term control of virus replication, animals challenged with SHIVAD8-EO by mucosal or intravenous routes, received a single 2-week course of 2 potent passively transferred bNAbs (3BNC117 and 10-1074). Viremia remained undetectable for 56-177 days, depending on bNAb half-life in vivo. Moreover, in the 13 treated monkeys, plasma virus loads subsequently declined to undetectable levels in 6 controller macaques. 4 additional animals maintained normal CD4+ T cell counts and low levels (300 to 600 Viral RA copies/ml plasma) of persistent viremia for over 2 years. The frequency of cells carrying replication-competent virus was undetectable or less than 1 per 106 circulating CD4+ T cells in the 6 elite controller macaques. Infusion of a T cell depleting anti-CD8 mAb to the elite controller animals led to a specific decline in levels of CD8+ T cells and rapid reappearance of plasma viremia. In contrast, macaques treated for 2 or for 15 weeks with combination anti-retroviral therapy (cART), beginning on day 3 after infection, experienced rebound plasma viremia shortly after treatment was interrupted. We conclude that passive immunotherapy during the acute SHIV infection differs from cART in that it facilitates the emergence of potent CD8+ T cell immunity able to durably suppress virus replication.

50 ANTI-ALPHA-4/BETA-7 ANTIBODY-MEDIATED CONTROL: UNDERSTANDING THE MECHANISM

James Arthos, *NIH, Bethesda, MD, USA*

A major focus of HIV prevention and vaccine research involves the interaction of the HIV-1 envelope protein gp120 with cell-surface receptors on CD4+ T cells. Particular attention has been devoted toward a more in depth understanding of the early events in transmission, focusing on the critical window of time when HIV first establishes infection in the host. α4β7 expressing memory CD4+ T cells are preferred targets in the earliest phases of HIV-1 infection. In mucosal tissues α4β7hi memory CD4+ T cells are metabolically activated and express high levels of CCR5, which render them highly susceptible to infection. The frequency of α4β7hi memory CD4+ T cells is directly correlated with risk of acquisition in both humans and macaques. Examination of mucosal biopsies obtained from HIV infected individuals reveals that α4β7hi memory CD4+ T cells are selectively depleted within the first weeks of infection. In a nonhuman primate model of transmission an anti α4β7 mAb protected macaques from mucosal transmission of SIV. The same mAb, when combined with ART allowed SIV infected macaques to control viremia in a durable way following treatment interruption. We determined, using an immuno-PET/CT imaging technique that anti α4β7 alone or in combination with ART alters virus distribution and preserves CD4+ T cells in later stages of infection. The precise mechanism(s) by which ART + α4β7 mAb therapy promoted virologic control remains to be defined. However, we identified a series of correlates that individually or in combination may have contributed to that control.

51 EARLY INTERVENTION THERAPIES IN HUMANS: ART, ANTIBODIES, AND VACCINES

Eugène Kroon, *Thai Red Cross AIDS Research Center, Bangkok, Thailand*

HIV cure is a desirable goal for individuals living with HIV who face stigma and life-long antiretroviral therapy (ART), while treatment costs pose a significant

challenge to national health programs and donors. Eliminating all cells capable of producing HIV seems a near unattainable goal with current therapies and a more achievable goal may be HIV remission, i.e. the ability to control HIV after ART interruption to levels below detection. Individuals treated since acute HIV infection (AHI) achieve significantly smaller HIV reservoirs, preserved immune function and little viral escape and are therefore targeted for early intervention therapy studies in humans. Interventions to date include latency reversing agents, harnessing antibodies to induce HIV remission, enhancing CTL-mediated killing of infected cells, and gene editing. The SEARCH 010/RV254 study is a cohort of over 500 individuals, predominantly Thai MSM, treated with ART since the earliest stages of HIV infection (Fiebig I-IV). In this cohort, proof of concept studies with these very interventions, with the exception of gene editing, are taking place, followed by analytic treatment interruption (ATI). Thus far, these single intervention HIV remission studies have demonstrated viral load rebound from 9 days to 10 months after ATI, while ATI appeared safe. This presentation will review the results of these single HIV remission studies as representative of findings of the field to date, including effects of early ART, additional therapeutic interventions, and ATI on endpoints, including timing and magnitude of viral load rebound, and HIV reservoir size. Immune mechanisms associated with these dynamics, such as effector CD8+ T cells contributing to lower viral loads after ATI, will also be described, as will safety parameters associated with ATI including assessment for acute retroviral syndrome, de novo resistance mutations, and virological failure. Given the risks and uncertainties associated with these early stage trials, compounded by the complex concepts of cure and remission, it is critical that community participation and social science studies continue to inform the conduct of these trials.

52 THE INFANT GUT: A GREAT DEFENSE SYSTEM?

Andrew Prendergast, *Queen Mary University of London, London, UK*

The infant gut undergoes major adaptation in response to genetic and environmental signals soon after birth and throughout infancy. Ontogeny of the intestinal epithelium, microbiota and mucosal immune system occur in tandem, are highly interdependent and are critical for healthy infant growth and development. Mothers and infants have a dynamic relationship during breastfeeding. It is becoming apparent that bi-directional signals between the mother-infant pair ensure that the infant's nutritional needs are met, while shaping development of the infant gut, microbiota and immune system. Exclusive breastfeeding improves child survival and reduces HIV breast milk transmission, but the mechanisms underlying these benefits remain poorly understood. In developing countries, a spectrum of enteropathies leads to altered gut structure and function, and this may impact infant growth, development and risk of breast milk viral transmission. This talk will provide an overview of our current understanding of healthy gut development, discuss the adaptive changes that occur in response to breastfeeding and environmental exposures, and highlight the delicate balance between protection and vulnerability to breast milk transmission of HIV and other viruses conferred by the infant gut.

53 MOTHER-TO-CHILD TRANSMISSION OF HTLV-1

Antoine Gessain, *Institut Pasteur, Paris, France*

Human T-cell Lymphotropic Virus type 1 (HTLV-1) is a human retrovirus that infects at least 5-10 million people worldwide mainly in highly endemic areas such as southern Japan, West/Central Africa, the Caribbean region, and parts of South America and Australo-Melanesia. HTLV-1 infection is mostly associated with two distinct types of diseases: a lymphoproliferation, the Adult T-cell Leukemia/Lymphoma (ATLL), and an inflammatory neurological disease, the tropical spastic paraparesis or HTLV-1 associated myelopathy (TSP/HAM). ATLL is one of the worst cancers with a median of survival of less than one year in the leukemic and lymphoma types. The virus preferentially infects CD4+ T cells, but CD8+ cells may also play an important role as reservoir in the host. Different modes of transmission have been identified for HTLV-1: 1/ sexual contact (mainly from men to women); 2/ transfusion of contaminated blood; and 3/ from mother-to-child (MTCT) during prolonged breast-feeding. In each case, such a transmission involves the transfer of HTLV-1 infected body fluid cells (semen, blood, milk, respectively). In the case of MTCT, different studies indicate that infection during childhood is a major risk factor for the development of ATLL. Based on epidemiological, virological and experimental data, it is now clear that the rate of HTLV-1 MTCT increases with: 1) the duration of breast-feeding, 2) the HTLV-1 proviral load in blood and milk of the infected mother and 3) the HTLV-1 antibody titers level in blood of the mother. However, the mechanisms of such a transmission remain largely unknown. For instance, the nature of the infected cells present in the milk, the anatomical sites of viral entry through the mucosa, the first cellular targets of infection, the role of anti-HTLV-1 antibodies present in breast milk, the role of other milk factors that may influence MTCT, as well as genetic bases of susceptibility for viral infection in children have not yet been completely addressed. As there is neither vaccination against HTLV-1 infection, nor therapeutic regimen to prevent HTLV-1 MTCT, the only way to act on such retroviral transmission should be to try refrain HTLV-1 seropositive mothers from breast-feeding. Such action, which is currently ongoing in several high endemic areas have been very successful, resulting in a huge reduction of HTLV-1 MTCT in some areas of Southern Japan and some Caribbean regions.

54 CAN WE ELIMINATE BREASTMILK TRANSMISSION OF HIV?

Ameena Goga, *South African Medical Research Council, Cape Town, South Africa*

Breastfeeding is a critical child survival strategy. Its importance for child health and survival beyond HIV has stood the test of rigorous research, even in high HIV prevalence settings. However, infants can acquire HIV infection through infected breastmilk. Following the implementation of Option B+ (lifelong triple antiretroviral therapy (ART) for pregnant and lactating women) to prevent mother to child HIV transmission, multiparous mothers are likely to conceive on ART, pregnant women are likely to initiate ART earlier in pregnancy and breastfeeding mothers should initiate ART during lactation. This earlier and increased antiretroviral use provides a platform for maternal HIV viral load suppression and for eliminating mother to child HIV transmission as a public health problem (MTCT). Eliminating MTCT is defined as less than five percent MTCT and ≤50 new paediatric HIV infections per 100 000 live births. This talk will synthesize current data and field-based experiences on the epidemiology, timing, virology and risk of breast milk HIV transmission including risks for mothers on ART, the role of post-exposure infant prophylaxis, the interplay between breastmilk intake and viral load suppression and dilemmas for resource poor settings, to answer the question: Can we eliminate breastmilk transmission of HIV? Data from Africa, where infectious diseases are the main contributors to infant and under-five morbidity and mortality, and breastfeeding is a key child survival strategy, suggest that maternal ART adherence is sub-optimal, few mothers receive regular viral load monitoring and where viral suppression is known, 16-78% of people living with HIV are virally suppressed. This questions the feasibility of eliminating breastmilk MTCT in real-life resource-limited settings. Additionally, the percent MTCT yielded by different clinical trials of mothers on ART, ranges from 1.1% at 6 months to 0.6% at 12 months, and 1.4% at 18 months. Using clinic/facility-level data, MTCT percentages of 3.5% at 6-12 weeks, 4.1% at 18 months and 3.2% at 24 months have been described. With 4.1% MTCT, the EMTCT target will only be achieved if maternal HIV prevalence is <0.12%. This massive decline in maternal HIV prevalence is unlikely; thus combination strategies of maternal ART with support for ART adherence and maternal and / or infant passive or active vaccination may be the next holy grail.

55 ART IN BREASTMILK: DEFINING THE RISK-BENEFIT RATIO

Catriona Waitt, *University of Liverpool, Liverpool, UK*

An estimated 1.5 million HIV-positive women become pregnant each year, 90% of whom live in regions where breastfeeding is WHO-recommended infant feeding option. Changes to WHO and national policies in recent years mean that an increasing number of infants are exposed to ART throughout pregnancy and breastfeeding. The clear benefit to the infant is the huge reduction in risk of HIV acquisition, from around 40% in the pre-ART era, through to less than 1% in clinical trials, even among breastfeeding populations. Less clear are the potential risks to the infant of long-term low dose ART exposure through breast milk. Potential risks include the development of HIV-drug resistance in the infant should HIV infection occur, and toxicities due to drug exposure. This talk will summarise the existing pharmacokinetic data regarding ART transfer into breast milk and to the breastfed HIV-negative infant, will summarise existing data regarding potential risk of HIV-drug resistance in the infant should transmission occur and will review available data regarding drug toxicity in the infant. Finally, current and future priorities for research and monitoring will be presented.

56 THE GLOBAL BURDEN OF TUBERCULOSIS AND MODELING CONTROL STRATEGIES

Nimalan Arinaminpathy, *Imperial College London, London, UK*

There is increasing recognition of tuberculosis (TB) as a major global health problem, with the post-2015 'End TB' strategy reflecting renewed ambition for TB elimination. However, maximizing the impact of current, curative tools against TB is not only about disease control: it is also about understanding the health systems through which these tools will be delivered. Mathematical models of TB transmission have been helpful in informing these strategies. In this talk I give an overview of TB burden and control; I discuss some ways in which mathematical modelling has informed TB elimination strategies. Finally, I will discuss some important obstacles in global TB control today: the basic gaps in our understanding of when and where TB transmission occurs; the problem of undiagnosed TB; and the emergence of multi-drug-resistance.

57 USING WHOLE GENOME SEQUENCING TO BETTER UNDERSTAND TB TRANSMISSION DYNAMICS

Neel R. Gandhi, *Emory University, Atlanta, GA, USA*

Significant advances in TB control are needed to achieve the global EndTB goals by 2035. The global incidence of tuberculosis (TB) will need to decline by 17% annually, but is currently declining by only 1.5% per year. Transmission of TB is the major driver the global epidemic, particularly in high burden countries. Transmission not only leads to new infections, but also undermines preventive therapy when individuals becoming reinfected after completing a course of preventive treatment. Despite its important role, insufficient emphasis has been placed on studying TB transmission and implementing transmission control measures. The advent of genotyping methods 30 years ago provided an important tool for investigating and confirming transmission; however. genotyping has primarily been utilized in high-income countries where TB incidence is low. Among molecular epidemiology studies that have been performed in high-TB incidence settings, many have suggested that transmission due to casual contact in the community may account for a substantial proportion of TB cases. Whole genome sequencing represents the next-generation of genotyping techniques and holds promise to further advance our understanding of TB transmission by providing significantly greater discrimination. This talk will review recent studies utilizing whole genome sequencing in low- and high-TB incidence settings and the advances that may be achieved with this powerful tool.

58 UNDIAGNOSED TUBERCULOSIS: PROMISE FOR PREVENTION

Neil A. Martinson, *Perinatal HIV Research Unit, Soweto, South Africa*

Early diagnosis and initiation of treatment in patients with pulmonary TB is a cornerstone TB control and is aimed at reducing morbidity, mortality and duration of infectiousness. WHO guidelines recommend symptom screening for TB disease at all health visits which, if symptoms are present, triggers laboratory investigation, usually of sputum. This is in contrast to HIV testing; where universal testing of adolescents and adults is recommended. Risk or symptoms do not determine who is tested for HIV. The strategy of universal testing for TB irrespective of the presence of symptoms suggestive of TB has been applied to groups at extreme risk for TB. Data from several sources suggest that testing sputum of all people with liquid culture detects several fold the number of cases of TB that symptom-based TB testing would diagnose. However, evidence of improved outcomes of this strategy is limited. Several of these high risk populations, - HIV-infected pregnant women, HIV-infected adults initiating antiretrovirals, household contacts and prisoners will be presented, together with the potential benefits and other implications of universal TB testing strategies.

59 NEW DEVELOPMENTS IN THE MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS

Serena Koenig, *Brigham and Women's Hospital, Boston, MA, USA*

Drug-resistant tuberculosis (DR-TB) is a global public health crisis. Isoniazid-resistant TB (INH-R TB), which is resistant to isoniazid but sensitive to rifampin, is the most common form of drug-resistant TB in the world, with an estimated 1.5 million cases occurring annually. In spite of the high burden of INH-R TB, there are very limited data from clinical trials to guide treatment, and current guidelines are based largely on observational studies, systematic reviews, meta-analyses, and expert opinion. Multi-drug resistant TB (MDR-TB), which is resistant to both isoniazid and rifampin, causes about 490,000 cases annually; of these, an estimated 6.2% are extensively drug-resistant (XDR-TB), with additional resistance to both fluoroquinolones and second-line injectable medications. Standard treatment for MDR-TB is lengthy (minimum of 18 months) and associated with a high rate of adverse events. However, there have recently been major advances in the treatment of MDR-TB, with the implementation of shorter regimens and new and repurposed drugs. This talk will review rapid testing for DR-TB, and the evidence base to guide treatment, including new drug regimens and data from ongoing and planned trials, with a particular focus on INH-R TB, MDR-TB, and XDR-TB.

60 THE EVOLVING HIV EPIDEMIC IN THE UNITED STATES

Carlos del Rio, *Emory University, Atlanta, GA, USA*

CDC estimates that approximately 1.2 million people in the United States are living with HIV. Southern states is the home to 38% of the US population yet is where 45% of people living with HIV reside and where 50% of new infections are occurring. Nationally it is estimated that 85% of people living with HIV know their serostatus but in 10 out of 17 Southern states, this percentage is lower. Similarly, the percent who know their status is lower for persons younger than 34 years-old. Despite evolving the new HIV epidemic in the US is very much like the old HIV epidemic with the great majority of new infections happening among gay and bisexual men, however black men who have sex with men (MSM) and Hispanic/Latino MSM account for the largest number of new HIV diagnosis. There are also important racial disparities in HIV with Black/African Americans comprising 12% of the population yet accounting for 44% of new HIV diagnoses. The number of new HIV infections declined 18% between 2008 and 2014 but this decline has been uneven across geographic regions and populations. HIV care continuum outcomes, particularly retention and viral suppression, are key in decreasing HIV transmission. Thus, it is not surprising that the impact of treatment on transmission has not been as significant in the South and among Black/African Americans where continuous retention and viral suppression has been less than optimal. The US is far from reaching the UNAIDS 909090 goals; approximately 85% of people living with HIV diagnosed, 36% are receiving ART and 30% are virally suppressed. It is thus a public health priority to develop and implement interventions to improve retention and viral suppression to decrease regional and racial disparities in HIV and to achieve the goals of the National HIV/AIDS Strategy for 2020.

61 HIV TESTING AND LINKAGE: THE GATEWAY TO TREATMENT AND PREVENTION

Hyman Scott, *San Francisco Department of Public Health, San Francisco, CA, USA*

HIV testing serves as the entry into the HIV treatment and prevention cascade. However, HIV testing uptake and implementation has been challenged in fragmented healthcare systems with structural, social, and individual factors (such as access, cost, and stigma) being significant barriers. New HIV testing technologies and implementation strategies have been used with varying success to address these challenges, especially with un- and under-tested populations, such as youth and black men who have sex with men. Reaching these populations is essential to increasing awareness of HIV status, and decreasing late diagnoses. Home HIV self-testing is a new technology approved by the US Food and Drug Administration in 2012, and can be effective at reaching never testers and infrequent testers among at-risk populations. In addition, partner services for those recently diagnosed with HIV or a sexually transmitted infection, and couple-based testing have the ability to reach individuals through their sexual partners. Increasing HIV testing in healthcare settings includes strategies to routinize HIV testing through opt-out testing, standing orders in urgent and emergency care settings, and passive reminders in primary care settings. The expansion of Electronic Health Records can facilitate identification of patients who have either never tested or have delayed testing, but implementation remains challenging. Linkage to HIV prevention or care services is essential after HIV testing, and often requires linking individuals to multilevel navigation support for linkage to be successful. New "status neutral" strategies tailored to support HIV testing and linkage to treatment and prevention for the most vulnerable populations in the US are needed to improve outcomes and reduce treatment and prevention disparities.

62 HIV CARE ENGAGEMENT: MAXIMIZING INDIVIDUAL AND POPULATION HEALTH

Michael J. Mugavero, *University of Alabama at Birmingham, Birmingham, AL, USA*

Enhancing engagement in care represents the greatest opportunity to achieve the individual and population health benefits afforded by scientific advances in HIV prevention and treatment science. In the era of HIV treatment as prevention (TasP), with robust scientific evidence substantiating PLWH with sustained undetectable viral loads cannot sexually transmit the virus (U=U), there is optimism towards 'bending the curve' via achievement of global targets for HIV testing, treatment, and viral suppression (90:90:90). However, effective implementation of innovative technologies and low tech strategies to optimize progression across the care continuum are hampered by disjointed delivery of supportive and treatment services within the fragmented U.S health care system. This presentation will review the current evidence for approaches to improve care engagement for PLWH, with particular emphasis on early retention in HIV medical care, and attention towards unique geographical considerations, with review of best evidence models and programs spanning clinical, community and public health agencies.

63 SYSTEMS OF CARE FOR VULNERABLE POPULATIONS IN THE UNITED STATES

Julia C. Dombrowski, *University of Washington, Seattle, WA, USA*

Maintaining continuous care engagement and viral suppression among persons living with HIV (PLWH) is a central goal of HIV care and prevention. However, many individuals fall out of care or sporadically engage in care. An effective population-based approach to improving retention in HIV care and viral suppression among PLWH requires a combination of strategies with varying intensity. Some patients who have disengaged from HIV care can be effectively re-engaged with low-intensity assistance or additional support services and case management outreach. However, individuals with extensive barriers to care – particularly unstable housing, substance use disorders, and untreated mental health conditions – may be unable or unwilling to engage in HIV care as it is traditionally organized. Unmet social needs compete with patients' ability to prioritize and access health care, and health systems factors such as the need for advanced scheduling, limited appointment availability, and uncoordinated services exacerbate the problem. Alternate models of care are needed to effectively care for high-need individuals within the fragmented U.S. healthcare system. This presentation will review the current evidence for approaches to identify and re-engage out-of-care PLWH, elements of an effective population-based approach to re-engaging out-of-care individuals in HIV care, and effective models of care for high-need patients with complex medical and social needs.

64 THE VAGINAL MICROBIOME AND ACQUISITION OF HIV INFECTION

Nichole Klatt, *University of Washington, Seattle, WA, USA*

More than one million women are infected with HIV annually. However, the biological mechanisms associated with transmission in women are not well understood. One factor that has consistently been associated with increased acquisition of HIV in women is imbalanced vaginal bacteria, i.e. vaginal microbiome dysbiosis. Lack of healthy *Lactobacillus* bacteria, but increased anaerobic bacteria and higher diversity of the microbiome in the female reproductive tract has been associated with clinical vaginosis, inflammation, and increased HIV infection. We recently demonstrated that dysbiotic vaginal bacteria can also alter the efficacy of topical pre-exposure prophylactic (PrEP) strategies. We found the mechanism by which dysbiotic bacteria decrease efficacy of topical antiretroviral-based PrEP is by direct metabolism of the drugs by bacteria. Here we will summarize what is currently known about vaginal microbial dysbiosis and HIV infection, and the potential mechanisms of how vaginal bacteria may influence HIV transmission in women.

65 ADDRESSING MENTAL HEALTH: A CRUCIAL COMPONENT TO ENDING THE HIV EPIDEMIC

Robert H. Remien, *New York State Psychiatric Institute and Columbia University, New York, NY, USA*

Mental health problems including substance abuse are one of the most significant areas of co-morbidity for people living with HIV/AIDS (PLWHA) worldwide and are more prevalent among PLWHA than the general population. An estimated 50% of PLWH meet criteria for one or more mental or substance use disorders, which are associated with suboptimal HIV treatment outcomes including late ART initiation and delayed viral suppression. Mortality rates for PLWHA having a Major Depressive Disorder (MDD) is twice as high as for those without a MDD. Positive mental health is associated with improved physical health outcomes across a range of chronic illnesses, but – in addition to negative psychological responses to an HIV diagnosis, disease progression, associated stigma, and loss of social support – the chronic inflammatory response to HIV infection is hypothesized to contribute to elevated rates of mental health problems among PLWHA. Further, HIV effects on the brain contribute to neuro-cognitive disorders as well as disturbed affect regulation among PLWHA. Unfortunately, the stigma embodied in discriminatory social structures, policy, and legislation, results in a disparity between physical and mental health care services, with lower availability, accessibility, and quality of services for the latter. Integration of services to screen and manage mental health and substance use disorders into HIV care settings is a promising strategy to improve mental health and HIV treatment outcomes among PLWHA, including in resource-constrained settings. A range of psychological interventions have been shown to improve mental health among PLWHA, including reducing depression and anxiety and increasing quality of life and psychological well-being. Further, treatment for mental disorders and behavioral (i.e., adherence) interventions has an additive effect, positively affecting HIV health outcomes. While significant challenges remain for meeting the high demand, especially in resource-constrained settings where HIV is most prevalent, addressing mental health co-morbidities (i.e., screening and treatment) in the context of HIV prevention and care is essential for achieving optimal outcomes along the HIV prevention and treatment continua. We may have the biological tools to "end AIDS," however we will not be able to achieve "ending the epidemic" (EtE) goals, if we do not address mental health co-morbidities among our most vulnerable populations.

66 PERSISTENT DETECTION OF HIV RNA+ CELLS WITH ART STARTED IN FIEBIG 1&2 VS FIEBIG 3-5

Eugène Kroon[1], Mark de Souza[1], Suthat Chottanapund[1], Jodi Anderson[2], Sopark Manasnayakorn[3], Siri Jorstad[2], Caitlin David[2], Adam Conner[2], Erika Helgeson[2], Cavan Reilly[2], Merlin L. Robb[4], Daniel Douek[5], Jintanat Ananworanich[4], **Timothy Schacker**[2]

[1]Thai Red Cross AIDS Research Center, Bangkok, Thailand, [2]University of Minnesota, Minneapolis, MN, USA, [3]Chulalongkorn University, Bangkok, Thailand, [4]US Military HIV Research Program, Silver Spring, MD, USA, [5]NIH, Bethesda, MD, USA

Background: The reservoir of HIV DNA+ cells is stable during treatment of chronic HIV infection; however, it is unknown if treatment during acute HIV infection (AHI) will limit reservoir size or the pathology of virus replication in lymph nodes (LN).

Methods: We obtained LNs from 2 groups enrolled into the RV254 study; 55 individuals sampled during AHI and 31 identified in acute infection but were sampled after a mean of 348 days of ART (range 269 – 849 days, Table). We analyzed LNs by in situ hybridization (ISH) to determine the frequency of viral RNA (vRNA+) and DNA (vDNA+) cells and by immunohistochemistry (IHC) to determine the extent of LN fibrosis as a marker of inflammatory damage.

Results: Prior to ART, the mean frequency of vRNA+ and vDNA+ cells was 2.3 x 10^{-5} cells/g LN (interquartile range 7.6 x 10^{-4} - 4.1 x 10^{-5}) and 5.4 x 10^{-5} cells/g LN (interquartile range 2.3 x 10^{-5} – 1.5 x 10^{-6}), respectively with no significant effect of Fiebig stage at the time of diagnosis. In the group receiving ART, the mean frequency of detection of vRNA+ and vDNA+ cells was 0.0 cells/g (interquartile range 0, 4.7 x 10^{-4}) and 3.0 x 10^{-5} cells/g (interquartile range 1.6 x 10^{-5}- 7.3 x 10^{-5}), respectively. However, 15/31 (48%) LNs did have vRNA+ detectable cells (mean 9.1 x 10^{-4} cells/g, range 2.2 x 10^{-3} – 2.4 x 10^{-5} cells/g) and people initiating ART in F1 or F2 were significantly more likely to have vRNA+ cells (adjusted O.R. 6.48, $p = 0.0354$). There was no significant difference in vDNA+ cells/g in the group sampled during AHI or the group receiving ART. Significant collagen deposition into the parafollicular T cell zone (TZ) began as early as F1 and did not decay as a result of ART, however there was no significant increase over time.

Conclusion: We found that the of reservoir of vDNA+ cells was established as early as F1 and did not decay with ART. Further, inflammatory damage occurred (as measured by TZ collagen) as early as F1 and did not appear to decrease if ART was started in acute infection, however it did not progress. Finally, the detection of persistent vRNA production in LNs in people treated very early suggests that interventions to both block viral replication and elicit immune clearance of infected cells in LNs will be important.

	AHI	Treated	Total
Fiebig 1	8 (14.5%)	7 (22.6%)	15 (17.4%
Fiebig 2	11 (20%)	8 (25.8%)	19 (22.1%
Fiebig 3	26 (47.2%)	10 (32.7%)	36 (41.7%
Fiebig 4	6 (11.0%)	3 (9.7%)	9 (10.5%
Fiebig 5	4 (0.07%)	3 (9.7%)	7 (8.1%)
Age	25 (22,29)	28 (23.5,32.5)	26 (22,31.5
Time From ART to Biopsy (days)	1 (0,4)	348 (269,849.0)	4 (4,341)
Time From Diagnosis to Biopsy (days)	5 (3,7)	351 (271.5,849)	7 (4,341)
ART treated participants with vRNA+ cells detectable F1		6 (85.7%)	
ART treated participants with vRNA+ cells detectable F2		4 (50.0%)	
ART treated participants with vRNA+ cells detectable F3		3 (30.0%)	
ART treated participants with vRNA+ cells detectable F4		1 (33.0%)	
ART treated participants with vRNA+ cells detectable F4		1 (33.0%)	
vRNA+ cells/gram LN	2.3e5 (7.7e4-4.1e5)	0 (0-4.7e4)	7.2e4 (2.4e3-2.5e5)
vDNA+ cells/gram LN	5.4e5 (2.3e5-1.5e6)	3.0e5 (1.6e5-7.3e5)	4.0e5 (1.9e5-1.1e6)
% Area TZ collagen +	23.9 (21.0,27.3)	25.1 (21.4,27.8)	24.2 (21, 27.3)

Table 1: Summary of participants in RV254. All participants were identified during acute infection (Fiebig stages 1-5); AHI indicates the biopsy was obtained during acute infection whereas treated means the biopsy was obtained a mean of 349 days after ART had begun. Medians and quartiles are provided for continuous variables and counts and percents are provided for categorical variables. In a logistic regression model that tested for an effect of being in F1 or F2 vs. other stages that adjusts for age, viral load, and CD4 levels among those who were treated, F 1 & 2 is significantly associated with having detectable vRNA+ cells with an adjusted OR ratio of 6.48 (p = 0.0354).

67 CD8+ T CELL RESPONSES IN TREATED HYPERACUTE HIV INFECTION LIMIT HIV RESERVOIR SIZE

Zaza Ndhlovu[1], Samuel W. Kazer[2], Thandeka Nkosi[3], Funsho Ogunshola[3], Amber D. Moodley[3], Krista Dong[1], Alex K. Shalek[2], Thumbi Ndungú[3], Bruce D. Walker[1]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]MIT Institute for Medical Engineering & Science, Cambridge, MA, USA, [3]University of KwaZulu-Natal, Durban, South Africa

Background: Early initiation of cART has the potential to enhance protective immunity by preserving CD4+ T cells and limiting T cell exhaustion. However, the quality of HIV-specific CD8+ T responses induced in the context of limited HIV antigen exposure and the impact on the dynamics of HIV reservoir accumulation are underexplored.

Methods: Studies were performed in persons identified and treated at the onset of HIV plasma viremia (n=34, 27 Fiebig Stage I, 7 Fiebig stage III/V), and compared to chronic treated persons (n=10). Flow cytometry and transcriptional analyses coupled with HIV DNA measurements were used to longitudinally define the relationships between HIV-specific CD8+ T cells responses, viral persistence and reservoir decay.

Results: More than 90% of individuals initiating treatment in Fiebig I mounted detectable HIV-specific CD8+ T cell responses. The breadth of the initial responses was driven by cumulative HIV plasma viral burden (viremia copy days, VCD), defined as the area under plasma viral load curve. There was a strong positive correlation between VCD and immune responses measured by three different assays namely, activation (CD8+CD38+HLA-DR+) (r=0.08, p=0.0001), frequency of tetramer+ CD8+ T cells (r=0.8, p=0.006) and breadth of HIV-specific CD8+ T cell responses measured by IFN-γ ELISPOT (r=0.5, p=0.02). Tetramer-stained HIV-specific CD8+ T responses of early treated subjects had significantly higher expression of CD127 (p=0.0009) and had a pro-survival transcriptional profile compared to responses from untreated hyperacute HIV infection. The breadth of HIV-specific CD8+ T cells measured by IFN-γ ELISPOT positively correlated with HIV DNA reservoir decay over a one-year period (r=0.8, p=0.04).

Conclusion: These results demonstrate that HIV-specific CD8+ T cell responses generated in early treated persons exhibit enhanced CD127 expression, and the breadth of early responses is associated with reservoir decay. Together these data suggest that early therapy enhances HIV-specific CD8+ T cell function, and provide important parameters by which to evaluate antiviral function induced by prophylactic and therapeutic vaccines.

68 EXPANDED CLONES HARBORING REPLICATION-COMPETENT VIRUS WAX AND WANE OVERTIME

Zheng Wang[1], Mithra R. Kumar[1], Janet Siliciano[1], Robert Siliciano[1]
[1]The Johns Hopkins University, Baltimore, MD, USA

Background: The latent reservoir for HIV-1 in resting CD4+ T cells is a major barrier to cure. Recent studies suggest that the latent reservoir could be maintained through cellular proliferation. Several mechanisms potentially contribute to persistence of latently infected cells, including antigen-driven cell expansion, homeostatic proliferation and proliferation driven by effects related to the site of HIV-1 integration. Most infected cells carry defective proviruses, and only ~1/10-6 resting CD4+ T cells carry inducible replication-competent proviruses in individuals on suppressive antiretroviral therapy. However, a recent study revealed a clonal population of infected CD4+ T cells carrying replication-competent HIV-1 that led to persistent plasma viremia in a patient with squamous cell carcinoma. We hypothesize that clones harboring replication-competent provirus expand and contract overtime.

Methods: To determine whether expanded clones harboring replication-competent virus persist, we recovered the infectious virus from 8 infected individuals at 2 or 3 time points spanning 2 to 3 years apart. We amplified the highly variable V3-V4 region of the env gene by RT-PCR from viral RNA in the supernatants of all p24+ wells from the QVOA. Sequences from each individual were clustered for phylogenetic analysis.

Results: Longitudinal sampling of replication-competent virus from all 8 participants revealed that they all have one or more sets of independent isolates with identical env sequences at all time points. In 7 out of 8 individuals, we found sequences that were present and prevalent at time point 1, at time point 2 or time point 3, suggesting some clones persisted overtime. In 7 out of 8 individuals, we observed clonal populations carrying different replication-competent viruses at time point 2 and time point 3.

Conclusion: We showed that the clonal populations harboring replication-competent HIV-1 change overtime. The result revealed that expanded clones carrying infectious HIV-1 in the latent reservoir wax and wane. The finding will help us to model what mechanism contributes to persistence of the latent reservoir.

69LB DETERMINANTS OF HIV-1 RESERVOIR SIZE AND LONG-TERM DYNAMICS UNDER SUPPRESSIVE ART

Nadine Bachmann[1], Chantal von Siebenthal[1], Valentina Vongrad[1], Kathrin Neumann[1], Teja Turk[1], Niko Beerenwinkel[2], Jasmina Bogojeska[3], Jacques Fellay[4], Volker Roth[5], Roger Kouyos[1], Karin Metzner[1], Huldrych F. Günthard[1]
[1]University Hospital Zurich, Zurich, Switzerland, [2]ETH Zurich, Zurich, Switzerland, [3]IBM Research–Zurich, Zurich, Switzerland, [4]École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, [5]University of Basel, Basel, Switzerland

Background: The HIV-1 reservoir is the major hurdle to cure. Thus, understanding factors affecting size and decay of this reservoir is crucial for development of cure strategies.

Methods: In 1,078 patients (pt) enrolled in the Swiss HIV Cohort Study, who after initiating their 1st triple combination antiretroviral therapy (cART) were fully suppressed for >5 yr (< 50 HIV RNA cp/ml of plasma), we measured total HIV-1 DNA levels at 3-4 time points using droplet digital PCR (in total 3,546 samples). Focusing on the time after the 1st rapid decay of HIV-1 DNA we chose the 1. time point 1.49 yr (IQR=[1.27,1.7], N=1,078) after ART initiation, the 2. time point 2 yr later (IQR=[1.87,2.16], N=1,068) and the 3. time point on average 1.93 yr (IQR=[1.77,2.15], N=1,071) thereafter. Total HIV-1 DNA in a 4th sample was quantified for a subset of pt 4.92 yr (IQR=[3.28,6.02], N=429) later. This extensive data set enabled a systematic investigation of parameters that potentially steer decay dynamics of the HIV-1 reservoir in infected individuals on long-term successful ART.

Results: Total HIV-1 DNA levels significantly decreased between our sampling times with diminishing differences over time (Fig 1). Further, our data identified pre-cART RNA levels, viral subtype, risk group injecting drug user, time to suppression, blips before 1st sample and infection stage at cART start to be independent drivers of the initial total HIV-1 DNA level. Studying decay slopes for each pt, pre-cART CD4 cell count, pre-cART CD4/CD8 ratio, pre-cART viral load and viral blips were significant drivers in the univariate model. The type of treatment (NNRTI vs boosted PI based cART) showed no differential effect on the decay. However, in multivariable analysis a very strong and independent inhibitory effect on total HIV-1 DNA decay was governed by viral blips. To conclude, our data confirm relevant drivers of the establishment and the depletion of the viral reservoir and reflect a highly interesting causal interplay between intermittent replication and dynamics of total HIV-1 DNA of patients on successful therapy.

Conclusion: The size of the viral reservoir as measured by total HIV-1 DNA in this large study is strongly governed by time of cART initiation. Strikingly, the main independent predictor of total HIV-1 DNA decay were viral blips, which had a strong inhibiting effect. Thus, viral blips are of biological relevance for the latent reservoir and this may have implications for cure research.

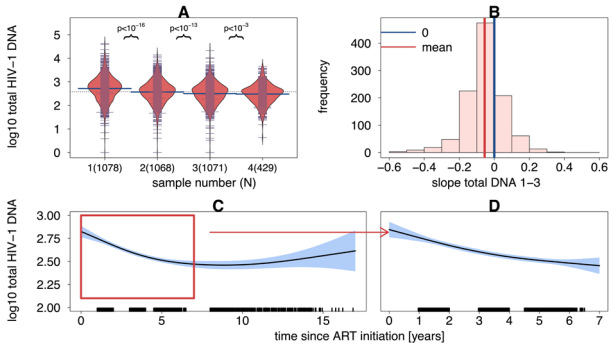


Figure 1: *The decay of total HIV-1 DNA levels over time.* ***A.*** *Beanplot of total HIV-1 DNA levels of individuals on long-term suppressive ART at 4 different time points and the respective sample size.* ***B.*** *Histogram of linear regression slope over the first three measurements.* ***C.*** *Spline fitted to the all HIV-1 DNA values dependent on the patient's time since ART initiation, showing the 95%- confidence and sampling times.* ***D.*** *Spline fitted to the first three total HIV-1 DNA values dependent on the patient's time since ART initiation.*

70 NO EVIDENCE FOR ONGOING HIV REPLICATION IN LYMPH NODES DURING SUPPRESSIVE ART

William R. McManus[1], Michael J. Bale[1], Jonathan Spindler[1], Ann Wiegand[1], Andrew Musick[1], Xiaolin Wu[2], David Wells[2], Stephen H. Hughes[1], Brandon Keele[2], Rebecca Hoh[3], Jeffery Milush[3], John M. Coffin[4], John W. Mellors[5], Steven G. Deeks[3], **Mary F. Kearney**[1]

[1]NIH, Frederick, MD, USA, [2]Leidos Biomedical Research, Inc, Frederick, MD, USA, [3]University of California San Francisco, San Francisco, CA, USA, [4]Tufts University, Boston, MA, USA, [5]University of Pittsburgh, Pittsburgh, PA, USA

Background: Lymph nodes have been implicated as potential sanctuary sites of ongoing HIV replication during ART due to inadequate drug penetration. To investigate this possibility, we characterized HIV proviral populations, their levels of expression, and their sites of integration in paired lymph node (LNMC) and peripheral blood (PBMC) samples collected after long-term ART.

Methods: PBMC and LNMC were obtained from five donors: four had <40 cps/ml on ART for 4.3-12.9 years and one was ART-naïve. Pre-ART samples were obtained for three of the treated patients. Longitudinal on-ART LNMC were obtained from two patients one year apart, including sampling from two different inguinal nodes in both individuals. Proviral populations and expression were characterized by cell associated RNA- and DNA- single genome sequencing of p6-PR-RT. Proviral sequences were compared phylogenetically and by testing for panmixia. Infected cell clones were identified by integration sites assay (ISA) in PBMC and LNMC from one donor.

Results: Comparisons of the proviral sequences on ART in PBMC (n=176) and LNMC (n=234) showed no increase in branch length, diversity, or divergence from pre-ART plasma or PBMC due to ongoing viral replication in either location. A test for panmixia of proviral sequences in PBMC and LNMC and across two separate lymph nodes sampled at the same time point showed no evidence for compartmentalization (probability of panmixia p>0.3). Proviruses with identical sequences were found in LNMC and PBMC and were transcriptionally active at both sites, although a greater fraction of infected cells in LNMC was expressing HIV RNA than in PBMC (13% vs. 6%). High-expressing cells (>20 HIV RNA copies/cell) were observed in samples obtained prior to but not during ART, with the exception of one LNMC. In one patient, forty clones of infected cells were identified by ISA. There were no differences in the locations of these clones in PBMC vs. LNMC (p=0.8).

Conclusion: Comparison of proviral populations, including clones of infected cells, and their expression in LNMC and PBMC, showed that populations of infected cells were well-mixed. There was no evidence of tissue compartmentalization. There was also no evidence for divergence from pre-ART populations in PBMC or in LNMC whether ART was initiated in acute or chronic infection, which is not consistent with the HIV reservoir being maintained by ongoing cycles of viral replication in either PBMC or LNMC during suppressive ART.

71 NO RESIDUAL VIRUS REPLICATION IN A RANDOMISED TRIAL OF DOLUTEGRAVIR INTENSIFICATION

Thomas A. Rasmussen[1], James McMahon[2], J. Judy Chang[3], Jennifer Audsley[3], Ajantha Solomon[3], Surekha Tennakoon[3], Ashanti Dantanarayana[3], Tim Spelman[3], Tina Schmidt[2], Stephen J. Kent[3], Vincent Morcilla[4], Sarah Palmer[4], Julian Elliott[2], Sharon R. Lewin[3]

[1]Aarhus University Hospital, Aarhus, Denmark, [2]Alfred Hospital, Melbourne, VIC, Australia, [3]Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia, [4]University of Sydney, Westmead, NSW, Australia

Background: Whether residual virus replication (RVR) persists in HIV-infected individuals on suppressive antiretroviral therapy (ART) remains controversial. One strategy used to demonstrate RVR is to intensify ART with an integrase inhibitor and measure an early increase in 2-long terminal repeat (2-LTR) circles. Two previous studies with raltegravir demonstrated RVR in a subset of individuals on ART. Here we investigated the effects of dolutegravir.

Methods: In a randomised, placebo-controlled, double-blinded clinical trial, HIV-infected adults with virological suppression for >3 years were randomly assigned 1:1 to dolutegravir 50 mg or placebo daily for 56 days in addition to background ART. The primary outcome measure was the level of 2-LTR circles in CD4+ T cells at day 7. Cell-associated unspliced (CA-US) HIV RNA, total and integrated HIV DNA, and plasma HIV RNA using a single copy assay (SCA) were quantified by real-time PCR; T cell expression of HLA-DR, CD38 and PD-1 by flow cytometry, and plasma levels of interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP), d-dimer and soluble CD14 (sCD14) by ELISA. We used repeated-measures analysis of variance (ANOVA) as the protocol-defined primary analysis. Student's t-test or rank sum test, were used to compare changes from baseline to specific time points across study arms.

Results: We enrolled 40 HIV-infected individuals; 21 were allocated to dolutegravir and 19 to placebo with 14 and 11% receiving a protease-inhibitor based ART regimen respectively. All participants completed the study. There was no significant difference in the primary endpoint, 2-LTR circles in peripheral blood CD4+ T cells, as assessed by repeated-measures ANOVA over 7 days (p=0.17) or any other time point (Figure). Median (IQR) 2-LTR circles fold-change from baseline to day 7 was -0.17 (-0.90 to 0.90) in the dolutegravir and -0.26 (-1.00 to 1.17) in the placebo groups. We found no consistent difference in the levels of CA US HIV-RNA, total and integrated HIV DNA (Figure), SCA, T cell activation markers or plasma levels of sCD14, d-dimer, IL-6 or hs-CRP. PD-1 expression in CD4+ T cells declined slightly after 56 days in placebo recipients compared to dolutegravir (p=0.03).

Conclusion: In a randomised, double-blinded, placebo-controlled trial of dolutegravir intensification, there was no evidence of RVR on ART.

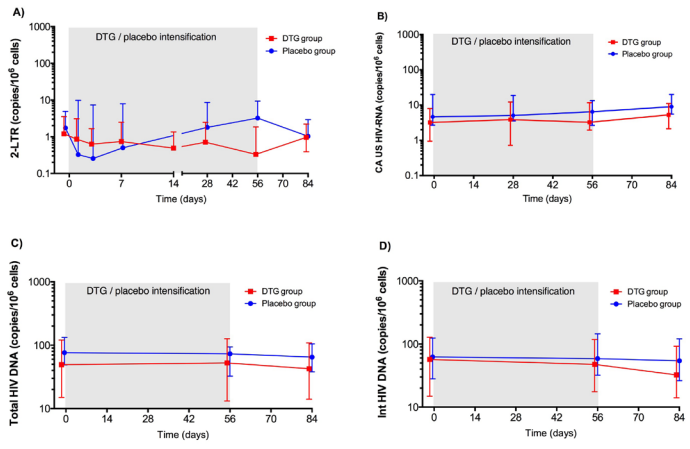


Figure. Virological markers in participants receiving dolutegravir (DTG; red) or placebo (blue). Median (IQR) levels are shown.

72 SINGLE ROMIDEPSIN INFUSIONS DO NOT INCREASE HIV EXPRESSION IN PERSONS ON ART (A5315)

Deborah McMahon[1], Lu Zheng[2], Joshua C. Cyktor[1], Evgenia Aga[2], Bernard J. Macatangay[1], Catherine Godfrey[3], Michael Para[4], Ronald T. Mitsuyasu[5], Evelyn Hogg[6], Joseph Hesselgesser[7], Edward P. Acosta[8], Rajesh T. Gandhi[2], John W. Mellors[1]

[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]Harvard University, Cambridge, MA, USA, [3]NIH, Bethesda, MD, USA, [4]The Ohio State University, Columbus, OH, USA, [5]University of California Los Angeles, Los Angeles, CA, USA, [6]Social & Scientific Systems, Silver Spring, MD, USA, [7]Gilead Sciences, Inc, Foster City, CA, USA, [8]University of Alabama at Birmingham, Birmingham, AL, USA

Background: Romidepsin (RMD) is a potent histone deacetylase inhibitor reported to increase HIV RNA in plasma and cells after single or multiple infusions of 5 mg/m2. We sought to determine the safest, lowest effective dose of RMD for induction of HIV expression.

Methods: Three single-dose cohorts (0.5 mg/m2, 2 mg/m2, 5 mg/m2) of HIV-infected participants were sequentially enrolled in a double-blind, randomized, placebo-controlled (3:1 active/placebo per cohort) study, target 15/cohort. Enrollees were virally suppressed on EFV, RAL, or DTG-containing ART with plasma HIV RNA ≥0.4 but <50 cps/mL. Viremia was measured by single copy assay (SCA) before and after RMD/placebo 4 hr infusion at hrs 6, 12, 24, 48 and days 7, 14, 28. Cell-associated HIV DNA (CAD) and unspliced RNA (CAR) were measured by qPCR in resting CD4+ cells pre- and post-infusion (hr 24; day 14). Histone-3 acetylation (H3-Ac) was measured by flow in total CD3+ T-cells pre-infusion and at hrs 12, 24, 48 and days 7, 14, 28. RMD was measured pre- and post-infusion at hrs 4, 6, 12, 24. Pre-specified primary comparisons were between the pooled RMD and pooled placebo groups using the Wilcoxon test.

Results: 43 participants enrolled (36 RMD; 7 placebo); 40 male; 27 white, 14 black; median screening SCA 1.5 cps/mL; median CD4 667 cells/mm^3. All completed the infusions; all but one completed 28-day follow-up. No Grade 3 events were deemed treatment-related. Median RMD levels at hr 4 were 12.0, 75.2, 89.0 ng/mL in the 0.5, 2.5 and 5 mg/m2 cohorts, respectively, and declined rapidly. The primary efficacy measure of SCA change from pre-infusion to the average of 24 and 48 hr post was similar between the pooled RMD and placebos (median: 0.12 vs. 0.12 $\log_{10}$ cps/mL, p=0.88, [95% CI on difference: -0.48, 0.33]). There was no significant difference in change in CAR from pre-infusion to 24 hr post (-0.09 vs. 0 $\log_{10}$ cps/106 resting CD4+ cells, p=0.37, [-0.54, 0.23]) or in CAD (-0.04 vs. 0.05 $\log_{10}$ cps/106 resting CD4+ cells, p=0.73, [-0.33, 0.32]). No significant increases in any virologic measure or in H3-Ac were observed in any of the RMD dose arms compared to pooled placebos or from pre-infusion to other timepoints (all p > 0.05).

Conclusion: In contrast to prior uncontrolled studies, in this placebo-controlled, dose-escalation study, single RMD doses that achieved a range (>5-fold) of systemic exposures were well-tolerated but did not increase HIV expression OR H3-Ac. Multiple or higher RMD doses may be needed to induce HIV expression.

Parameter	Timepoints	Romidepsin			Combined Romidepsin	Combined Placebos
		0.5 mg/m^2 Median (Q1,Q3)	2 mg/m^2 Median (Q1,Q3)	5 mg/m^2 Median (Q1,Q3)	Median (Q1,Q3)	Median (Q1,Q3)
SCA $\log_{10}$ (cps/mL)	Intra-participant Δ BSL to Avg Hrs 24, 48*	0.15 * (-0.22, 0.27)	-0.06 * (-0.27, 0.67)	0.23 * (0.00, 0.49)	0.12* (-0.18, 0.42)	0.12 (-0.24, 0.67)
Histone Acetylation (Median Fluor-essence Intensity)	Baseline	7,926 (5,546, 9,493)	4,204 (3,349, 8,066)	3,734 (2,476, 6,607)	5,935 (3,590, 8,598)	7,291 (6,218, 8,610)
	Hour 24	7,431 (4,957, 8,633)	4,569 (3,245, 8,139)	4,635 (2,870, 7,132)	6,122 (3,745, 8,122)	6,956 (4,348, 8,590)
	Hour 48	7,857 (7,114, 11,202)	6,667 (4,973, 7,870)	6,084 (4,053, 12,700)	7,118 (5,248, 10,484)	6,813 (5,349, 7,521)
	Intra-participant Δ BSL to Hr 48*	1,183* (-2,281, 4,055)	1,279* (-1,194, 3,625)	204* (99, 1,908)	400* (-905, 3,745)	-1,810 (-3,385, 1,227)
RMD Conc (ng/mL)	Hour 4	12 (6.6, 16.7)	75.2 (54.1, 84.0)	89 (53.3, 127.5)	-	-
	Hour 6	3.2 (-,-)	2.7 (1.7, 4.2)	2.6 (2.0, 5.0)	-	-

* comparison vs. combined placebos: p>0.14

73LB PGT121 COMBINED WITH GS-9620 DELAYS VIRAL REBOUND IN SHIV-INFECTED RHESUS MONKEYS

Erica Borducchi[1], Peter Abbink[1], Joseph Nkolola[1], Mark G. Lewis[2], Romas Geleziunas[3], **Dan Barouch**[1]

[1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]BIOQUAL, Inc, Rockville, MD, USA, [3]Gilead Sciences, Inc, Foster City, CA, USA

Background: Previous studies have shown that broadly neutralizing antibodies (bNAbs) administered at the time of ART discontinuation can provide direct antiviral effects, but whether bNAbs can effectively target the viral reservoir during ART suppression remains to be determined. In this study, we assessed the impact of the V3 glycan-dependent bNAb PGT121 combined with the TLR7 agonist GS-9620 in ART suppressed, SHIV-infected rhesus monkeys.

Methods: 44 rhesus monkeys were infected with SHIV-SF162P3 and initiated ART (TDF/FTC/DTG) on day 7 of infection. Following 96 weeks of continuous daily suppressive ART, animals received 10 mg/kg PGT121 by infusion (every 2 weeks x 5 doses), 0.15 mg/kg GS-9620 by oral gavage (every 2 weeks x 10 doses), both PGT121 and GS-9620, or sham controls (N=11/group). At week 130, which was 16 weeks after the final PGT121 and GS-9620 doses, ART was discontinued and viral rebound was monitored.

Results: PGT121 administration resulted in 10 weeks of therapeutic antibody levels, followed by a decline to undetectable levels in peripheral blood, lymph nodes, and colorectal tissue for >8 weeks prior to ART discontinuation. Autologous cellular immune responses were minimal and were not increased by PGT121+GS-9620 administration. Viral DNA in lymph nodes was markedly lower in PGT121+GS-9620 treated animals as compared with sham controls (P=0.004, Mann-Whitney test). Following ART discontinuation, 100% (11 of 11) of sham controls exhibited rapid viral rebound with a median rebound time of 21 [IQR 21-42] days. In contrast, only 55% (6 of 11) of PGT121+GS-9620 treated animals rebounded by day 140 following ART discontinuation (P=0.03, Fisher's exact test) and demonstrated a substantial delay in median rebound time of 112 [IQR 84-140+] days (P=0.0005, Mann-Whitney test) as well as a 2.64 log reduction of peak viral loads and a 1.52 log reduction of setpoint viral loads as compared with sham controls (P<0.0001, Mann-Whitney test). All PGT121+GS-9620 treated animals exhibited setpoint viral loads <400 RNA copies/ml. Intermediate outcomes were observed in the animals that received PGT121 alone.

Conclusion: PGT121 combined with GS-9620 during ART suppression substantially delayed and controlled viral rebound following ART discontinuation in SHIV-infected rhesus monkeys that initiated ART during acute infection. These data suggest that bNAb administration together with innate immune stimulation during ART suppression may effectively target the viral reservoir.

74 IL-6, D-DIMER OR T-CELLS: WHICH BEST PREDICT EVENTS OR EXPLAIN BENEFITS OF EARLY ART?

Jason V. Baker[1], Birgit Grund[2], Shweta Sharma[2], Abdel Babiker[3]

[1]Hennepin County Medical Center, Minneapolis, MN, USA, [2]University of Minnesota, Minneapolis, MN, USA, [3]University College London, London, UK

Background: In START, immediate ART led to immune recovery, reduced inflammation, and lower risk of AIDS and serious non-AIDS (SNA). We compare early measures of immunologic and inflammatory biomarkers for their ability to predict prognosis and/or explain the treatment effect in START.

Methods: Plasma biomarkers studied included IL-6, D-dimer and CD4 and CD8 T-cells at baseline and month 8. Associations of latest biomarker levels (only baseline or month 8) with subsequent event risk were estimated with Cox regression adjusted for treatment group. Hazard ratios (HR) were calculated per 1 SD (standard deviation) of the biomarker at baseline, so that HRs are comparable. We calculated the percent of treatment effect (TE) explained by biomarkers as the reduction in the HR (immediate vs deferred ART) when adjusted for the latest biomarker levels, expressed as a percentage of the TE.

Results: Analyses include 4273 (92%) START participants with IL-6, D-dimer and CD4 counts at baseline. Mean follow-up was 3.1 years; 129 participants had primary events (57 AIDS, 72 SNA events or non-AIDS deaths), with 23 occurring before month 8 and 106 after. Levels (assessed at baseline and month 8) of D-dimer, IL-6, CD8, and CD4:CD8, but not CD4, demonstrated strong associations with subsequent risk of AIDS and SNA (Table). IL-6 and D dimer levels were each significantly associated with event risk after adjusting for treatment group and CD8, adjusted HR (95%CI) per SD of IL-6 and D dimer: 1.33 (1.14, 1.57) and 1.57 (1.37, 1.80), respectively. D dimer also was significantly associated with risk after adjusting for treatment group, CD8 and IL-6 (adjusted HR 1.50 [1.30, 1.74]). The percent of TE explained in START by baseline and month 8 biomarker levels appeared similar for CD8 and D-dimer, but strongest for the CD4:CD8 ratio (20%). The effect of IL-6 and D-dimer (10%) for explaining the TE in START appeared additive when combined with the CD4:CD8 ratio (29% for all three; table).

Conclusion: In START, D-dimer, IL-6, CD8 and the CD4:CD8 ratio have similar ability to predict prognosis. When considering only early biomarker assessments, the CD4:CD8 ratio explained the largest percent of TE (immediate vs. deferred ART) in START. Although adding IL-6 and D-dimer to T-cell assessments added to risk prediction and the percent of TE explained, additional study of these and other pathways over time is needed to better understand the causes of clinical risk and the benefits of early ART among HIV+ with high CD4 counts.

Table: Latest levels (baseline and month 8) of IL-6, D-dimer and T-cells as predictors of AIDS, SNA and death, and the percent of treatment effect (TE) explained in START (n= 4273; n=129 events).

		HR per 1 SD[#]		HR* (Imm./Def.)	Percent
Predictor	SD	HR (95% CI)	*p*-value	(95% CI)	of TE*
Unadjusted model				0.43 (0.30, 0.63)	
Latest log_2 IL-6 (pg/mL)	0.93	1.36 (1.16, 1.59)	<0.001	0.45 (0.31, 0.65)	2.8%
Latest log_2 D-dimer (µg/mL)	0.92	1.58 (1.38, 1.81)	<0.001	0.48 (0.33, 0.70)	8.5%
Latest CD4 (cells/µL)	171	1.05 (0.91,1.21)	0.51	0.45 (0.30, 0.67)	3.1%
Latest CD8 (cells/µL)	557	1.36 (1.19, 1.56)	<0.001	0.48 (0.33, 0.70)	8.5%
Latest log_2 CD4:CD8 ratio	0.66	1.34 (1.14, 1.58)	<0.001	0.55 (0.37, 0.81)	19.9%
Latest log_2 IL-6 & D-dimer	--	--	--	0.49 (0.33, 0.71)	9.5%
Latest CD8 T-cells and log_2 IL-6 and D-dimer	--	--	--	0.53 (0.36, 0.78)	18.0%
Latest log_2 CD4:CD8 ratio, IL-6 and D-dimer	--	--	--	0.60 (0.40, 0.89)	29.3%

*[#] HR of AIDS, serious non-AIDS or death, for latest values of biomarkers (at baseline or month 8), adjusted for treatment group; HR is per one SD higher for IL-6, D-dimer and CD8, and per one SD lower for CD4 and CD4:CD8. *HR for treatment effect (TE) in START (Imm vs Def) after adjustment for latest levels of corresponding biomarker(s); Percent of TE (i.e., 1-HR for the unadjusted model) explained then represents the attenuation after adjusting for corresponding latest biomarker values.*

75 SERIOUS CLINICAL OUTCOMES IN HIV-POSITIVE PERSONS WITH CHRONIC KIDNEY DISEASE (CKD)

Lene Ryom[1], Jens D. Lundgren[1], Matthew Law[2], Ole Kirk[1], Wafaa M. El-Sadr[3], Fabrice Bonnet[4], Rainer Weber[5], Eric Fontas[6], Antonella D'Arminio Monforte[7], Andrew N. Phillips[8], Colette Smit[9], Camilla Ingrid Hatleberg[1], Caroline Sabin[8], Amanda Mocroft[8]

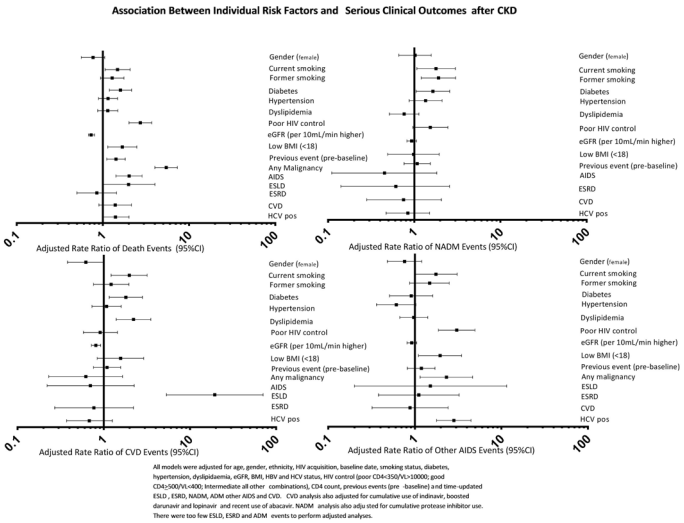
[1]Rigshospitalet, Copenhagen, Denmark, [2]Kirby Institute, Sydney, NSW, Australia, [3]Columbia University, New York, NY, USA, [4]INSERM, Bordeaux, France, [5]University Hospital Zurich, Zurich, Switzerland, [6]CHU de Nice, Nice, France, [7]University of Milan, Milan, Italy, [8]University College London, London, UK, [9]Academic Medical Center, Amsterdam, Netherlands

Background: Risk factors for CKD amongst HIV-positive persons have been well established, but insights into the prognosis after CKD including the role of modifiable risk factors for serious clinical outcomes (SCO) are limited.

Methods: D:A:D participants developing CKD (confirmed, >3 months apart, eGFR<60mL/min/1.73 m^2 or 25% eGFR decrease when eGFR<60mL/min/1.73m^2) after 2004 were followed from date of CKD date incident SCO (end stage renal (ESRD) and liver disease (ESLD), cardiovascular disease (CVD), AIDS- and non-AIDS defining malignancies (ADM and NADM), other AIDS events or death), 6 months after last visit or Feb 1st 2016. SCO rates in persons with CKD were compared to rates in persons without CKD followed from eGFR> 60mL/min/1.73 m^2 to CKD, 6 months after last visit or Feb 1st 2016. Poisson regression models considered associations between individual SCO and modifiable risk factors.

Results: 2467 persons with and 33427 persons without CKD were included. During 2.7 (IQR 1.1-5.1) years median follow-up after CKD 595 persons with CKD (24.1%) developed a SCO (IR 68.9/1000PYFU [95%CI 63.4-74.4]) with 7.9% [6.9-9.0] estimated to have a SCO at 1 year. In persons without CKD the SCO IR was 23.0/1000PYFU [22.4-23.6] with 2.8% [2.6-3.0] estimated to have a SCO at 1 year. In persons with CKD, death was the most common SCO (12.7%), followed by NADM (5.8%), CVD (5.6%), other AIDS (5.0%), ESRD (2.9%), ESLD (1.0%) and ADM (0.8%). In adjusted models poor HIV control (2.72 [2.01-3.69]), low BMI (1.68 [1.14-2.48]), diabetes (1.60 [1.19-2.15]), smoking (1.48 [1.06-2.07]) and higher eGFR (0.74 [0.68-0.80]) were strongly associated with death; poor HIV control (3.05 [1.87-4.95]), low BMI (1.96 [1.11-3.47]) and smoking (1.75 [1.02-3.00]) with other AIDS; smoking (1.78 [1.07-2.99]) and diabetes (1.65 [1.05-2.57]) with NADM; dyslipidaemia (2.22 [1.40-3.52]), smoking (1.98 [1.22-3.19]), diabetes (1.81 [1.16-2.81]) and higher eGFR (0.81 [0.72-0.92]) with CVD (figure).

Conclusion: In an era where many HIV-positive persons require less monitoring due to efficient antiretroviral treatment, persons with CKD have a high SCO burden requiring close monitoring. Our data suggest modifiable risk factors including smoking, diabetes, BMI, HIV-control and dyslipidaemia play a central role for post-CKD morbidity and mortality.



76 INCREASED RISK OF PERIPHERAL ARTERY DISEASE IN PERSONS WITH HIV COMPARED TO CONTROLS

Andreas D. Knudsen[1], Jens D. Lundgren[1], Marco Gelpi[1], Ashley Roen[2], Amanda Mocroft[2], Shoaib Afzal[3], Børge Nordestgaard[3], Henrik Sillesen[1], Andreas Ronit[1], Anne-Mette Lebech[1], Lars Køber[1], Klaus F. Kofoed[1], Susanne D. Nielsen[1]

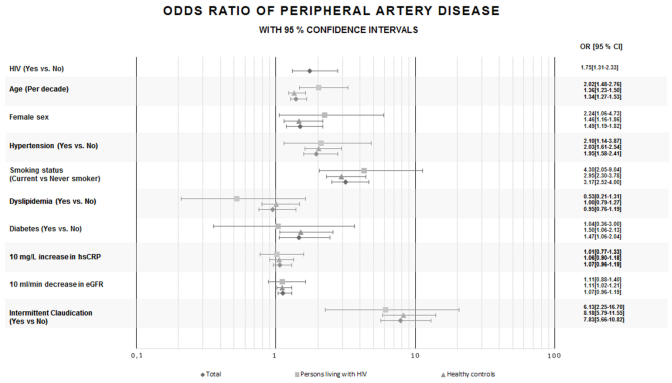
[1]Rigshospitalet, Copenhagen, Denmark, [2]University College London, London, UK, [3]University of Copenhagen, Copenhagen, Denmark

Background: Risk of cardiovascular disease (CVD) is higher among persons living with HIV (PLWH) than among the background population. Peripheral artery disease (PAD) is a manifestation of CVD that is less well-explored in PLWH with conflicting reports on prevalence and risk factors. Ankle-brachial index (ABI) is an excellent diagnostic tool for diagnosing PAD. In this study, we aimed to determine the prevalence and risk factors for PAD in PLWH compared to uninfected controls. We hypothesized that prevalence of PAD would be higher among PLWH than among controls and that HIV is an independent predictor of PAD.

Methods: PLWH aged ≥40 were recruited from the Copenhagen comorbidity in HIV infection (COCOMO) study. Sex and age matched uninfected controls were recruited from the Copenhagen General Population Study. Blood pressure, lipids, glucose, eGFR and hsCRP were measured. Questionnaires were used to obtain data on smoking history and medication. ABI was measured with the Doppler method. We defined PAD as ABI ≤ 0.9 and non-compressibility as ABI ≥ 1.4 and excluded the latter from PAD analyses. We assessed predictors of PAD using a logistic regression model adjusted for age, sex, smoking status, dyslipidemia, diabetes, hsCRP and hypertension.

Results: Among 908 PLWH and 11,106 controls, the PLWH were slightly younger (median 52 vs 53 p=0.0010), had a lower prevalence of hypertension (48 % vs 61% p<.0001), but higher proportions of current smokers (28% vs 13% p<.0001) and persons with intermittent claudication (4 % vs 2 % p<.0001) than controls. PAD was detected in 112 (12% [95% 10-14]) and 623 (6% [95% 5-6]), respectively (p<0.0001); odds ratio (OR)=2.4 [95% 1.9-2.9], adjusted OR=1.7 [95% 1.3-2.3, p=.0002]. Furthermore, age, female sex, smoking status, hypertension, intermittent claudication, and kidney function were independently associated with risk of PAD, irrespective of HIV status (Fig 1). In PLWH, neither previous AIDS, CD4 nadir, CD4 count, CD4:CD8-ratio, HCV coinfection, cART nor duration of infection were associated with PAD. Interaction of HIV with age was borderline significant (p=0.0517).

Conclusion: Prevalence of PAD was higher among PLWH compared to healthy controls, and remained so after adjusting for common CVD risk factors. Our findings expand the evidence base that PLWH have excess arterial disease to also include PAD. The exact biological mechanisms causing this excess risk remain to be elucidated. Until then, focus on management of modifiable traditional risk factors is important.



Odds ratio of peripheral artery disease with 95 % confidence intervals. Logistic model was adjusted for age, sex, smoking status, dyslipidemia, diabetes, hsCRP and hypertension. OR: Odds ratio; CI: Confidence Interval.

77 HIV INFECTION IS ASSOCIATED WITH PROGRESSION OF HIGH RISK CORONARY PLAQUE IN THE MACS

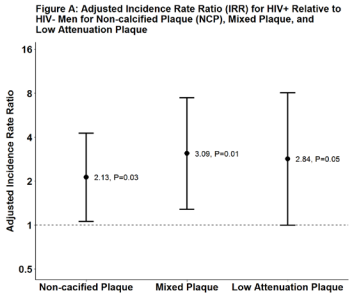
Wendy Post[1], Sabina Haberlen[2], Long Zhang[2], Mallory Witt[3], Lisa Jacobson[2], Todd T. Brown[2], Frank J. Palella[4], Lawrence Kingsley[5], Matthew Budoff[3]
[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Johns Hopkins University, Baltimore, MD, USA, [3]Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, USA, [4]Northwestern University, Chicago, IL, USA, [5]University of Pittsburgh, Pittsburgh, PA, USA

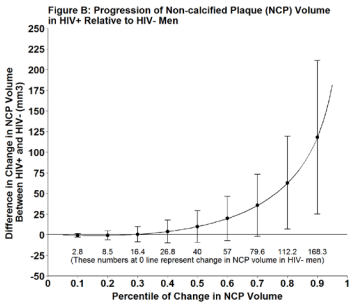
Background: HIV infection is associated with coronary atherosclerosis, especially non-calcified plaque (NCP) and mixed plaque; however, development and progression of atherosclerosis associated with HIV has only been shown with coronary artery calcium scanning, which cannot detect more potentially unstable plaques. We prospectively evaluated the association between HIV serostatus and the progression and composition of coronary plaque among men in the Multicenter AIDS Cohort Study (MACS).

Methods: We performed baseline and follow-up coronary CT angiography in 409 men (253 HIV+, 156 HIV-; median interscan interval=4.5 yrs). Calcified and NCP volumes, including lipid-rich low attenuation plaque (LAP), were measured in each coronary segment. We used Poisson regression to test the association between HIV serostatus and incident plaque among men without baseline plaque, and generalized gamma regression to test the association with progression among men with baseline plaque, adjusting for time between scans, demographics and CVD risk factors. We also evaluated plaque progression differences between HIV- men and HIV+ men with suppressed viral load (<50 copies/mL, ≤ 1 "blip" <500 copies/mL) and those with viremia during the inter-scan interval.

Results: Mean age was 54 yrs (53 HIV+, 57 HIV-) and 32% were black (35% HIV+, 27% HIV-). 70% of HIV+ men were aviremic during the interval. There were 118 men (74 HIV+, 44 HIV-) with no baseline plaque. Incident plaque was seen in 36 (30%) men; 24 developed both NCP and calcified plaque (mixed plaque) and 12 developed only NCP. LAP developed in 27 men. HIV+ men had a greater adjusted incidence of NCP (IRR 2.13, p=0.03), LAP (IRR 2.84, p=0.05) and mixed plaque (IRR 3.09, P=0.01) than HIV- men. In addition, compared to HIV- men, the incidence of LAP was greatest among HIV+ men with viremia (IRR 5.4, p=0.009; aviremic men IRR 2.4, p=0.096). There were 291 men with baseline plaque (179 HIV+, 112 HIV-). Among men with the greatest NCP volume change, the adjusted increases were significantly greater among HIV+ compared to HIV- men (e.g. 80th %tile of change in NCP was 175 mm^3 for HIV+ compared to 112 mm^3 for HIV-, P=0.03), with similar trends for total plaque and LAP.

Conclusion: This is the first study to demonstrate that HIV infection is associated with an elevated incidence and progression of high risk coronary plaque and suggests the need for additional studies to determine the importance of controlling viremia to limit the excess burden of CVD events in this population.





78 CAROTID ARTERY ATHEROSCLEROSIS IS ASSOCIATED WITH MORTALITY IN HIV+ WOMEN AND MEN

David B. Hanna[1], Jee-Young Moon[1], Kathryn Anastos[1], Sabina Haberlen[2], Audrey French[3], Frank J. Palella[4], Stephen J. Gange[2], Mallory Witt[5], Seble Kassaye[6], Jason Lazar[7], Phyllis Tien[8], Lawrence Kingsley[9], Wendy Post[10], Robert C. Kaplan[1], Howard Hodis[11]
[1]Albert Einstein College of Medicine, Bronx, NY, USA, [2]The Johns Hopkins University, Baltimore, MD, USA, [3]Cook County Health & Hospitals System, Chicago, IL, USA, [4]Northwestern University, Chicago, IL, USA, [5]Harbor–UCLA Medical Center, Torrance, CA, USA, [6]Georgetown University, Washington, DC, USA, [7]SUNY Downstate Medical Center, Brooklyn, NY, USA, [8]University of California San Francisco, San Francisco, CA, USA, [9]University of Pittsburgh, Pittsburgh, PA, USA, [10]Johns Hopkins Hospital, Baltimore, MD, USA, [11]University of Southern California, Los Angeles, CA, USA

Background: Using carotid artery intima-media thickness (cIMT) measured by ultrasound as a surrogate marker for cardiovascular disease is standard, yet long-term studies of carotid artery ultrasound parameters predicting major health events in persons with HIV are lacking. We evaluated associations of carotid artery measurements with all-cause mortality in the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS).

Methods: Participants without self-reported coronary heart disease underwent B-mode carotid artery ultrasound in 2004-2006, with measurement of 1) cIMT at the common carotid artery; 2) plaque (focal cIMT >1.5 mm) at the common or internal carotid arteries or carotid bifurcation; and 3) Young's modulus of elasticity, a measure of arterial stiffness. Participants were followed for a median 9 years (total 22,432 person-years), and death was ascertained by active surveillance and the National Death Index. Cox models estimated the association of each measure at baseline with time to death, controlling for HIV status and demographic, behavioral, cardiometabolic, and HIV-related factors. We tested interactions by cohort and HIV status.

Results: Among 1,722 women (median age 40 years, 88% black or Hispanic, 71% HIV+, 62% on ART at baseline) and 880 men (median age 49, 35% black or Hispanic, 66% HIV+, 72% on ART), 10% (206 women, 83 men) died during follow-up. In adjusted analyses, cIMT was not associated with mortality. Presence of carotid artery plaque was associated with 56% greater mortality risk (95% CI 1.13-2.15) and varied by cohort (HR 1.25 among women, 95% CI 0.83-1.89; HR 2.48 among men, 95% CI 1.35-4.38; p for interaction 0.045). The highest quartile of Young's modulus, indicating greatest stiffness, was associated with 58% greater mortality risk compared with the lowest quartile (95% CI 1.05-2.38, p for interaction by cohort 0.29). While the association of plaque with mortality was more pronounced in HIV- vs. HIV+ participants (p for interaction=0.01), potentially owing to AIDS deaths in the HIV+ group, the relationship was statistically significant in each group (Table). The association of Young's modulus showed a similar pattern, but the interaction by HIV status was marginally significant (p=0.08).

Conclusion: Carotid artery measurements were independently associated with all-cause mortality in both HIV+ and HIV- persons. To our knowledge our study is the first to show that carotid artery plaque is predictive of major health events in HIV+ adults.

Table. Adjusted associations of carotid artery plaque and Young's modulus with all-cause mortality.

	Hazard ratio	95% confidence interval	P-value
Plaque vs. no plaque			
HIV+ and HIV- combined, N=2,602	1.56	1.13-2.15	0.01
HIV+ only, N=1,809	1.48	1.03-2.11	0.03
HIV- only, N=793	3.18	1.14-8.88	0.03
Young's modulus, 4Q vs. 1Q			
HIV+ and HIV- combined, N=2,602	1.58	1.05-2.38	0.03
HIV+ only, N=1,809	1.44	0.93-2.22	0.10
HIV- only, N=793	7.06	1.57-31.75	0.01

Cox models include cIMT at the common carotid artery (non-significant), plaque, and Young's modulus, and are also adjusted for age, race/ethnicity, education, income, study site, IDU history, crack/cocaine use, current smoking, current alcohol use, history of HCV, BMI, systolic blood pressure, total and HDL cholesterol, use of anti-hypertension or anti-cholesterol medications, history of diabetes, baseline CD4+ count, ART use in past 6 months, history of AIDS.

79 IMPACT OF LDMTX ON IMMUNE ACTIVATION AND ENDOTHELIAL FUNCTION IN TREATED HIV

Priscilla Hsue[1], Heather Ribaudo[2], Steven G. Deeks[1], Michael M. Lederman[3], Carl Fichtenbaum[4], Annie F. Luetkemeyer[1], Eric Daar[5], Benigno Rodriguez[3], Babafemi Taiwo[6], David Haas[7], Victoria Johnson[8], James H. Stein[9], Judith S. Currier[5]

[1]University of California San Francisco, San Francisco, CA, USA, [2]Harvard University, Cambridge, MA, USA, [3]Case Western Reserve University, Cleveland, OH, USA, [4]University of Cincinnati, Cincinnati, OH, USA, [5]University of California Los Angeles, Los Angeles, CA, USA, [6]Northwestern University, Chicago, IL, USA, [7]Vanderbilt University, Nashville, TN, USA, [8]University of Alabama at Birmingham, Birmingham, AL, USA, [9]University of Wisconsin, Madison, WI, USA

Background: Chronic inflammation in treated HIV infection predicts mortality and non-AIDS morbidities including cardiovascular disease (CVD). Low dose methotrexate (LDMTX) is an anti-inflammatory drug that is associated with reduced risk of CVD in the RA population. We evaluated the safety and potential efficacy of LDMTX in treated HIV.

Methods: This was a randomized placebo-controlled study in ART-treated HIV-infected individuals ≥40 years of age with or at increased risk for CVD and with CD4+ T-cells >400 cells/mm^3. Participants received weekly LDMTX or placebo (+ folic acid) for 24 weeks and were followed for an additional 12 weeks. HIV disease indices, safety events, and endothelial function (ultrasound brachial artery flow-mediated dilation [FMD]) were assessed. The primary endpoints of this study were: 1) safety; 2) endothelial function, and 3) markers of inflammation/ immune activation. A5314 was powered to demonstrate no more than a 15% point higher rate of safety events with LDMTX and to detect a 1.5% difference in 24-week FMD change between groups.

Results: The 176 participants had a median (Q1, Q3) age of 54 (49, 59) years, 90% were male, and median entry CD4+ T cells of 726 (552, 940) cells/mm^3. Median change in CD4+ T-cells after 24 weeks was -58 (-163, 47) vs. 2 (-101, 97) cells/mm^3 in the LDMTX vs. placebo group (p=0.003) with partial rebound (p=0.09) by 36 weeks. Median change in CD8+ T-cells after 24 weeks was -103 (-228, 0) vs. -2 (-142, 84) cells/mm^3 in the LDMTX vs. placebo group (p=0.001). Safety event rates were 12.8% (11 events) with LDMTX vs. 5.6% (5 events) with placebo (Δ=7.2%, upper 1-sided 90% CI=13.4%). FMD did not improve with LDMTX (Δ=0.09% [95% CI -0.67%, 0.85%]); hsCRP, IP-10, IL-6, sCD14, sCD163, D-Dimer, Fibrinogen, and sVCAM also did not change with LDMTX. Across all study weeks, there were LDMTX-related decreases in the frequency of activated and proliferating CD8+ T cells (p<0.019).

Conclusion: In older HIV-infected adults with CVD or at risk for CVD, we observed high rates of adverse events in both arms. These rates were higher with LDMTX but within the non-inferiority bound. LDMTX had no effect on endothelial function or soluble inflammatory markers. LDMTX-mediated declines in CD8+ T cell numbers, activation and proliferation suggest that the immunomodulatory effects of this drug are mediated through T cells and their activation state. Future studies to evaluate the impact of LDMTX on persistent T cell dysfunction are ongoing.

80 PLATELET FUNCTION UPON SWITCHING TO TAF VS CONTINUING ABC: A RANDOMIZED SUBSTUDY

Patrick W. Mallon[1], Alan Winston[2], Frank Post[3], Dermot Kenny[4], Colm Bergin[5], Robert T. Maughan[1], Elena Alvarez-Barco[1], Willard Tinago[1], Eimear Dunne[4], Mingjin Yan[6], Moupali Das[6], Martin Rhee[6]

[1]University College Dublin, Dublin, Ireland, [2]Imperial College London, London, UK, [3]King's College Hospital NHS Foundation Trust, London, UK, [4]Royal College of Surgeons in Ireland, Dublin, Ireland, [5]St. James's Hospital, Dublin, Ireland, [6]Gilead Sciences, Inc, Foster City, CA, USA

Background: Abacavir (ABC) use has been associated with increased risk of myocardial infarction (MI), with altered endothelial and platelet function as proposed underlying mechanisms. We hypothesized that a switch from ABC to tenofovir alafenamide (TAF) would result in decreased platelet reactivity.

Methods: In a platelet function substudy of a randomized double-blind trial of virally suppressed, HIV1-positive individuals on ABC/lamivudine (3TC), randomized to switch to TAF/emtricitabine (FTC) or remain on ABC/3TC while continuing their 3rd agent, we measured platelet aggregation (PAg) at baseline (BL), week (W) 4, and 12 in response to increasing concentrations of five agonists: collagen (Col), thrombin receptor-activating peptide (TRAP), adenosine diphosphate (ADP), epinephrine (Epi) and arachidonic acid (AA). We compared population-derived agonist concentrations inducing 50% platelet aggregation (EC_{50}) between-groups at BL, W4 and 12 by four parameter logistic regression. We measured platelet surface expression of the GPVI receptor, CD42b and P-selectin (P-sel) by flow cytometry and compared between-group differences at BL and W12 pre- and post-stimulation with collagen-related peptide (CRP) by Wilcoxon rank sum test.

Results: The 61 participants (29 in TAF/FTC and 32 in ABC/3TC group) were well matched at BL. Although baseline PAg in response to Col, TRAP and ADP was similar between groups, W4 PAg with Col, TRAP and ADP was significantly lower in the TAF/FTC arm (reflected by greater EC_{50}) compared to the ABC/3TC arm (Table). Reduced PAg in response to Col persisted through W12, while differences in PAg with TRAP and ADP were no longer significant at W12. PAg with Epi and AA did not differ between groups at any time point. Expression of the collagen receptor GPVI, which mediates endothelial-platelet interactions, was higher at W12 in the TAF/FTC group (P=0.031) while W12 GP42b and P-sel were similar between groups (P=0.10, P=0.8). There were no between-group differences in GPVI shedding or induction of P-sel with CRP activation (all P>0.1).

Conclusion: Within a randomized trial, switching from ABC/3TC to TAF/FTC was associated with significantly lower platelet reactivity to TRAP and ADP at W4 and Col through W12. Together with higher surface GPVI expression, these observations suggest improvements in measures of platelet function involving endothelial-platelet pathways with a switch from ABC/3TC and point to a potential underlying mechanism for increased risk of MI with ABC.

Table. Demographics and platelet function

	TAF/FTC (n=29)	ABC/3TC (n=32)	P value
Age (yrs)	50 (43, 53)	49 (38, 54)	-
Male (n (%))	21 (72.4%)	22 (68.8%)	-
CD4+ count (cells/mm3)	659 (503, 833)	616 (512, 774)	-
Caucasian n(%)	15 (51.7%)	19 (59.4%)	-
Current smoker	5 (17.2%)	7 (21.9%)	-
Col EC_{50} W4 (umol/L)*	**0.027 (0.022, 0.033)**	**0.017 (0.014, 0.022)**	**0.005**
TRAP EC_{50} W4 (umol/L)	**2.25 (1.99, 2.55)**	**1.75 (1.55, 1.96)**	**0.004**
ADP EC_{50} W4 (umol/L)	**1.56 (1.33, 1.87)**	**1.22 (1.05, 1.42)**	**0.03**
GPVI BL (10^3/platelet)	5.27 (4.16, 6.63)	5.28 (4.11, 6.05)	0.7
GPVI W12 (10^3/platelet)	**5.52 (4.51, 6.52)**	**4.49 (4.06, 5.61)**	**0.031**
%GPVI shed W12** (%)	-46.6 (-50.5, -41.5)	-46.9 (-49.4, -40.3)	0.47

Data are median (IQR) unless specified. EC_{50} = concentration of collagen required to induce 50% platelet aggregation. W = week. BL=baseline. *data are mean (95% confidence internal). **%GPVI shed after exposure to CRP.

81LB A TREATMENT AS PREVENTION TRIAL TO ELIMINATE HCV IN HIV+ MSM: THE SWISS HCVREE TRIAL

Dominique L. Braun[1], Benjamin H. Hampel[1], Huyen Nguyen[1], Markus Flepp[2], Marcel Stoeckle[3], Charles Béguelin[4], Patrick Schmid[5], Julie Delaloye[6], Mathieu Rougemont[7], Enos Bernasconi[8], Dunja Nicca[3], Roger Kouyos[1], Jürg Böni[1], Huldrych F. Günthard[1], Jan S. Fehr[1]

[1]University of Zurich, Zurich, Switzerland, [2]Centre for Infectious Diseases, Zurich, Switzerland, [3]University of Basel, Basel, Switzerland, [4]University of Bern, Bern, Switzerland, [5]St. Gallen Cantonal Hospital, St Gallen, Switzerland, [6]Lausanne University Hospital, Lausanne, Switzerland, [7]University Hospitals of Geneva, Geneva, Switzerland, [8]Ospedale Regionale di Lugano, Lugano, Switzerland

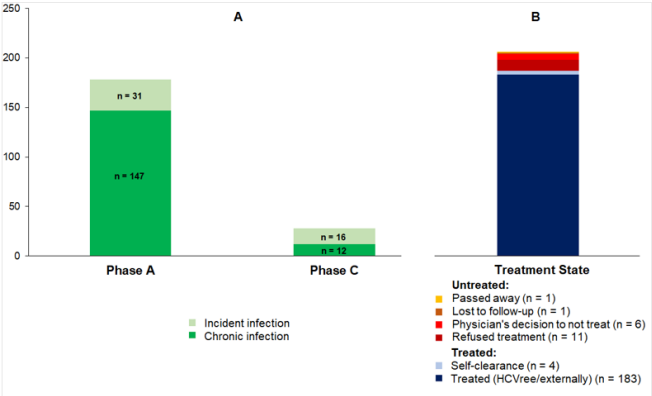
Background: Incidence of sexually transmitted hepatitis C virus (HCV) infections among HIV+ men who have sex with men (MSM) is rising worldwide. The Swiss HCVree Trial (ClinicalTrials.gov NCT02785666) aimed to test the feasibility of a HCV elimination approach among HIV+ MSM participating in the Swiss HIV Cohort Study (SHCS).

Methods: During phase A (10/1/2015-5/31/2016) we systematically tested all MSM in the SHCS by HCV-RNA PCR. During phase B (6/1/2016-2/28/2017) HCV treatment with the DAA grazoprevir/elbasvir ± ribavirin was offered to all MSM with GT 1 or 4 with the goal to reduce the pool of potential transmitters. Individuals with GT 2 or 3 and individuals not eligible for phase B were treated externally with standard of care DAAs. MSM reporting unprotected sex with occasional partners were asked for participation in a behavioral intervention program during phase B to reduce sexual risk behavior to prevent re-infection. During phase C (3/1/-11/30/2017), we re-tested all MSM in the SHCS by HCV-RNA PCR.

Results: During phase A we screened 3'722 out of 4'257 active MSM from the SHCS database (87%) and identified 177 (4.8%) with a replicating HCV infection. Of these 177 infections 31 (18%) were incident (Figure 1A). During phase B we treated 122 out of these 177 replicating infections (69%) within the Swiss HCVree Trial and achieved a SVR12 of 99%. 39 infections (22%) were treated externally using standard of care DAAs (SVR 12 100%). Re-screening of 3'723 MSM during phase C identified 28 infections (0.8%), of them 16 were incident. The remaining 12 infections were chronic infections not treated during phase A. Of the 28 infections identified during phase C, 22 patients (79%) started DAA before end of period C. Overall, we identified and treated 183 out of 206 replicating infections (89%) during phase A and C within and outside the Swiss HCVree Trial (Figure 1B). Of 68 MSM eligible for the behavioral intervention program, 51 (75%) agreed to participate and 46 (68%) completed the program.

Conclusion: A systematic, population based HCV RNA screening approach among HIV+ MSM from the SHCS identified a high number of potential HCV spreaders. Treatment initiation in 89% of individuals with replicating HCV reduced incident HCV infections by 50% during the study. A systematic population based screening followed by prompt treatment of identified infections combined with a strong behavioral intervention can serve as a model to reach WHO elimination targets by 2030 in HIV/HCV co-infected MSM.

Figure1: **A:** Type of HCV infections detected during phase A compared to phase C; **B:** Cumulative treatment state of identified replicating HCV infections during phase A and C



82 PROTECTION AGAINST REPEATED VAGINAL SHIV CHALLENGES BY BNAB 3BNC117 AND 10-1074

David A. Garber[1], Debra Adams[1], James Mitchell[1], Shanon Ellis[1], Till Schoofs[2], Michael S. Seaman[3], Janet McNicholl[1], Michel Nussenzweig[2], Walid Heneine[1]
[1]CDC, Atlanta, GA, USA, [2]The Rockefeller University, New York, NY, USA, [3]Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: Passive immunization using highly potent broadly neutralizing antibodies (bNAbs) against HIV is a promising strategy for pre-exposure prophylaxis. In preclinical models, bNAbs 3BNC117 and 10-1074, which target the CD4 binding site and V3 glycan supersite on HIV Env, respectively, have been shown to protect macaques against rectal SHIV challenge. Here we compared the protective efficacy of a single subcutaneous injection of these antibodies against repeated vaginal SHIV challenges in macaques.

Methods: Groups of six female rhesus macaques were injected subcutaneously once with either a single bNAb (3BNC117, 10mg/kg) or two bNAbs (3BNC117 and 10-1074, 10mg each/kg) and repeatedly challenged (once weekly) intravaginally with 300 $TCID_{50}$ $SHIV_{AD8-EO}$, until systemic SHIV infection was confirmed via a plasma viral load assay. Three control macaques were challenged similarly. All study macaques received DMPA (30mg) intramuscularly at 2 weeks before the first SHIV challenge (corresponding to 1 week before bNAb injection in treatment groups), and every 4 weeks thereafter to normalize SHIV susceptibility. Longitudinal plasma samples were assayed to determine bNAb concentrations.

Results: Maximum bNAb concentrations were observed in plasma at 1 week post-administration. Mean Cmax for 10-1074 (38.8ug/ml) was ~6 times as high as 3BNC117 (6.5ug/ml; P=0.001, t-test). Estimated plasma half-life of 3BNC117 ($t_{1/2}$ = 10.7+/-2.9 days) was similar to 10-1074 ($t_{1/2}$ = 8.4+/-1.9 days). Macaques administered 3BNC117 alone exhibited significantly delayed SHIV acquisition (median of 5 challenges to infection vs 2 in untreated controls, P=0.002, Log-rank test). Initial detection of SHIV viremia correlated with plasma 3BNC117 levels ≤0.8ug/ml (mean = 0.5+/-0.2 ug/ml). Animals that received 10-1074 in combination with 3BNC117 exhibited significantly greater protection against SHIV acquisition (median 11.5 challenges) compared to 3BNC117-alone (P=0.0005) or to untreated controls (P=0.002, Log-rank test). In this group, first SHIV acquisition corresponded to a plasma 10-1074 level <0.4ug/ml, at which time 3BNC117 was undetectable in all animals.

Conclusion: One subcutaneous administration of 3BNC117 singly, or in combination with 10-1074, conferred significant protection in macaques against repeated vaginal challenges with SHIV. The greater protection observed in the 2-bNAb group appears due to the longer persistence of 10-1074.

83 LONG-ACTING CABOTEGRAVIR PROTECTS MACAQUES AGAINST REPEATED PENILE SHIV EXPOSURES

Charles Dobard[1], Natalia Makarova[1], Kenji Nishiura[1], Mara Sterling[1], Chuong Dinh[1], James Mitchell[1], David A. Garber[1], William Spreen[2], Walid Heneine[1], Gerardo Garcia-Lerma[1]
[1]CDC, Atlanta, GA, USA, [2]ViiV Healthcare, Research Triangle Park, NC, USA

Background: Cabotegravir long-acting (CAB LA) is an investigational HIV integrase inhibitor that is currently in clinical development as a PrEP agent. In pre-clinical proof-of-concept studies in macaques, CAB LA was highly effective against rectal, vaginal, and intravenous infection with simian HIV (SHIV). Penile transmission accounts for nearly one-half of all HIV infections globally, and whether CAB LA can also protect against this important route has not been adequately addressed primarily due to the lack of a validated in vivo model of penile transmission. Here we used a novel macaque model of repeated penile SHIV exposures to investigate the efficacy of CAB LA against penile infection.

Methods: Rhesus macaques (n=22) were exposed once a week (up to 12 weeks) to low doses of SHIV162p3 administered into the foreskin pouch (200 TCID50) and urethra (16 TCID50). Of these, 6 received CAB LA (50 mg/kg) and 10 received no drug. CAB LA was administered intramuscularly every 4 weeks to sustain plasma drug levels above 4 times the protein-adjusted IC90 (4xPA-IC90) to model plasma concentrations in humans treated with CAB (600 mg) every 8 weeks. For model validation, an additional group of 6 macaques received oral FTC/TDF (20/22 mg/kg) 24h before and 2h after each penile SHIV exposure. Infection was monitored weekly by PCR amplification of SHIV RNA in plasma. Plasma CAB levels were measured weekly by HPLC.

Results: All 10 controls were infected after a median of 3 penile SHIV exposures (range=1-12). In contrast, 5 of 6 animals that received CAB LA were SHIV negative during 12 penile challenges and remain aviremic 5 weeks after the last challenge (estimated efficacy of 94%, p=0.0003). Plasma CAB concentrations during the challenge period (median = 2,175 ng/ml, range = 303-5,025) remained above the 4xPA-IC90 (664 ng/ml) in all 5 protected animals. Plasma CAB levels in the breakthrough infection fell below the 4xPA-IC90 at weeks 4, 8, and the week prior to detecting SHIV RNA in plasma (week 12). Consistent with clinical efficacy in men, oral FTC/TDF was highly protective with 5 of 6 animals uninfected after 12 SHIV challenges (estimated efficacy of 94%, p=0.0007).

Conclusion: Monthly injections of CAB LA was as effective as oral FTC/TDF in a macaque model of penile SHIV infection that mimics high-risk HIV exposures in men. The high efficacy by CAB LA was related to high plasma drug concentrations that remained above 4xPA-IC90. These data support advancement of CAB LA as a PrEP candidate for men.

84 GRIFFITHSIN/CARRAGEENAN INSERTS PREVENT SHIV, HSV-2, AND HPV INFECTIONS IN VIVO

Nina Derby[1], Manjari Lal[2], Meropi Aravantinou[1], Larisa Kizima[1], Patrick Barnable[1], Aixa Rodriguez[1], Manshun Lai[2], Asa Wesenberg[1], Shweta Ugaonkar[1], Brooke Grasperge[3], James Blanchard[3], Agegnehu Gettie[4], Natalia Teleshova[1], Jose A. Fernandez-Romero[5], Thomas M. Zydowsky[1]
[1]Population Council, New York, NY, USA, [2]PATH, Seattle, WA, USA, [3]Tulane National Primate Research Center, Covington, LA, USA, [4]Aaron Diamond AIDS Research Center, New York, NY, USA, [5]Borough of Manhattan Community College, New York, NY, USA

Background: Griffithsin (GRFT) is a potent HIV entry inhibitor (EC_{50} = 1.6 ng/ml in vitro). We have demonstrated that the GRFT/carrageenan (CG) combination provides synergistic antiviral activity against herpes simplex virus (HSV) and inhibits human papillomavirus (HPV).
Methods: The pharmacokinetics (PK) and antiviral efficacy of GRFT/CG fast dissolving inserts (FDIs) were examined in mice (PK and efficacy against HSV-2 and HPV) and rhesus macaques (RMs, for PK and efficacy against SHIV). Mouse-sized (0.1 mg GRFT, 0.3 mg CG) and RM-sized (1 mg GRFT, 3 mg CG) FDIs were inserted vaginally in depot medroxyprogesterone acetate (DMPA)-treated animals. In PK studies, vaginal fluid (VF, from mice and RMs) and plasma (from RMs) were collected at baseline and different time-points following FDI insertion. GRFT was quantified by ELISA. For efficacy testing, the same formulations in addition to placebo controls (hydroxyethyl cellulose or CG only) were evaluated in highly stringent vaginal models (SHIV-SF162P3 in RMs, HSV-2 and HPV16 PsV in mice). Formulations were applied vaginally 4 hours before virus challenge in each model. Statistical significance was assessed by Fisher's exact test (SHIV and HSV-2) and Mann Whitney U test (HPV).
Results: The GRFT/CG FDIs significantly protected RMs against SHIV-SF162P3 infection: 8/10 uninfected RMs in the GRFT/CG group vs. 0/10 uninfected in the CG group, 80% protection, p=0.0003 vs. CG. Similarly, the GRFT/CG FDIs protected mice (6 mice per formulation) against HSV-2 (60-73% uninfected in the GRFT/CG FDI group, p <0.0052 vs. placebo) and HPV PsV (100% uninfected in the GRFT/CG FDI group, p<0.0001 vs. placebo). GRFT was not detected in RM plasma. GRFT concentrations above 2 µg/mL (270x the EC_{90}) were found in both mouse and RM VF 4 hours after FDI insertion.
Conclusion: GRFT/CG FDIs showed potent and broad spectrum in vivo activity against three incurable viral pathogens. The FDIs significantly protected RMs from SHIV-SF162P3 and mice from HSV-2 and HPV16 PsV infections, showing excellent safety profiles at 4 hours post dosing. These data support the further preclinical and clinical development of GRFT/CG FDIs.

85 ORAL FTC/TAF COMBINATION PREVENTS VAGINAL SHIV INFECTION IN PIGTAIL MACAQUES

Ivana Massud[1], Mian-er Cong[1], Susan Ruone[1], James Mitchell[1], Frank Deyounks[1], Angela Holder[1], Chuong Dinh[1], James F. Rooney[2], Darius Babusis[2], Yeojin Park[2], Scott McCallister[2], Christian Callebaut[2], Walid Heneine[1], Gerardo Garcia-Lerma[1]
[1]CDC, Atlanta, GA, USA, [2]Gilead Sciences, Inc, Foster City, CA, USA

Background: Tenofovir alafenamide (TAF) is a novel tenofovir prodrug with improved properties relative to tenofovir disoproxil fumarate (TDF) that makes it an attractive candidate for PrEP. We recently showed that the combination of TAF and emtricitabine (FTC) was highly effective in preventing rectal simian HIV (SHIV) infection in rhesus macaques. Here we investigated the efficacy of FTC/TAF against vaginal SHIV infection
Methods: The pharmacokinetic profile of TAF was studied at first dose. Tenofovir (TFV) was measured in plasma and vaginal and rectal secretions. Intracellular tenofovir di-phosphate (TFV-DP) and FTC-triphosphate (FTC-TP) were measured in PBMCs and/or rectal and vaginal biopsies. The efficacy of FTC/TAF in preventing vaginal infection was investigated using an established model of vaginal SHIV exposure consisting of up to 16 once-weekly virus challenges with 50 TCID50 of SHIV162p3. Six macaques received FTC/TAF (20 and 1.5 mg/kg, respectively) orally 24h before and 2h after each weekly virus exposure and 5 received placebo. Infection was monitored by serology and RT-PCR.
Results: As observed in humans, plasma TFV levels with 1.5 mg/kg of TAF were low (Cmax = 17 [5-42] ng/ml). In PBMCs, TFV-DP concentrations peaked at 5-24 hr (median = 154 [34-295] fmol/106cells) and gradually declined with a half-life of 38 (33-122) hr. TFV exposure in vaginal fluids (AUC0-24h = 2,001 [216-11,569] ng*h/mL) was lower than in rectal fluids (17,205 [216-313,122] ng*h/mL) although the difference was not statistically significant (p = 0.38). 24h after dosing, TFV-DP levels in vaginal and rectal tissues were similar (9 [6-10] and 11 [7-19]) fmol/mg, respectively, p = 0.25). All 5 untreated controls exposed vaginally to SHIV were infected after a median of 5 [2-14] exposures. In contrast, 5 of the 6 animals that received FTC/TAF remained uninfected after 16 virus challenges (p = 0.012 log-rank test). All the protected animals had detectable TFV-DP and FTC-TP in PBMCs (median = 237 [123-829] and 1837 [1256-2653] fmols/106 cells, respectively) at the time of virus exposure. In contrast, the PrEP breakthrough animal only had detectable FTC-TP (median=1499 fmols/106 cells).
Conclusion: A clinically equivalent dose of FTC/TAF administered orally to macaques 24h before and 2h after vaginal SHIV exposure prevented infection to a degree similar to that previously observed with FTC/TDF. These results support the evaluation of FTC/TAF for PrEP against vaginal HIV infection.

86 BY RACE/ETHNICITY, BLACKS HAVE HIGHEST NUMBER NEEDING PrEP IN THE UNITED STATES, 2015

Dawn K. Smith, Michelle Van Handel, Jeremy A. Grey
CDC, Atlanta, GA, USA

Background: To effectively measure progress in delivering PrEP, it is necessary to have national and subnational estimates of the number of persons with indications for its use that account for racial/ethnic disparities and differences in HIV infection rates by transmission risk group (risk group).
Methods: We used data on new HIV diagnoses and population-based estimates of risk group size to derive estimated numbers of persons with indications by jurisdiction. For each jurisdiction, we multiplied the estimated number of men who have sex with men (MSM) by the proportion of MSM with indications to calculate the number of MSM with indications. For heterosexually active adults (HET) and persons who inject drugs (PWID), we calculated ratios of the numbers of HIV diagnoses in 2015 attributed to HET or PWID to the number attributed to MSM. The ratios were multiplied by the number of MSM with indications to calculate the numbers of HET and PWID with indications. Proportions of HIV diagnoses in 2015 by race/ethnicity or sex (HET only) were multiplied by estimates for each risk group to calculate numbers with indications by risk group, race/ethnicity and sex. We summed subnational estimates to produce national estimates.
Results: Nationally, an estimated 1.1 million persons had indications in 2015, of whom 500,340 were black (44%), 303,230 were white, 282,260 were Hispanic/Latino (Latino), and 58,720 were of other race/ethnicities (Table). Of 813,970 MSM (71% of total) with indications, 38% were black, 29% were white, and 27% were Latino. Of 258,080 HET with indications, 64% were black, 18% were Latino, and 14% were white; while 68% (176,670) were female and 32% were male. Among 72,510 PWID with indications, 39% were white, 37% were black, and 21% were Latino. States in the South and DC had the highest proportions of blacks with indications.
Conclusion: Blacks comprised the highest number of persons with PrEP indications overall and among MSM and HET. In light of other studies showing that PrEP use is low in black persons, these findings strongly support the highest priority for increasing awareness of, access to, and utilization of PrEP by this group. All MSM, and especially black MSM, must remain a high priority for PrEP delivery because of their high numbers compared to other risk groups. Use of these estimates as denominators will allow for the assessment of PrEP coverage and impact on HIV incidence by race/ethnicity and risk group over time at subnational levels.

Table: Estimated numbers of adults with indications for PrEP, by transmission risk group and race/ethnicity, United States, 2015

	Transmission Risk Group			
	MSM	HET	PWID	Total
	# (% of total MSM)	# (% of total HET)	# (% of total PWID)	# (% of total with indications)
Black/African American, non-Hispanic	309,190 (38.0)	164,660 (63.8)	26,490 (36.5)	500,340 (43.7)
Hispanic/Latino	220,760 (27.1)	46,580 (18.0)	14,920 (20.6)	282,260 (24.7)
White, non-Hispanic	238,670 (29.3)	36,540 (14.2)	28,020 (38.6)	303,230 (26.5)
Total	813,970 (71.1)	258,080 (22.5)	72,510 (6.3)	1,144,550 (100)

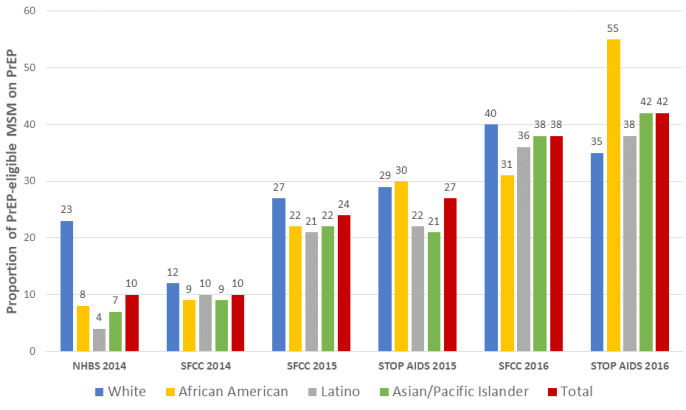
Notes. PrEP = preexposure prophylaxis (daily oral tenofovir disoproxil fumarate+emtricitabine); MSM= gay, bisexual, or other men who have sex with men; HET= heterosexually active adults; PWID = persons who inject drugs; Row and column percentages do not add to 100 because of lack of a row for "other race/ethnicity".

87 GETTING TO ZERO NEW HIV DIAGNOSES IN SAN FRANCISCO: WHAT WILL IT TAKE?

Susan P. Buchbinder[1], Stephanie E. Cohen[1], Jen Hecht[2], Ling Hsu[1], Robert P. Kohn[1], Henry F. Raymond[1], Albert Y. Liu[1], Hyman Scott[1], Oliver Bacon[1], Tracey Packer[1], Susan Philip[1], Diane V. Havlir[3], Susan Scheer[1]
[1]San Francisco Department of Public Health, San Francisco, CA, USA, [2]San Francisco AIDS Foundation, San Francisco, CA, USA, [3]University of California San Francisco, San Francisco, CA, USA

Background: San Francisco's Getting to Zero (SF GTZ) initiative aims to reduce new HIV diagnoses by 90% from 2013-2020; SF GTZ protocols are replicated by other cities. This analysis reports on progress toward this goal and potential facilitators and barriers.
Methods: Data are collected on SF residents with newly diagnosed HIV using active and passive surveillance of mandatory lab reporting. Data on PrEP use came from men who have sex with men (MSM) in the 2014 National HIV Behavioral Surveillance Survey (NHBS, n=411), a community-based survey (STOP AIDS, n=1049 in 2015, n=910 in 2016) and the municipal sexually transmitted disease clinic (SFCC, n=4954 in 2014, n=5224 in 2015, n=5432 in 2016). MSM were considered eligible for PrEP if they were not known to be HIV infected and reported condomless anal sex, a sexually transmitted infection, or an HIV positive partner in the prior 12 months.
Results: New HIV diagnoses declined 43%, from 392 in 2013 to 223 in 2016. In 2016, 79% of new diagnoses were in MSM, 11% in cis women and 2% in trans women. HIV diagnosis rates/100,000 men in 2016 were highest in African Americans (96) and Latinos (77), and lowest in Whites (39) and Asian/Pacific Islanders (25). Median time from diagnosis to viral suppression declined from 134 days to 61 days from 2013-2016. Among those living with HIV who were last known to reside in SF, 73% were virally suppressed at the end of 2015 but viral suppression was less common among women (66%), African Americans (67%), Latinos (69%), persons under 50 years (66%) and the homeless (31%) ($p<0.0001$ for all). The estimated proportion of PrEP-eligible MSM reporting PrEP use was similar between datasets and increased from 10% in 2014 to 38-42% in 2016 (Figure). Uptake increased in all racial/ethnic groups over time, although Latino MSM had consistently lower rates than average in all surveys except SFCC 2014. The largest cohort of African American MSM was in SFCC; uptake in that group was lower than for all others in 2016. We estimate the number of eligible MSM on PrEP in SF increased from about 4700 in 2014 to 12,300 in 2016.
Conclusion: New HIV diagnoses have declined at a much faster rate in SF than the national average, likely a result of faster viral suppression after diagnosis and increased PrEP uptake in recent years. However, disparities in viral suppression and PrEP uptake suggest slower progress in people of color, younger people, women and the homeless; population-specific efforts will be required to achieve the GTZ SF 2020 goals.

Proportion of PrEP-eligible MSM reporting PrEP use in the prior 12 months



88 RAPID REDUCTION IN HIV DIAGNOSES AFTER TARGETED PrEP IMPLEMENTATION IN NSW, AUSTRALIA

Andrew Grulich[1], Rebecca J. Guy[1], Janaki Amin[2], Heather-Marie Schmidt[3], Christine Selvey[3], Jo Holden[3], Karen Price[4], Robert Finlayson[5], Mark Bloch[6], Iryna Zablotska[1], Fengyi Jin[1], David Smith[7], Anna McNulty[8], David A. Cooper[1]
[1]University of New South Wales, Sydney, NSW, Australia, [2]Macquarie University, North Ryde, NSW, Australia, [3]New South Wales Ministry of Health, Sydney, NSW, Australia, [4]ACON, Sydney, NSW, Australia, [5]Taylor Square Private Clinic, Sydney, NSW, Australia, [6]Holdsworth House Medical Practice, Sydney, NSW, Australia, [7]North Coast HIV Sexual Health Services, Lismore, NSW, Australia, [8]Sydney Sexual Health Centre, Sydney, NSW, Australia

Background: Randomized trials of pre-exposure prophylaxis (PrEP) in men who have sex with men (MSM) have reported efficacy of more than 85%. Modelling predicts PrEP will have greatest population-level efficacy if rapidly targeted, with high coverage, to those at high risk. In New South Wales (NSW), more than 80% of HIV diagnoses occur in MSM. Despite substantial increases in testing and treatment since 2012, and the state approaching the UNAIDS 90/90/90 targets, annual HIV diagnoses varied little over the decade to 2016.
Methods: The expanded PrEP Implementation in Communities in NSW study (EPIC-NSW) is an open-label implementation study of the use of co-formulated TDF/FTC to prevent HIV. Commencing March 1 2016, we aimed to recruit all estimated 3700 MSM at high-risk of HIV in NSW by end 2016, in over 20 clinics across the state. High-risk eligibility criteria were based on local epidemiologic data. Co-primary outcomes of the study are (a) HIV incidence among study participants, collected by electronic data capture from clinic data management systems and (b) state-wide HIV diagnoses in MSM, utilizing NSW Ministry of Health HIV surveillance data. HIV surveillance data were reported as (a) all diagnoses and (b) early infection, defined as likely HIV infection in the last 12 months, based on HIV testing history and/or clinical and/or laboratory diagnosis of recent infection.
Results: The initial target of 3700 high-risk MSM was reached in October 2016, with an average monthly recruitment of 499 (range: 442-555). Recruitment is continuing (currently 7293). By September 2017 only one HIV seroconversion in a study participant was documented. In the first half-year of 2017 there were 101 HIV diagnoses in MSM in NSW, 35% lower than the 156 diagnoses in the half-year immediately prior to commencement of recruitment (June-Dec 2015). This was the lowest half-yearly number of HIV diagnoses in MSM since HIV surveillance commenced in NSW in 1985. Early HIV infections in MSM declined from 82 to 46, a 44% decrease.
Conclusion: The high-level, targeted and rapid roll-out of PrEP in NSW led to a 35% decline in state-wide HIV diagnoses in MSM, and a 44% decline in early HIV infections in MSM, to levels unprecedented since the beginning of the HIV epidemic. This was achieved less than one year after the target recruitment was reached. In a concentrated epidemic with high testing and treatment coverage, PrEP scale up led to a rapid decline in HIV transmission at the population level.

89LB LOW DOSE MK-8591 PROTECTS RHESUS MACAQUES AGAINST RECTAL SHIV INFECTION

Martin Markowitz[1], Agegnehu Gettie[1], Leslie St. Bernard[1], Hiroshi Mohri[1], Brooke Grasperge[2], James Blanchard[2], Li Sun[3], Kerry Fillgrove[4], Daria Hazuda[4], Jay Grobler[4]
[1]Aaron Diamond AIDS Research Center, New York, NY, USA, [2]Tulane National Primate Research Center, Covington, LA, USA, [3]Merck & Co, Inc, Upper Gwynedd, PA, USA, [4]Merck & Co, Inc, West Point, PA, USA

Background: MK-8591 (4'-ethynyl-2-fluoro-deoxyadenosine; EFdA), a nucleoside reverse transcriptase translocation inhibitor (NRTTI), was previously shown to completely protect rhesus macaques (RM) against SHIV infection following intrarectal (IR) challenge when dosed at 3.9 mg/kg weekly. At this dose, the mean intracellular MK-8591-triphosphate (TP) concentration of 805 fmol/10Λ6 PBMCs at time of challenge exceeds the lowest MK-8591-TP C168hr that demonstrated potent antiviral activity in HIV infected patients. To determine the lowest drug levels that confer protection, RMs were challenged at progressively lower doses until protection was no longer observed.
Methods: The eight male RM that had been successfully treated with 3.9 mg/kg MK-8591 after 20 weeks (w) were dosed with 1.3 mg/kg MK-8591 orally on day 0 and qw for 6 doses. All animals were again challenged IR with 1 mL of 50TCID50 of SHIVC109P3 on day 6 and weekly thereafter for up to 4 challenges or until infection was confirmed. Prior to challenge, blood was drawn for virology and PK. Infection was confirmed by real-time RT PCR in plasma. Proviral DNA was measured qw by PCR and virus-specific antibody responses were assessed. Intracellular levels of MK-8591- TP were measured by LC/MS/MS. After a 4 w washout, the treatment sequence was repeated on uninfected RM, (0.43 mg/kg weekly for 6 doses) with challenge on day 6 and weekly for up to 4 challenges or

until infection was confirmed. After 10 w, this was repeated on the remaining uninfected RM at a dose of 0.1 mg/kg.

Results: All 8 animals remained uninfected after challenges at the 1.3 & 0.43 mg/kg dosing levels. At 0.1 mg/kg, 2/8 animals became infected, with one animal infected after 3 challenges and the other after 4 challenges. Mean levels of intracellular MK-8591-TP at the time of challenge were 282 and 102 fmol/10^6 PBMCs at the 1.3 and 0.43 mg/kg dosing levels, respectively. At the 0.1 mg/kg dose MK-8591-TP levels are estimated to be ~24 fmol/10^6 PBMCs.

Conclusion: In rhesus macaques MK-8591 completely protects against SHIV infection at weekly doses of 1.3 and 0.43 mg/kg and is partially protective at 0.1 mg/kg (HR 7.2, p=0.0004). MK-8591-TP levels that are protective in this model are achievable in humans at weekly doses of less than 250 µg weekly or 10 µmg daily, suggesting MK-8591 utility in extended duration prophylaxis against HIV infection.

90 HIV TREATMENT, PREVENTION, AND INCIDENCE IN A HYPERENDEMIC UGANDAN FISHING COMMUNITY

Joseph Kagaayi[1], Gertrude Nakigozi[1], Godfrey Kigozi[1], Mary K. Grabowski[2], Victor Ssempijja[3], Fred Nalugoda[1], Ronald H. Gray[2], Robert Ssekubugu[1], Caitlin E. Kennedy[2], Thomas C. Quinn[3], David Serwadda[4], Maria Wawer[2], Steven J. Reynolds[3], Larry W. Chang[2]

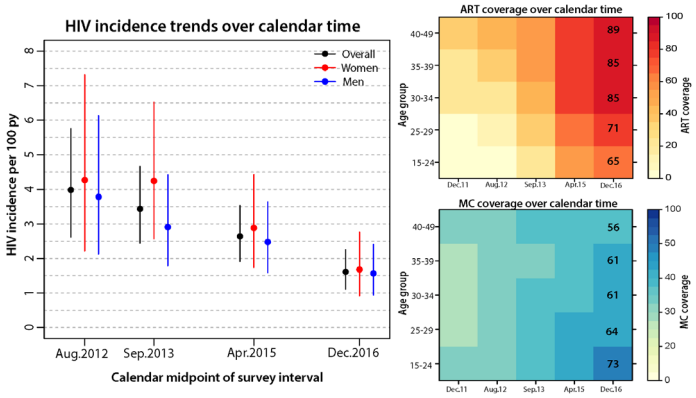
[1]Rakai Health Sciences Program, Kalisizo, Uganda, [2]Johns Hopkins University, Baltimore, MD, USA, [3]NIAID, Bethesda, MD, USA, [4]Makerere University College of Health Sciences, Kampala, Uganda

Background: In a prospective population-based cohort study conducted in an HIV hyperendemic fishing community (HIV prevalence ~40%), we measured trends in uptake of antiretroviral therapy (ART) and voluntary medical male circumcision (MC), population-level viral load suppression, sexual risk behaviors, and HIV incidence.

Methods: From Nov 2011 to Feb 2017, four surveys were conducted in a fishing community on Lake Victoria in Rakai, Uganda as part of an open cohort of all consenting persons aged 15-49. We assessed trends in self-reported ART/MC coverage, population-level HIV viral load suppression (proportion of HIV-positive population with <1000 copies/ml), sexual risk behaviors, and HIV incidence. Poisson multivariate regression with generalized estimating equations and robust variance estimators was used to estimate incidence rate ratios (IRR) and 95%CI of HIV incidence comparing the first to the final survey interval.

Results: 5005 individuals participated in the cohort, including 1823 HIV-negative persons with at least one follow-up who contributed 5188 person-years (py) and 134 incident HIV cases. Over the study period, ART coverage increased among all HIV-infected participants from 19% (95%CI: 16-22%) to 81% (95%CI:75-87%), and MC coverage increased among all men from 39% (95%CI: 35-42%) to 63% (95%CI: 59-67%). ART and MC increases occurred in all age groups (Figure). Population-level HIV viral suppression was 78% (95%CI: 72-83%) by study end. Sexual behaviors remained unchanged. Overall HIV incidence declined (Figure) from 3.98/100 py to 1.61/100 py (adjIRR=0.46; 95%CI: 0.27-0.80). Declines in HIV incidence were similar in men (3.78/100py to 1.57/100py) and women (4.27/100py to 1.68/100py). Declines in HIV incidence were observed in persons aged 15-24 years (5.53/100py to 1.87/100py), 25-34 years (3.56/100py to 1.56/100py) and 35+ years (2.96/100py to 1.47/100pys). Overall, HIV prevalence declined from 41% to 36% (p=0.002). Figure: HIV incidence trends; ART and MC coverage over calendar time by age group.

Conclusion: Over about 5 years, HIV incidence significantly declined by approximately 54% as ART and MC coverage increased in a hyperendemic fishing community. These results suggest that HIV treatment and prevention interventions can be rapidly scaled and have substantial population-level impact on HIV incidence in high prevalence settings.



91 PROGRESS TOWARD 90-90-90: 2016 LESOTHO POPULATION-BASED HIV IMPACT ASSESSMENT RESULTS

Kyaw Thin[1], Koen Frederix[2], Stephen McCracken[3], Andrea Low[4], Hetal Patel[3], Nahima Ahmed[4], Bharat S. Parekh[3], Jessica E. Justman[4], Amee M. Schwitters[5]

[1]Ministry of Health, Maseru, Lesotho, [2]ICAP at Columbia University–Lesotho, Maseru, Lesotho, [3]CDC, Atlanta, GA, USA, [4]ICAP at Columbia University, New York, NY, USA, [5]CDC, Maseru, Lesotho

Background: Lesotho is severely impacted by the HIV epidemic. As the leading cause of premature death, HIV has contributed to Lesotho reporting the shortest life expectancy at birth among 195 countries and territories. In 2016, as part of the national response, Lesotho became the first country in sub-Saharan Africa to implement Test and Start. The 2016 Lesotho Population-based HIV Impact Assessment (LePHIA) was conducted nationwide to measure HIV prevalence, incidence, and viral load suppression. Progress towards meeting the UNAIDS 90-90-90 targets among adults 15-59 years of age is presented here.

Methods: A nationally representative sample of eligible households was conducted in 418 enumeration areas between November 2016 and May 2017; analyses account for the survey design. Consenting participants provided socio-demographic information and blood samples for rapid HIV testing as per the national algorithm, with confirmation of positive results using a supplemental assay and viral load were performed on all HIV+ samples at central labs. Viral load suppression (VLS) was defined as an HIV RNA <1000 cp/ml.

Results: In total, 11,682 adults provided interviews and blood samples (response rate: ~90%). Interview and blood draw participation among eligible adults was higher among females than males (91% v. 88% and 95% v. 87%, respectively). Among participants, 25.6% of adults 15-59 (female 30.4%, male 20.8%) were HIV infected. Viral load suppression among all HIV positive adults regardless of ART use was 67.6% (female 70.6%, male 63.4%). Among adults who tested HIV positive during the survey, 77.2% reported already knowing their HIV status (female 81.5%, male 71.0%) (1st 90), 90.2% (female 90.6%, male 89.4%) of PLHIV who reported knowing their status also reported ART use (2nd 90), and 88.3% (female 88.3%, male 88.4%) of these PLHIV who reported ART use were virally suppressed (3rd 90).

Conclusion: Although HIV prevalence remains high in Lesotho, significant progress is being made towards meeting the UNAIDS 90-90-90 targets. The high prevalence of reported ART use among HIV+ individuals and high VLS prevalence provide evidence of an effective national HIV response, although differences remain between males and females. Enhanced testing is needed to identify persons unaware of their HIV+ positive status, particularly among males and youth. Continued support of innovative prevention and treatment programs are needed to reach epidemic control in Lesotho.

Indicator	Males	Females	Total
HIV prevalence among adults 15-59, % [95% CI]	20.8 [19.6,22.0]	30.4 [29.2,31.5]	25.6 [24.7,26.4]
Viral load suppression (VLS) all HIV positive adults 15-59, % [95% CI]	63.4 [60.4,66.4]	70.6 [68.3,72.8]	67.6 [65.8,69.5]
90-90-90 Indicators			
HIV+ adults 15-59 who report knowing their status (1st 90), % [95% CI]	71.0 [68.2,73.9]	81.5 [79.7,83.3]	77.2 [75.6,78.8]
Self-reported ART use among HIV+ adults 15-59 who report knowing their status (2nd 90), %, [95% CI]	89.4 [87.1,91.7]	90.6 [88.9,92.3]	90.2 [88.7,91.6]
VLS among HIV+ adults 15-59 who report ART use and knowing their status (3rd 90), % [95% CI]	88.4 [85.5,91.2]	88.3 [86.4,90.1]	88.4 [86.7,89.9]

92 CLINICAL PRESENTATION OF HIV DIFFERS BY AGE IN VACS (2010-2015)

Amy C. Justice[1], Kirsha S. Gordon[2], Shelli Feder[2], Neel R. Gandhi[3], Lydia A. Barakat[2], Maria Rodriguez-Barradas[4], Vincent C. Marconi[3], Sheldon T. Brown[5], Julie A. Womack[2], Janet Tate[2]

[1]VA Connecticut Healthcare System, West Haven, CT, USA, [2]Yale University, New Haven, CT, USA, [3]Emory University, Atlanta, GA, USA, [4]Michael E. DeBakey VA Medical Center, Houston, TX, USA, [5]James J. Peters VA Medical Center, Bronx, NY, USA

Background: Many clinicians tell concerning stories about older people being diagnosed with advanced HIV after undergoing extensive and extended workups for alternative causes at respected medical centers. While provider's failure to consider HIV may explain some of the problem, we ask at time of HIV diagnosis: 1) Does HIV present differently among older compared with younger individuals? and 2) Among 60+ year old individuals, do conditions co-occurring at diagnosis differ from uninfected controls?

Methods: Using a previously validated algorithm requiring detectable HIV-1 RNA prior to ART initiation, we reviewed incident HIV diagnoses from 2010-2015 within the Veterans Healthcare System and compared with demographically matched uninfected controls. Electronic health record data including diagnostic codes and laboratory data were obtained from the national corporate data warehouse. AIDS defining illnesses were identified using validated ICD-9 codes and present if assigned within 1 year before or 6 months after a confirmed HIV diagnosis.

Results: 3000 incident HIV infections were matched to 5449 controls with complete data. Despite HIV+ diagnosed at 60+ years having been in care twice as long as HIV+ diagnosed under 40 years (5 vs. 10 years, p<0.001), those diagnosed at 60+ years were 1.5-2.4 times more likely to have advanced HIV disease indicated by AIDS defining conditions, CD4 count <200/ ml., or HIV-1 RNA>106 /ml (Table, p<0.001). Compared to HIV+ diagnosed when < 40 years of age, bacterial pneumonia, herpes zoster, anemia, lymphocytopenia, and thrombocytopenia were 2-3 times more common at diagnosis among HIV+ 60+ years. While these conditions also increased with age for controls, they remained 2-7 times more common among HIV+ than uninfected 60+ year olds.

Conclusion: At the time of diagnosis with HIV, older people present with more advanced disease than younger counterparts. Associated conditions including: pneumonia, herpes zoster, anemia, lymphocytopenia, and thrombocytopenia are more common among HIV+ at all ages, but increase with age among both HIV+ and controls which may contribute to the delay in HIV diagnosis.

	Age and HIV Status									
	<40 yrs.		40-49 yrs.		50-59 yrs.		60+ yrs.		p for trend	
Condition	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
n	855	1526	681	1221	894	1632	570	1070	3000	5449
Any AIDS illness	8.4%		12.3%		16.6%		19.8%		p<0.001	
CD4 Count<200/ ml.	18.6%		32.4%		39.3%		42.6%		p<0.001	
HIV-1RNA>106/ml.	28.9%		35.6%		35.1%		42.5%		p<0.001	
Bact. Pneumonia	6.6%	1.3%	8.5%	2.0%	11.9%	2.3%	13.7%	2.1%	p<0.001	p=0.05
Herpes zoster	2.9%	0.1%	5.9%	0.6%	6.2%	0.4%	6.8%	0.9%	p<0.001	p=0.01
Lymphocytes<150 K/ml.	11.4%	3.2%	19.4%	5.9%	23.8%	5.9%	22.5%	9.9%	p<0.001	p<0.001
Hemoglobin<12 g/dL	9.6%	1.5%	15.8%	2.4%	19.8%	5.3%	26.3%	9.1%	p<0.001	p<0.001
Platelets<100 K/ml.	1.7%	0.1%	3.1%	0.6%	5.1%	1.5%	5.2%	2.6%	p<0.001	p<0.001

93 THE RAPID ART PROGRAM INITIATIVE FOR HIV DIAGNOSES (RAPID) IN SAN FRANCISCO

Oliver Bacon[1], Jennie C. Chin[1], Ling Hsu[1], Stephanie E. Cohen[1], Darpun Sachdev[1], Diane Jones[2], Jonathan Fuchs[1], Susan Scheer[1], Susan P. Buchbinder[1], Diane V. Havlir[2]

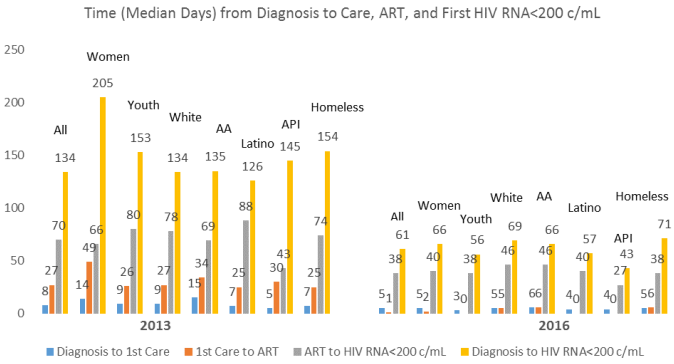
[1]San Francisco Department of Public Health, San Francisco, CA, USA, [2]University of California San Francisco, San Francisco, CA, USA

Background: Early virologic suppression after HIV infection improves individual health outcomes and decreases onward transmission. In 2015 San Francisco Getting to Zero (SFG2Z) adapted the Citywide RAPID initiative, to link all new HIV cases to care within 5 days of diagnosis and start ART at the first care visit. This analysis compares time from diagnosis to care enrollment, ART initiation, and virologic suppression in the post-RAPID (2016) to the pre-RAPID care era (2013), by gender, race/ethnicity, age, and housing.

Methods: HIV providers were trained on the RAPID protocol through passive (medical grand rounds, public SFG2Z consortium meetings) and active (public health detailing) capacity building, with sites caring for vulnerable populations prioritized early. Health Department (SFDPH) and community linkage navigators were trained on RAPID and made aware of RAPID-trained HIV clinicians. Dates of HIV diagnosis, first care visit, ART initiation, and first virologic suppression (HIV RNA<200 c/mL) were abstracted from the SFDPH HIV case registry.

Results: From 2013 to 2016, median time from diagnosis to first virologic suppression in San Francisco decreased 54%, from 134 to 61 days. Decreases were seen across the RAPID continuum, in time from diagnosis to care (38%, from 8 to 5 days), care to ART initiation (96%, from 27 to 1 day), and ART to first suppression (46% from 70 to 38 days). Among subpopulations (figure), by 2016, time from diagnosis to care ranged from 3 days (youth 13-29 years) to 6 days (African Americans); time from care to ART was lowest among youth, Latinos, and Asians/Pacific Islanders (0 days), and highest among African-Americans and the homeless (6 days), despite improvements in these latter two groups, with 82% and 76% decrease in 2013-2016, respectively.

Conclusion: During a multisector initiative to optimize ART initiation across San Francisco, time from diagnosis to first virologic suppression was cut by more than 50%. Immediate ART initiation at care was achieved across many populations, but challenges remain in subpopulations such as the homeless.



94 SAME-DAY ART INITIATION AFTER HOME-BASED HIV TESTING: A RANDOMIZED CONTROLLED TRIAL

Niklaus D. Labhardt[1], Isaac Ringera[2], Thabo I. Lejone[2], Thomas Klimkait[3], Josephine Muhairwe[2], Alain Amstutz[1], Tracy R. Glass[1]

[1]Swiss Tropical and Public Health Institute, Basel, Switzerland, [2]SolidarMed, Luzern, Switzerland, [3]University of Basel, Basel, Switzerland

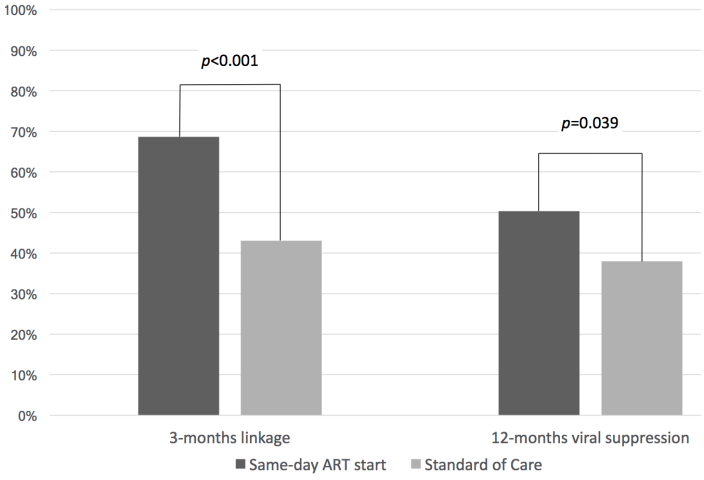
Background: In sub-Saharan Africa, home-based HIV testing is frequently used to increase awareness of HIV status. However, effectiveness of this approach is limited by low percentages of individuals tested positive who link subsequently to care and start antiretroviral therapy (ART). The CASCADE trial tests if same-day home-based ART initiation improves linkage to care, retention in care and viral suppression in rural Lesotho, Southern Africa.

Methods: This open-label randomized controlled trial assigned individuals to either same-day ART start ([SD] arm) or referral to nearest clinic for preparatory counseling and ART start after ≥2 pre-ART clinic visits (standard of care SOC arm). Consenting ART-naïve HIV-infected individuals aged ≥18 years found HIV positive during home-based testing were eligible. Primary endpoints were

linkage to care and viral suppression. Linkage to care was defined as presenting at the facility within 90 days after tested HIV-positive. Viral suppression was defined as viral load <100 copies/mL 12 months after tested HIV-positive. All analyses were done according to intention to treat. Trial registration: NCT02692027

Results: A total of 274 ART-naïve individuals were enrolled from February to July 2016 (137 in each arm). Baseline participant characteristics were balanced: 65.7% female, median age 39 years, median CD4-cell count of 378 cells/μL, 78.1% were clinically asymptomatic. Linkage to care within 90 days was 68.6% (94/137) in the SD and 43.1% (59/137) in the SOC arm (p<0.001). In the SD arm 50.4% (69/137) had suppressed viral load 12 months after tested HIV-positive versus 37.9% (52/137) in SOC (p=0.039, see figure 1). Ninety days after tested HIV positive, 68.6% (94/137) in the SD and 31.4% (43/137) in the SOC arm had initiated ART (p<0.001). Retention in care 12 months after tested HIV-positive remained higher in the SD arm (56.2% (77/137) versus 43.1% (59/137), p=0.03).

Conclusion: Offering same-day ART initiation increased effectiveness of home-based HIV testing through higher proportions linking to HIV care at the facility and being retained in care with viral suppression 12 months after tested HIV-positive. Same-day ART initiation requires little additional resources as health care workers providing home-based HIV testing are already at the patients' home. If confirmed in other settings, same-day home-based ART initiation could become policy in countries with established home-based HIV testing.



95 RANDOMIZED CONTROLLED TRIAL OF FINANCIAL INCENTIVES FOR ACHIEVING VIRAL SUPPRESSION

Harsha Thirumurthy[1], Devy Emperador[2], Alex Ndyabakira[3], Dalsone Kwarisiima[4], Carol S. Camlin[2], Moses R. Kamya[5], Diane V. Havlir[2], Gabriel Chamie[2]
[1]University of Pennsylvania, Philadelphia, PA, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]Makerere University–University of California San Francisco Research Collaboration, Kampala, Uganda, [4]Makerere University Joint AIDS Program, Kampala, Uganda, [5]Makerere University College of Health Sciences, Kampala, Uganda

Background: Viral suppression (VS) among HIV-positive individuals is essential for protecting health and preventing new infections. Financial incentives (FI) have shown promise in modifying health behavior in low-income countries but few studies have assessed whether they can increase the likelihood of VS.

Methods: Antiretroviral therapy (ART) eligible HIV-positive adults diagnosed at community health campaigns (CHCs) or at a rural clinic in Uganda were randomized to receive FI for achieving VS (viral load<400 copies/mL) at 6, 12, and 24 weeks or to a control group with no FI (NCT02890459). Viral load (VL) was measured at baseline, 6, 12, and 24 weeks; results were disclosed to all participants. At each interval, FI amounts rose from 15,000-45,000 Uganda Shillings (US$4–12.50) with a reset contingency if VS was not achieved. The primary outcome was VS at 24 weeks. The proportions achieving VS in intervention and control groups were compared using chi-squared tests. Intention-to-treat (ITT) analyses and per-protocol analyses were performed for participants enrolled at least 24 weeks prior to August 31, 2017.

Results: From June 2016-May 2017, 400 adults were enrolled (CHCs: 382, clinic: 18), 12 (3%) withdrew before 24 weeks, and 383 (96%) completed 24 weeks by August 31, 2017. Participants' mean age was 38 years, 57% were women, and median daily income was US$0.86. At baseline, the mean CD4 count among participants was 557 cells/μL and 76% had VL<400 copies/ml. In ITT analyses, 8% of participants in both groups did not have a 24-week VL measure and were considered unsuppressed. There was a trend towards higher VS at 6 weeks in the intervention group (83%) than the control group (76%, p=0.09). However, there was no significant difference between intervention and control groups in proportion achieving VS at 24 weeks (85% vs. 82%, p=0.42). Likewise, incentives had no effect among those not suppressed at baseline, with 60% and 53% achieving 24-week VS in the intervention and control group, respectively (p=0.55). Per-protocol analyses among 351 participants with 24-week VL measures showed no difference in VS, as 90% and 92% achieved VS in both groups (p=0.67).

Conclusion: Over a six-month period, FI had no effect on VS rates among HIV-positive ART eligible adults. Provision of VL results to the control group and high baseline VS may have contributed to high rates of VS in both study groups, and incentives may have been provided too infrequently to influence daily medication adherence.

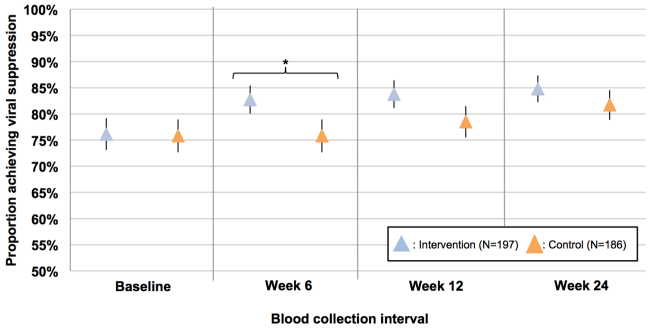


Figure 1: Proportion achieving viral suppression (viral load < 400 copies/mL) among all participants at baseline, week 6, week 12, and week 24 collection, by study group.
*p<0.10

96 EXTENDED-RELEASE NALTREXONE IMPROVES VIRAL SUPPRESSION IN HIV+ PRISONERS

Sandra Springer, Marwan Azar, Angela DiPaola, Russell Barbour, Breanne Biondi, Maua Herme, Frederick Altice
Yale University, New Haven, CT, USA

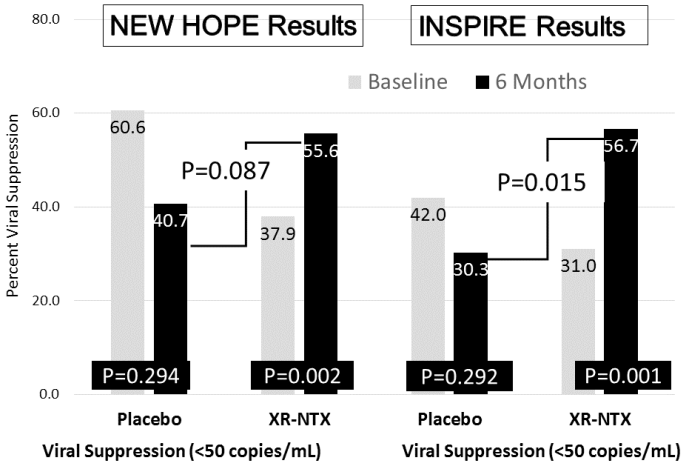
Background: People with HIV, opioid (OUD) and alcohol use disorders (AUD) are concentrated within the criminal justice system (CJS). Upon release from incarceration, drug and alcohol relapse is common and contributes to poor HIV treatment outcomes, increased HIV transmission risk, recidivism and mortality. The specific aim of these two studies was to evaluate extended-release naltrexone (XR-NTX), an FDA-approved medication for OUD and AUD, as a means to improve HIV viral suppression (VS) among persons living with HIV (PLH) released from prison or jail to the community with OUD and AUD.

Methods: Two separate double-blind placebo controlled randomized trials were conducted among HIV+ inmates with (1) AUD (INSPIRE, N=100); and (2) OUD (NEW HOPE, N=93) who were transitioning to the community. Participants were randomized 2:1 to receive 6 monthly injections of XR-NTX or placebo starting one week prior to release and continuing for 6 months post-release. The primary outcome was the proportion that maintained VS (<50 copies/mL) at 6 months in an intention to treat (ITT) analysis.

Results: Baseline characteristics did not statistically significantly differ between treatment groups in either study. For INSPIRE, the ITT analyses revealed the XR-NTX group was statistically more likely to achieve VS as compared to placebo at 6 months post-release (56·7% vs. 30·3%; p=0.015). After controlling for other factors, receipt of XR-NTX remained independently predictive of VS (aOR=4·54; 95%CI=1·43-14·43, p=0.009). Participants receiving 3 or more injections, irrespective of allocation, were also more likely to achieve VS (aOR=6.34; 95%CI=2.08-19.29, p=0.001 respectively), as were reductions in alcohol consumption (aOR=1·43; 95%CI=1·03-1·98, p=0.033) and white race (aOR=5·37; 95%CI=1·08-27·72, p=0.040). For NEW HOPE, the ITT analyses revealed that the XR-NTX group was more likely to achieve VS at 6

months (37.9% to 60.6%, p=0.002 as compared to placebo (55.6% to 40.7%, p=0.294). The XR-NTX group was also more likely than placebo to improve to VS (30.3% vs.18.5%); maintain VS (30.3% vs. 27.3); and less likely to lose VS (7.6% vs. 33.3%) at 6 months (p=0.041). Independent predictor of VS was only receiving XR-NTX (aOR=2.90; 95% CI=1.04-8.14, p=0.043). There were no serious adverse events in either study.

Conclusion: XR-NTX can improve or maintain HIV VS after release to the community for incarcerated PLH with OUD and AUD, thus benefiting both individual and public health.



97 HIGHER MORTALITY IN HIV - INFECTED VS - UNINFECTED ADULTS DESPITE ART, BOTSWANA

Tendani Gaolathe[1], Kathleen Wirth[2], Molly Pretorius Holme[2], Etienne Kadima[1], Unoda A. Chakalisa[1], Kutlo Manyake[1], Joseph Makhema[1], Mompati O. Mmalane[1], Jean Leidner[2], Scott Dryden-Peterson[2], Kathleen M. Powis[2], Mosepele Mosepele[1], Refeletswe Lebelonyane[3], Lisa A. Mills[4], Shahin Lockman[2]
[1]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [2]Harvard University, Cambridge, MA, USA, [3]Ministry of Health, Gaborone, Botswana, [4]CDC Botswana, Gaborone, Botswana

Background: Over the past 15 years, mortality in HIV-infected adults has declined markedly due to antiretroviral treatment (ART) coverage in southern African nations. The population-level impact of ART scale-up on the relative mortality among HIV-infected vs. –uninfected adults in these settings is unknown.

Methods: We prospectively followed a random, population-based sample of HIV-infected and –uninfected adults (age 16-64 years) in 30 rural and peri-urban communities in Botswana, as part of an HIV prevention trial (the Botswana Combination Prevention Project). In this analysis, we present mortality rates approximately 1 year after enrollment, according to baseline HIV and ART status. Cox proportional hazard models accounting for clustering were used, and additional age- and sex-adjusted analyses were performed

Results: We enrolled and followed 13,088 adults from 30 communities (median age 32.6 years, 64% female), 3,667 (28%) of whom were HIV-infected. At enrollment, 2,653 (72%) of HIV-infected individuals were already on ART (median CD4 of those not on ART 404 cells/mm^3). Median follow-up time was 12.6 months (IQR 12.2, 29.1), and vital status was available for 11,981 (92%) of 13,088. Overall, 84 (0.70%, 95%CI 0.54–0.91%) died. The crude mortality rate per 100 person-years was significantly higher in HIV-infected vs. in HIV-uninfected individuals (0.93 vs. 0.26, adjusted hazard ratio [aHR] 3.0, 95%CI 1.9-4.8). In HIV-infected participants, ART was protective: not being on ART (aHR 2.3, 95%CI 1.2-4.4) or being on ART for less than 1 year (aHR 3.8, 95%CI 1.7-8.5) were each associated with significantly higher mortality compared with being on ART for >1 year. Mortality was significantly higher in HIV-infected persons on ART for >1 year compared with HIV-uninfected adults (aHR 1.8, 95%CI 1.0-3.2). Among HIV-infected individuals who died, infection was a more frequent cause of death than among HIV-uninfected individuals who died; deaths from cancer and other chronic medical conditions were common in both groups (Table 1).

Conclusion: Despite high population ART coverage approaching 90 - 90 - 90 targets, mortality among HIV - infected adults remains 3 - fold higher than in uninfected individuals. Although mortality is highest among those not yet on ART (or those who recently initiated ART), mortality was also two-fold higher among those on ART for ≥ 1 year compared with individuals without HIV.

Table 1: Primary cause of mortality overall, and according to baseline HIV status

Primary cause of mortality	Overall (n=84)	Among HIV-Infected (n=49)	Among HIV-Uninfected (n=35)
Tuberculosis	9 (11%)	8 (16%)	1 (3%)
Pneumonia	6 (7%)	4 (8%)	2 (6%)
Sepsis	3 (4%)	3 (6%)	0
Other infection	3 (4%)	3 (6%) (1 bacterial meningitis, 1 diarrhea/wasting, 1 PCP)	0
Cancer	16 (19%)	10 (20%)	6 (17%)
Cervical	7	5	2
Esophageal	2	1	1
Head/neck	1		1
Pancreatic	1	1	
Breast	1		1
Lung	1		1
Colon	1	1	
Not recorded	2	2	
Cardiovascular	7 (8%)	3 (6%)	4 (11%)
Stroke	3	1	2
MI	1		1
CHF	2	1	1
DVT	1	1	
Renal or liver failure	5 (6%)	2 (4%) (1 of each)	3 (9%) (2 renal, 1 liver)
Other medical	10 (12%)	4 (8%) (1 encephalopathy, 1 ARV toxicity, 1 traditional medicine toxicity, 1 diabetes)	6 (17%) (1 subdural, 1 appendicitis, 1alcohol intoxication, 1 elevated ICP/shunt, 1 epilepsy, 1 pancreatitis)
Trauma	6 (7%)	1 (2%)	5 (14%)
Motor vehicle accident	3	1	2
Suicide	1		1
Homicide	2		2
Unknown	19 (23%)	11 (22%)	8 (23%)
By disease category			
Any infectious cause	21(25%)	18 (37%)	3 (9%)
Any non-infectious medical cause	38 (45%)	19 (39%)	19 (54%)
Trauma/unknown	25 (30%)	12 (24%)	13 (37%)

98 HIV ENV: STRUCTURE, FUNCTION, AND INHIBITION THEREOF

Peter D. Kwong, *National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA*

Like other type 1 fusion machines, the HIV-1 envelope (Env) trimer transitions between prefusion, pre-hairpin intermediate and postfusion conformations to merge viral and host cell membranes during virus entry. In addition to utilizing conformational change for entry, the HIV-1 Env trimer also uses conformational change to evade the humoral immune response. Single molecule FRET measurements indicate that the Env trimer spontaneously (and reversibly) transitions between three prefusion states: a pre-triggered state 1, a preferred intermediate state 2, and an activated state 3 that can be stably induced by receptor/co-receptor binding. This talk summarizes recent data connecting smFRET-defined states with high-resolution structures and details how small molecules and antibodies can freeze select Env conformations to inhibit entry. In specific, we have recently solved the structure of the HIV-1 Env trimer with small molecule inhibitors, including BMS-626529, the prodrug version of which is currently in late stage clinical trials. This structure indicates BMS-626529 to recognize an induced binding pocket and to prevent Env from transitioning to state 3. Meanwhile, most broadly neutralizing antibodies appear to bind preferentially to states 1 or 2, although many can also bind to state 3. By contrast, poorly or non-neutralizing antibodies either do not recognize the Env trimer or only recognize state 3, not states 1 or 2. These insights into antibody recognition and Env conformation are now being applied to the development of vaccines aimed at eliciting immune responses capable of neutralizing the diverse neutralization-resistant isolates that typify HIV-1 transmission. Recent results indicate the N terminus of the fusion peptide to be exposed in state 2 and that focusing the immune response to this functionally critical site can elicit humoral immune responses in mice and non-human primates with ~30% HIV-1 neutralization breadth.

99 ARCHITECTURE OF THE HIV-1 REVERSE TRANSCRIPTASE INITIATION COMPLEX

Elisabetta Viani Puglisi, *Stanford University, Stanford, CA, USA*

Reverse transcription of the HIV-1 RNA genome into double-stranded DNA is a central step in infection and a common target of antiretroviral therapy. The reaction is catalyzed by viral reverse transcriptase (RT) that is packaged in an

infectious virion along with 2 copies of dimeric viral genomic RNA and host tRNALys3, which acts as a primer for initiation of reverse transcription. Upon viral entry, initiation is slow and non-processive compared to elongation. We have applied cryo-electron microscopy (cryo-EM) to determine the three-dimensional structure of the HIV RT initiation complex. RT is in an inactive polymerase conformation with open fingers and thumb and the nucleic acid primer-template complex is shifted away from the active site. The primer binding site (PBS) helix formed between tRNALys3 and HIV RNA lies in the cleft of RT, extended by additional pairing interactions. The 5′ end of the tRNA refolds and stacks on the PBS to create a long helical structure, while the remaining viral RNA forms two helical stems positioned above the RT active site, with a linker that connects these helices to the RNase H region of the PBS. Our results illustrate how RNA structure in the initiation complex alters RT conformation to decrease activity, highlighting a potential target for drug action.

100 STRUCTURE AND MECHANISM OF THE SAMHD1 HIV-1 RESTRICTION FACTOR

Ian A. Taylor, *The Francis Crick Institute, London, UK*

SAMHD1 is a post-entry cellular restriction factor that inhibits HIV-1 replication in myeloid-lineage and resting CD4+ T cells. The mechanism of SAMHD1 restriction has been disputed but the predominant theory is that SAMHD1 dNTP triphosphohydrolase activity blocks HIV-1 infection by reducing the cellular dNTP pool to a level that does not support viral reverse transcription. A large body of structural and biochemical studies have demonstrated that the active form of SAMHD1 is a protein tetramer that contains four regulatory allosteric sites each accommodating a deoxynucleotide/nucleotide pair and four active sites that hydrolyse the dNTP substrates. In addition, other studies have shown that the dNTP triphosphohydrolysis reaction is regulated by tetramer stability, controlled by SAMHD1 phosphorylation at residue T592. However, although, this wealth of information has contributed significantly to our understanding of SAMHD1 restriction, regulation and activation the molecular details of the catalytic mechanism of dNTP hydrolysis have remained unclear. Therefore, to elucidate the molecular mechanism of dNTP triphospho-hydrolysis by SAMHD1, we now have undertaken comprehensive enzymological studies employing deoxynucleotide substrate and activator analogues and determined crystal structures of catalytically active SAMHD1 with dNTP-mimicking, competitive inhibitors. These analogue studies uncovered inhibitors of SAMHD1 and also revealed the capacity for SAMHD1 to be activated by and hydrolyse existing antiviral and anticancer drugs. The SAMHD1-inhibitor co-crystal structures show in atomic detail how dNTP substrates are coordinated at the SAMHD1 active site and reveal how the protein chemically activates a water molecule to mount a nucleophilic attack on the phospho-ester bond in the dNTP substrate. In conclusion, these studies now provide the molecular details of the SAMHD1 reaction mechanism demonstrating how dNTP substrates are hydrolysed and enable more accurate prediction of whether new and existing antiviral and anticancer drugs are hydrolysed by SAMHD1.

101 STRUCTURE AND MECHANISM OF VPS4, THE ENZYME THAT DRIVES HIV BUDDING

Christopher P. Hill, *University of Utah, Salt Lake City, UT, USA*

Many cellular membrane fission reactions are driven by ESCRT pathways, which culminate in remodeling and disassembly of ESCRT-III polymers by the AAA ATPase Vps4. HIV-1 and many other viruses recruit an ESRCT pathway in order to bud from cells. Recent advances in understanding of the budding machinery will be summarized, with special emphasis on HIV and findings from our 3.2 Å resolution cryo-EM structure of the active Vps4 hexamer in complex with its cofactor Vta1, ADP·BeFx, and an ESCRT-III substrate peptide. Five Vps4 subunits form a helix, with interfaces between the first four of these subunits apparently bound to ADP.BeFx (ATP) and the interface between the fourth and fifth subunit bound to ADP, as if it is just commencing dissociation from the helix. The final Vps4 subunit completes a notched-washer configuration as if transitioning between the ends of the helix. The ESCRT-III peptide binds in an extended (beta-strand) conformation against the five helical subunits. Two classes of side chain binding pockets are formed primarily by Vps4 pore loop 1 residues, with four copies of each pocket propagating along the highly solvated pore through the Vps4 hexamer. The pockets accommodate a wide range of residues, while main chain hydrogen bonds help dictate substrate-binding orientation. The structure supports a 'conveyor belt' model of translocation in which ATP binding allows a Vps4 subunit to join the growing end of the helix and engage the substrate, while hydrolysis and release promotes helix disassembly and substrate disengagement at the lagging end. In this manner Vps4 may disassemble ESCRT-III to reveal a metastable membrane configuration that resolves by fission and virus budding. This model likely applies to other ESCRT pathways and may be generally applicable to multiple other protein-translocating AAA ATPases.

102 LIFE EXPECTANCY IN THE MODERN ART ERA

Caroline Sabin, *University College London, London, UK*

The last decade has seen a dramatic improvement in the life expectancy (LE) of people with HIV (PWH) in settings with access to effective antiretroviral therapy. As a result, there has been a change in the spectrum of clinical events that are now commonly seen in PWH, with a reduction in the incidence of most AIDS events but an increase in the incidence of co-morbidities usually seen in an ageing population. The jury is still out on whether successfully treated PWH experience an increased risk of these age-related co-morbidities compared to their HIV-negative counterparts. This presentation will summarise the latest data on LE and the co-morbidities that are seen in PWH and will consider whether LE has now 'normalised' in comparison with that of the HIV-negative population, drawing attention to the possible methodological biases that may be present when undertaking such a comparison. The presentation will also investigate whether there are important subsets of PWH in whom LE remains substantially shorter than desired, and where interventions to further improve LE may be required.

103 IMPACT OF PHYSICAL AND MENTAL COMORBIDITIES ON LIFE EXPECTANCY

Keri N. Althoff, *Johns Hopkins University, Baltimore, MD, USA*

In settings where tuberculosis is not the dominant cause of morbidity and mortality among people with HIV (PWH), evidence continues to build showing a greater-than-expected burden of physical and mental comorbidities in PWH, including hypertension, diabetes, renal impairment, and depression. This presentation will highlight the role of traditional, modifiable risk factors, such as smoking, substance use and other untreated mental health conditions, weight changes, and social cohesion, as well as the interplay between physical and mental comorbidities, on the clinical outcomes. The timing of ART initiation and the changing side-effects of ARTs may create sub-groups with different burdens of physical and mental comorbidities. Effective interventions to reduce modifiable risk factors will be highlighted. Future research is needed to determine how to appropriately leverage existing HIV care infrastructures to be vehicles for interventions that reduce the burden of physical and mental comorbidities so that the quality, not just the quantity, of life can be maximized for PWH.

104 INFLAMMATION AND DISEASE RISK AMONG HIV-SEROPOSITIVE INDIVIDUALS

Jason V. Baker, *Hennepin County Medical Center, Minneapolis, MN, USA*

Ongoing systemic inflammation contributes to increased clinical risk among contemporary HIV+ patients despite antiretroviral therapy (ART) treatment with viral suppression. This presentation will review epidemiologic data showing that blood biomarkers, reflecting generalized inflammation, innate immune response (e.g., monocyte activation), adaptive immune response (e.g., T-cell activation), and coagulation activity, predict risk for a broad spectrum of end-organ diseases among HIV+ patients. Strategies to mitigate HIV-associated inflammation will then be reviewed. Effective ART with viral suppression reduces inflammation, but the degree of improvement appears incomplete when compared to uninfected persons. In addition, delaying ART treatment (e.g., from delayed diagnosis) may lead to excess inflammation even after viral suppression is achieved. Novel, broadly anti-inflammatory, treatment(s) have shown promise in the general population, but the safety (i.e., risk from infection) among HIV+ individuals requires further study. Ultimately, future research should focus on minimizing residual inflammation with ART treatment, as well as identifying safe anti-inflammatory treatments to be given in addition to ART, for HIV+ patients that remain at excess inflammation-associated disease risk.

105 THE INTERSECTION OF PrEP AND SEXUALLY TRANSMITTED INFECTIONS

Julia A. Schillinger, *CDC, Atlanta, GA, USA*

Bacterial sexually transmitted infections (STI) are increasing in the United States at the same time as increases in the awareness and utilization of biomedical advances in HIV treatment (TasP) and prevention (PrEP). In this environment, rates of reported new HIV infections have stabilized, and even declined in some areas. This presentation will examine a confluence of factors which may be contributing to observed increases in bacterial STI. Trends in chlamydia, gonorrhea, syphilis, and HIV in the years before and after the availability of PrEP will be described using national and local surveillance data. On the population level, the uptake of PrEP could contribute to increasing STI rates because the regular, biannual (at least) STI screening recommended for all people on PrEP may increase detection of asymptomatic, or recent infections. However, broad increases in STI screening and detection are likely occurring independently of PrEP, due to increased availability of extragenital (anorectal and oropharyngeal) nucleic acid amplification tests for Neisseria gonorrhoeae and Chlamydia trachomatis, improved provider adherence to longstanding national recommendations for screening all men-who-have-sex-with-men (MSM) for these largely asymptomatic pathogens, and the ease afforded by patient self-collected specimens. Changes in sexual behavior may also be expected in the context of TasP and PrEP. Sexual risk compensation related to PrEP may play a role in increasing STI transmission among people who are, and are not on PrEP. A decreased fear of HIV infection, and knowledge of the low risk of transmission from persons with an undetectable viral load may also result in changes in sexual behaviors that increase the risk of other STI.

106 IMPACT OF PrEP ON HIV INCIDENCE

Roel Coutinho, *University Medical Center Utrecht, Utrecht, Netherlands*

Among persons at high risk to acquire HIV, oral PrEP has been shown to be effective, with good adherence the infection risk being reduced with 70% or more. Based on these studies PrEP is now recommended for people at substantial risk to acquire HIV. Preventing HIV among high incidence groups will potentially also have a significant impact on onward HIV transmission to sexual (and needle sharing) partners. In most high income countries the majority of newly diagnosed HIV infections are among MSM. In some countries there is evidence of a declining incidence in this group due to earlier HIV detection and immediate ART initiation. Modelling studies show that providing PrEP to MSM at highest risk will have a significant additional impact on the HIV incidence by the combined effect of averting HIV among high risk MSM taking PrEP and the prevention of onward sexual transmission to others, estimates ranging from 15-60% reduction. A lowering impact of PrEP on the HIV incidence can also be expected among injecting drug users (IDUs). In this group PrEP should be combined with other prevention measures (needle exchange, early detection of HIV infection and immediate ART initiation) and embedded within a social and medical care program. Heterosexual migrants from high endemic countries are eligible for PrEP on an individual basis but molecular studies indicate that onward HIV transmission to others is limited so the overall impact on the HIV incidence will be low. In high endemic countries PrEP can be an additional individual tool to reduce HIV incidence in high incidence key populations like young women, sex workers and MSM. Rolling out PrEP programs in high endemic countries should be carefully balanced against and/or offered in combination with other effective interventions especially early HIV detection followed by immediate treatment. PrEP implementation requires a medical infrastructure to uninterrupted deliver PrEP with regular health checks. Investigating novel options to deliver PrEP (e.g. injectable), to circumvent problems of adherence/delivery will be beneficial. To evaluate the impact of PrEP on the HIV incidence in real world settings it is essential to set up monitoring programs to see whether those at highest risk are adequately being reached.

107 FIVE CONTROVERSIES IN PrEP SCALE UP

Linda-Gail Bekker, *University of Cape Town, Cape Town, South Africa*

We know that PrEP is protective and recommended for HIV prevention across populations, with good tolerability and very few safety risks. So what are the remaining controversies that are challenging us as we head towards PrEP scale-up? This talk will tackle five of the debates currently raging: (1) The potential impact of PrEP as a safer conception measure; (2) The time to protection at different mucosal surfaces; (3) PrEP isn't an option in adolescent populations; (4); There isn't sexual disinhibition with PrEP; (5) PrEP can be cost-effective especially when used intermittently? Are these controversies real? Are they myths? What is the known evidence?

108 TAKING THE LEAP IN PrEP SCALE-UP: A GOOD TYPE OF CHALLENGE

Nelly R. Mugo, *Kenya Medical Research Institute, Nairobi, Kenya*

The HIV prevention field finally has a highly effective biomedical intervention in oral PrEP. There has been a purposeful effort to expedite population level PrEP delivery, with different trajectories by different countries. During this session, we shall review the various strategies that guide PrEP scale up. Walking through the journey and process taken by different countries in PrEP scale up, we will explore the characteristics of early adopters and factors that drive uptake and broad scale uptake by populations that most need it. We will discuss considerations raised by skeptics and their role in informing delivery process and the social and health benefits, beyond HIV prevention.

109 GROWING UP WITH HIV

Patricia M. Flynn, *St. Jude Children's Research Hospital, Memphis, TN, USA*

The World Health Organization estimates that over 4 million children have been infected with HIV, most via vertical transmission. Before effective treatment, mortality rates of 50% within the first two years of life were expected. The availability of safe and effective ART has radically changed this outcome and most children living with HIV infection who have access to ART are now thriving. However, long-term effects of HIV infection and its therapy have significant impact on aging up adolescents and young adults living with perinatal HIV infection. Most adolescents and young adults living with perinatal HIV infection in high-income countries have been exposed to sequential antiretroviral regimens, including monotherapy. Combined with adherence difficulties, many have evidence of viral resistance and cannot take advantage of once daily fixed drug combination ART. Many of the complications of long-term HIV infection seen in adults are also present in adolescents and young adults living with perinatal HIV infection, including renal and metabolic diseases and bone loss. However, the main impact of long-standing HIV infection and its treatment has been on growth and development, including neurodevelopment. Interpretation of research in this area is complicated by the identification of optimal control subjects, survivor bias, and contribution of the underlying social and economic characteristics of those at risk for perinatal HIV infection. Deficiencies in cognitive development, most notably executive function deficits, combined with normal maturational changes in adolescents affect behavior and academic success further complicating ART adherence and maturation into independent adults. Risk-taking behavior, common in normal adolescents, may also be heightened by cognitive difficulties resulting in increased risk of HIV transmission to sexual partners and unplanned pregnancies with potential for perinatal HIV transmission. In 2015, it was estimated that there were 1.8 million children less than 15 years of age living with HIV infection; 1.6 million of these children live is Sub-Saharan Africa. A better understanding of the complexities of growing up with HIV infection will help prepare low and middle-income countries of the world where ART is now available to successfully manage their aging up populations of adolescents and young adults living with perinatal HIV infection.

110 ARE WE ON THE FAST TRACK TO "BEND AND END" THE HIV EPIDEMICS?

Helen A. Weiss, *London School of Hygiene & Tropical Medicine, London, UK*

Goals of the HIV community include dramatically reducing the number of new infections and ensuring that people living with HIV have a long life of high quality, using rights-based approaches. This talk will examine global progress towards reaching ambitious aims such as reducing the number of new HIV infections from 1.8 million in 2016 to 500,000 in 2020, and 200,000 in 2030. This goal is operationalized as "90-90-90" i.e. that by 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy, and 90% of all people receiving antiretroviral therapy will have viral suppression. Immense progress has been made recently to increase uptake of HIV testing (for example through expansion of community-based and HIV self-testing kits), linkage to care (including through offering immediate ART to those newly diagnosed) and improving adherence (including through community-based and psycho-social support strategies). There are striking gaps in the uptake of testing and treatment for many groups, including the young, males and key populations, but several recent studies are using innovative strategies to improve uptake in these groups. To "bend and end" the HIV epidemic curve, greater focus is

needed on i) expanding use of innovative strategies for HIV prevention and treatment access for the young, males and vulnerable populations, ii) expansion of flexible and adaptive strategies to respond rapidly to diverse epidemics, and iii) sustained funding to enable expanded coverage of HIV treatment and prevention services.

111 IDENTIFICATION OF HIV-1 ENV MUTATIONS THAT CONFER BROAD RESISTANCE TO ARVs IN VITRO

Rachel Van Duyne, Phuong Pham, Eric O. Freed
National Cancer Institute, Frederick, MD, USA

Background: We have identified compensatory mutations within the HIV-1 envelope (Env) glycoprotein that rescue defects in replication conferred by mutations in Gag. Despite severe deficiencies in cell-free infectivity, these Env mutants replicate with wild-type (WT) kinetics and are capable of efficient cell-to-cell transmission. The goal of this study was to characterize the ability of the Env mutant viruses to confer a broad replication advantage and determine whether they can overcome or escape inhibition by antiretrovirals (ARVs).
Methods: We passaged Env mutants in T-cell lines to establish a spreading infection and measured replication kinetics in the presence or absence of ARVs. We also selected for viral isolates exhibiting at least partial resistance to ARVs as indicated by efficient replication in the presence of the inhibitors.
Results: We demonstrate that the Env compensatory mutants replicate with WT or faster-than-WT kinetics despite severe defects in cell-free, single-cycle infectivity. We also observed that the Env mutants can rescue a replication-defective integrase mutant, suggesting that they might also be able to confer resistance to ARVs. Indeed, we found that the Env mutants exhibit markedly reduced sensitivity to Ritonavir (RTV), Nelfinavir (NFV), Dolutegravir (DTG), Tenofovir (TFV), and Rilpivirine (TMC) at drug concentrations that block or delay WT virus replication. Remarkably, long-term passage of WT virus in the presence of several of these inhibitors resulted in the selection of partially resistant ARV-escape mutants containing substitutions in Env. This escape occurred in the absence of resistance mutations in enzyme targets of these drugs. The positions of the selected Env mutations are highly conserved (>90%) across all clade B viruses, highlighting the specificity of selection of mutations at these positions.
Conclusion: These results demonstrate that mutations in Env that promote efficient cell-cell transfer, at the expense of cell-free particle infectivity, can broadly contribute to drug resistance in vitro. Cell-to-cell HIV-1 transmission occurs more efficiently and rapidly than cell-free infection, supporting the relevance of this mode of viral dissemination in vivo. These results also raise the possibility that the acquisition of Env mutations represents an unrecognized, transient stepping stone towards the development of high-level HIV-1 drug resistance.

112 STRAIN-DEPENDENT ACTIVATION AND INHIBITION OF HIV-1 ENTRY BY A PF-68742 DIASTEREOMER

Connie A. Zhao[1], Amy Princiotto[1], Mark Farrell[2], Amos B. Smith[2], Navid Madani[1], Joseph G. Sodroski[1]
[1]Dana–Farber Cancer Institute, Boston, MA, USA, [2]University of Pennsylvania, Philadelphia, PA, USA

Background: HIV-1 entry into cells is mediated by the envelope (Env) trimer of gp120-gp41 heterodimers. Sequential binding to target cell receptors, CD4 and CCR5 or CXCR4, triggers the metastable Env to undergo entry-related conformational changes. PF-68742 was recently identified as a small molecule that inhibits infection of a subset of HIV-1 strains by interfering with an Env function other than receptor binding, with resistance determinants mapping to the gp41 disulfide loop and fusion peptide. We investigated the antiviral mechanism of PF-68742.
Methods: Recombinant luciferase-expressing HIV-1 pseudotyped by wild-type or mutant HIV-1 Envs was incubated with increasing concentrations of PF-68742 alone or in the presence of other entry inhibitors or antibodies. The virus-inhibitor mixture was added to CD4+ CCR5+, CD4+ CXCR4+, or CD4- CCR5+ target cells, and luciferase activity was measured 48 to 72 hr later.
Results: Of the four PF-68742 diastereomers, only one, MF275, inhibited the infection of CD4+ CCR5+ cells by some HIV-1 strains. Unexpectedly, MF275 activated the infection of CD4- CCR5+ cells by several HIV-1 strains resistant to the compound's inhibitory effects in CD4+ CCR5+ target cells. In both cases, the strain susceptibility profiles were unique from those of other entry inhibitors. Sensitivity to other entry inhibitors indicated that MF275-activated virus entry requires CCR5 binding as well as gp41 heptad repeat (HR1) formation and exposure. In contrast to CD4 complementation by CD4-mimetic compounds, activation of CD4-independent infection by MF275 did not depend upon availability of the gp120 Phe 43 cavity; moreover, the MF275-activated state was long-lived relative to that induced by CD4-mimetic compounds. While MF275 and a CD4-mimetic both enhanced susceptibility of some HIV-1 strains to the 17b and 19b antibodies against a CD4-induced epitope and the gp120 V3 loop, respectively, only MF275 enhanced susceptibility to the broadly neutralizing antibody 4e10 against the gp41 membrane-proximal external region.
Conclusion: MF275 apparently binds a site on the HIV-1 Env unique from the CD4 binding site to activate a conformational cascade that leads to virus entry. This pathway is parallel to but distinct from that triggered by CD4 and CD4-mimetic compounds. Thus, HIV-1 Env samples conformations within an energy landscape in which there are multiple pathways to entry (or inactivation). An understanding of the mechanisms of activity of MF275 should assist efforts to optimize its utility.

113LB TRISPECIFIC ANTIBODIES FOR PREVENTION AND TREATMENT OF HIV-1 INFECTION

Amarendra Pegu[1], Zhi-yong Yang[2], Ling Xu[2], Ercole Rao[2], Nicole Doria-Rose[1], Jochen Beninga[2], Krisha McKee[1], Dana M. Lord[2], Ronnie R. Wei[2], Gejing Deng[2], Stephen Schmidt[1], Wang Keyun[1], Mario Roederer[1], John R. Mascola[1], Gary Nabel[2]
[1]Vaccine Research Center, NIAID, Bethesda, MD, USA, [2]Sanofi, Cambridge, MA, USA

Background: Broadly neutralizing anti-HIV-1 antibodies (bnAbs) are promising candidates for use in both prevention and treatment of HIV-1. These bnAbs have been shown to be efficacious in animal models and ongoing clinical studies suggest they mediate anti-viral activity in HIV-1 infected humans. Due to the diversity of circulating HIV-1 strains, the use of a single bnAb will likely lead to development or selection of resistant strains. Therefore, a combination of two or more bnAbs will be required for effective anti-HIV-1 therapy or to cover diverse strains for immunoprophylaxis.
Methods: Here, we engineered trispecific antibodies (Abs) that allow a single molecule to interact with three independent HIV-1 envelope determinants: 1) the CD4 binding site, 2) the membrane proximal external region (MPER) and 3) the V1V2 glycan site. These trispecific Abs were then assessed in neutralization assays against a representative global panel of HIV-1 viruses. The most potent and broad trispecific Abs were then evaluated for pharmacokinetics and protective efficacy in non-human primates (NHPs).
Results: Trispecific Abs exhibited higher potency and breadth than any previously described single bnAb. They showed pharmacokinetics like human bnAbs in naive rhesus macaques. Compared to single bnAbs that allowed breakthrough infection from mixed SHIV challenge of rhesus macaques, the trispecific Ab conferred complete immunity against a mixture of SHIVs.
Conclusion: Trispecific Abs thus constitute a platform to engage multiple therapeutic targets through a single protein, and could be applicable for diverse diseases, including infections, cancer and autoimmunity.

114 MOLECULAR DETERMINANTS OF HIV HYPERMUTATION

Diako Ebrahimi, Christopher Richards, Michael A. Carpenter, Jennifer McCann, Adam Cheng, Terumasa Ikeda, Daniel Salamango, Reuben S. Harris
University of Minnesota, Minneapolis, MN, USA

Background: The human genome encodes seven APOBEC3 (A3) enzymes, at least four of which (A3D, A3F, A3G, and A3H) can induce G-to-A mutations in HIV-1 genomes. These enzymes leave two distinct hypermutation signatures: GG-to-AG and GA-to-AA. The former signature is dominant in viral sequences hypermutated in vitro by A3G, whereas the latter is prevalent in sequences hypermutated in vitro by A3D, A3F, or A3H. Current, in vitro based models posit that all HIV-restrictive A3 enzymes are ubiquitously active and cooperate to hypermutate HIV. However we have discovered that an in vivo hypermutated virus typically bears a dominant GG-to-AG signature or a dominant GA-to-AA signature, which would be expected from independent encounters with A3G or A3D/F/H, but not from both enzyme classes simultaneously. This hypermutation bias towards GG-to-AG or GA-to-AA suggests the existence of a mechanism that prevents A3 proteins from simultaneously targeting HIV-1.
Methods: We performed four independent analyses: 1) We analyzed all reported in vivo hypermutated HIV-1 sequences (1164 sequences from 988 patients) using two independent methods (non-alignment-based and alignment-based); 2) We analyzed all of the 564 SNPs of the A3 locus in 2504 individuals from 26 populations (1000 Genomes Project). 3) We quantified, using RNAseq data, all of the reported A3 transcripts in 461 donors from the

1000 Genome Project ; 4) We quantified, the linkage disequilibrium in 120 kb A3 locus.
Results: By analyzing A3 SNPs, RNAseq, and hypermutated viral sequences from thousands of HIV-1 patients and healthy donors, we have generated three independent datasets that indicate the source of skewed hypermutation patterns is natural genetic variations in A3G and A3H. First, only one hypermutation signature predominates in most clinical HIV-1 isolates. Second, A3G and A3H form two continuous haplotype blocks as a result of strong genetic linkage. Block 1 is prevalent outside Africa (particularly Asia) and contains the hypo-functional A3H HapI (GKE). Block 2 is prevalent in Africa and contains the hyper-functional A3H HapII (RDD). Third, A3H HapI and HapII and their respective A3G haplotypes a-g-t-t-t and g-c-c-c-c are expressed differentially.
Conclusion: Overall, these results indicate that A3G and A3H are expressed differentially in different human populations and that these enzymes are the main sources HIV-1 hypermutation. The mutually exclusive function of A3G and A3H may be a source of weakness in our immunity to HIV-1.

115 HIV-1 SPLICING SUPPRESSION AS A POSSIBLE THERAPEUTIC TARGET

Ann Emery[1], Matthew Takata[2], Jeffery Levengood[3], John Collins[4], Alice Telesnitsky[4], Blanton Tolbert[3], Paul Bieniasz[2], Ronald Swanstrom[1]
[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]The Rockefeller University, New York, NY, USA, [3]Case Western Reserve University, Cleveland, OH, USA, [4]University of Michigan, Ann Arbor, MI, USA

Background: HIV-1 splicing produces more than 50 alternatively spliced RNAs. The initial product is a full-length transcript and all other RNAs are made by splicing. Short 1.8 kb mRNAs remove all introns, but long 4 kb mRNAs retain the env intron. Unspliced mRNAs retain all introns. Transcripts with introns require Rev for nuclear export. Splicing has been studied as a possible theraputic target, but transmitted/founder viruses tolerate wide variation among spliced transcript levels. HIV-1 is unique in that the majority of transcripts retain introns, and viral infection was shown to cause intron retention in transcripts of cellular genes (Sherrill-Mix 2015). This suppression of splicing is unique to HIV-1 and thus a potential theraputic target. We present evidence of early and complete splicing suppression, mutations that override suppression, and possible roles of Rev in splicing suppression.
Methods: Our Primer ID tagged deep sequencing assay quantifies HIV-1 spliced transcripts within the two RNA size classes. A second assay uses a Primer ID-tagged random reverse primer coupled with a fixed forward primer upstream of the major splice donor to detect changes in the amounts of full-length, long spliced transcripts (containing the env intron), and short fully spliced transcripts.
Results: Mutations to exonic splicing silencers activated the upstream proximal acceptor site. They also lifted suppression of splicing (i.e. activated splicing) at the major 5' splice donor D1 but not at splice donor D4. Activating mutations were made both to known silencers, and novel silencer elements were discovered by synonymous mutagenesis of the HIV-1 genome. We observed that the absence of Rev decreases but does not eliminate unspliced or partially spliced transcripts. We looked for but did not find evidence of transcripts that fail to use D1 (retain the gag/pro/pol intron) but use D4 to splice out the env intron. Additionally, we found no transcripts that used D2 or D3 without first using D1, making D1 suppression a marker for suppression of all splice donors.
Conclusion: Silencer elements that activate acceptor sites can also lift suppression of splicing from D1. As splicing is cotranscriptional and efficient, the absence of spliced gag/pro/pol transcripts suggests unspliced transcripts are suppressed early and completely from all splicing, long before the other downstream splice donors or the Rev Response Element (RRE) are transcribed. The role of Rev in splicing suppression remains to be fully studied.

116 A LONG INTERNAL LOOP GOVERNS THE SENSITIVITY OF THE ANTI-HIV PROTEIN SERINC5 TO NEF

Weiwei Dai, Yoshiko Usami, Yuanfei Wu, Heinrich Gottlinger
University of Massachusetts, Worcester, MA, USA

Background: We have recently identified the multipass transmembrane proteins SERINC3 and SERINC5 as novel antiviral proteins that restrict HIV-1 infectivity. Nef enhances HIV infectivity by removing SERINCs from the plasma membrane, which prevents their incorporation into progeny HIV-1 virions. However, the determinants that govern the sensitivity of SERINCs to Nef remain unknown.
Methods: We examined the inhibitory function of widely divergent SERINC5 proteins from different vertebrate species. To identify determinants responsible for the responsiveness of SERINC5 to Nef, we generated chimeras between Nef-sensitive and Nef-resistant SERINCs. We examined their ability to inhibit HIV-1 infectivity, their incorporation into HIV-1 virions, and their cell surface expression in the absence or presence of Nef.
Results: We find that the ability to inhibit HIV-1 infectivity is conserved among vertebrate SERINC5 proteins, whereas the sensitivity to downregulation by Nef is not. For instance, human and frog SERINC5 inhibited HIV-1 infectivity with similar potency, but frog SERINC5 was resistant to HIV-1 Nefs from different clades. Furthermore, our results indicate that sensitivity to Nef is, at least in part, governed by the fourth intracellular loop of SERINC5. A Nef-resistant SERINC5 became Nef-sensitive when intracellular loop 4 was replaced by that of human SERINC5. Conversely, human SERINC5 became resistant to Nef when its intracellular loop 4 was replaced by that of a Nef-resistant SERINC protein. We previously showed that HIV-1 SF2 Nef selectively inhibits the incorporation of SERINC5 but not of SERINC3 into progeny virions. Thus, we replaced the fourth internal loop of human SERINC3 by that of human SERINC5, and found that HIV-1 SF2 Nef strongly inhibited the incorporation of the resulting chimera into HIV-1 virions. In general, the fourth intracellular loop from SERINCs that exhibited resistance to a given Nef conferred resistance to the same Nef when transferred to a sensitive SERINC, and vice versa.
Conclusion: Taken together, our results identify a major determinant of Nef responsiveness, and establish that human SERINC5 can be made to restrict HIV-1 infectivity even in the presence of Nef.

117 PROTECTIVE GENE EXPRESSION SIGNATURE IN RESPONSE TO RHCMV/SIV VACCINE VECTORS

Connor Driscoll[1], Richard Green[1], Fredrik Barrenas[2], Jean Chang[1], Elise Smith[1], Lynn Law[1], Scott Hansen[3], Louis J. Picker[3], **Michael Gale**[1]
[1]University of Washington, Seattle, WA, USA, [2]Uppsala University, Uppsala, Sweden, [3]Oregon Health and Sciences University, Portland, OR, USA

Background: The simian immunodeficiency virus (SIV)-targeted vaccine vectors based on rhesus cytomegalovirus (RhCMV) strain 68-1 harboring deletion of viral open-reading frames UL128 and UL130 elicit potent cellular immune responses that fully protect rhesus macaques (RM) against SIV infection through T cell-mediated viral clearance. When these viral ORFs were restored, the resulting 68-1.2 vaccine vectors failed to protect RM against SIV challenge. To define the molecular features of the protective 68-1 vaccine response, we interrogated and compared the transcriptomic host response from five groups of RMs: two groups vaccinated with 68-1 (subcutaneous or oral delivery), one group with 68-1.2 (subcutaneous delivery), one group with 68-1.2 DUL128 (subcutaneous delivery), and one group with a combination of 68-1 and 68-1.2 (subcutaneous delivery).
Methods: Following vaccination, animals were subjected to repeated limiting dose intrarectal SIVmac239 challenge until infected by either detection of plasma virus or de novo development of T cell responses to SIVvif. Regardless of delivery mode, slightly over half of the animals that received the 68-1 vaccine manifested stringent aviremic control of the virus. There was no such control in any animal that received only a version of the 68-1.2 vaccine. Transcriptomic analysis (mRNA-seq) was performed on blood samples from all groups obtained during the vaccination phase. Bioinformatics analyses compared the transcriptional profiles between the protected and non-protected animal groups.
Results: These analyses identified gene expression changes as early as three days after the first vaccination that distinguish protected from non-protected animals. Specifically, differences in the RNA profiles between protected and non-protected animals included magnitude and directionality of differentially expressed genes involved in several innate immune networks including innate immune activation, inflammation, and immune programming.
Conclusion: These defined gene signatures for both protected and non-protected animals are being used to guide efforts to 1) understand the mechanisms responsible for the unique "control and clear" efficacy manifested by the 68-1 RhCMV vectors, 2) define intracellular response pathways of protection, 3) develop a modified vaccine that further enhances these features to achieve efficacy beyond the current ~55%, and 4) translate these vectors from nonhuman primates to people for protection against HIV infection.

118 CROSS-SPECIES CMV VACCINATION REVEALS DETERMINANTS OF NON-CLASSICAL T CELLS

Justin Greene, Daniel Malouli, Scott Hansen, Travis Whitmer, Abigail Ventura, Roxanne Gilbride, Luke Uebelhoer, Jennie Womack, Matthew McArdle, Junwei Gao, Alfred Legasse, Michael K. Axthelm, Louis J. Picker, Klaus Fruh, Jonah Sacha
Oregon Health and Sciences University, Portland, OR, USA

Background: Rhesus macaques (RM) vaccinated with strain 68-1 rhesus CMV (RhCMV) vaccine vectors expressing SIV antigens demonstrate unprecedented protection against highly virulent SIVmac239 replication, with protected RM eventually clearing the virus. This protection is associated with unconventional CD8+ T cell responses that are either MHC-II or MHC-E restricted. These unconventional CD8+ T cell responses may be the result of the unique MHC complexity present in RM, or the result of conserved immunoregulatory mechanisms utilized by CMV.

Methods: In order to parse out the importance of host immunogenetics from strain-specific CMV mechanisms, additional nonhuman primate models of CMV infection are needed. Mauritian-origin cynomolgus macaques (MCM) are a particularly attractive nonhuman primate model due to a significant population bottleneck 400 years ago that resulted in highly limited immunogenetics. We captured MCM CMV (CyCMV) as a BAC and subsequently developed an SIV Gag-expressing vector with deletions corresponding to those found in RhCMV 68-1.

Results: Vaccination of MCM with "strain 68-1 like" CyCMV induced unconventional CD8+ T cell responses including MHC-E and MHC-II restricted responses, including "supertope" responses that are present in every RhCMV strain 68-1 vaccinated RM. Interestingly, both RhCMV vaccinated RM and CyCMV vaccinated MCM target identical supertope peptides that are restricted by MHC-E.

Conclusion: These results demonstrate that species-specific CMV is required for non-classical T cell generation. Furthermore, as CMV-vectors advance toward human clinical trials, these results suggest a similarly designed human CMV may induce unconventional CD8+ T cell responses in humans.

119 HIV-1 PERSISTS IN CSF CELLS IN HALF OF INDIVIDUALS ON LONG-TERM ART

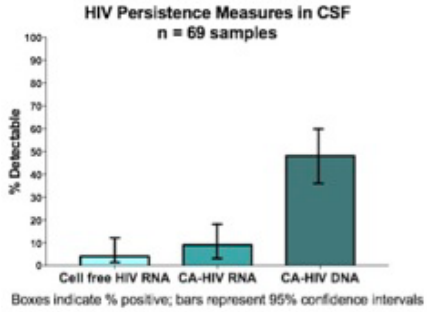
Serena S. Spudich[1], Rajesh T. Gandhi[2], Joshua C. Cyktor[3], Christina Lalama[4], Ronald Bosch[4], Bernard J. Macatangay[3], Charles Rinaldo[3], Kevin Robertson[5], Ann Collier[6], Catherine Godfrey[7], Evelyn Hogg[8], Joseph J. Eron[5], Deborah McMahon[3], John W. Mellors[3]
[1]Yale University, New Haven, CT, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA, [4]Harvard University, Boston, MA, USA, [5]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [6]University of Washington, Seattle, WA, USA, [7]NIAID, Bethesda, MD, USA, [8]Social &Scientific Systems, Silver Spring, MD, USA

Background: The frequency of HIV persistence in the cerebrospinal fluid (CSF) and the factors associated with persistence in individuals on long-term antiretroviral therapy (ART) are incompletely understood.

Methods: Participants who initiated ART during chronic HIV infection with documented sustained long-term viral suppression in ACTG A5321 underwent paired lumbar puncture and blood collection. Cell-associated (CA) HIV DNA and RNA were measured by qPCR assays in PBMCs and cell pellets derived from ~13 mls of CSF and normalized by amplifiable CCR5 cell equivalents. Cell-free HIV RNA was quantified by single copy assay (SCA) in 3-5 mls of CSF supernatant and blood plasma. Inflammatory biomarkers (IL-6, IP-10, neopterin, MCP-1, sCD14, sCD163) were measured in cell-free CSF and plasma.

Results: 69 participants (97% male) had median age 50 years, current CD4 696 cells/mm^3, pre-ART CD4 288 cells/mm^3 and 8.6 (range 5.4-16.4) years on ART. In CSF, cell-free RNA was detected in only 4% of participants (at 0.4, 0.7, and 1.2 cps/mL), while CA-RNA was detected in 9% (6/69) and CA-DNA in 48% (33/69) (Figure). Among those with detectable CA-DNA in CSF, median levels were 2.1 (0.12 -7.00) cps/103 cells. Participants with detectable cell-free HIV RNA in CSF had higher levels of plasma HIV RNA by SCA than those with undetectable CSF HIV RNA (median plasma VL, 5.9 vs < 0.4 cps/ml, p=0.007). By contrast, detection of CA-DNA in CSF was not associated with HIV DNA levels in PBMCs. CSF inflammatory biomarkers, especially indicators of myeloid cell activation, correlated within CSF and between CSF and plasma, but not with CSF CA-DNA, CA-RNA or cell-free HIV RNA. Higher CSF neopterin, IP-10, MCP-1, sCD14 and sCD163 correlated with older age (p≤0.016); higher CSF neopterin correlated with lower pre-ART CD4:CD8 ratio (r=−0.29, p=0.017). Plasma HIV RNA by SCA correlated with CSF sCD14 (r=0.34, p=0.004) and sCD163 (r=0.29, p=0.017).

Conclusion: Almost half of individuals on long-term ART have HIV-infected mononuclear cells in CSF; transcribed HIV RNA is detectable in CSF cells in a small subset. Persistence of HIV-infected cells in CSF was not associated with higher levels of HIV DNA in blood or with levels of inflammation in blood or CSF, but the level of residual plasma viremia was associated with both cell-free HIV RNA and myeloid cell activation in CSF. These findings highlight the need to develop interventions in addition to ART to clear persistently infected cells from the CSF compartment.



120 LONGITUDINAL TRAJECTORY OF BRAIN VOLUME AND CORTICAL THICKNESS IN PRIMARY INFECTION

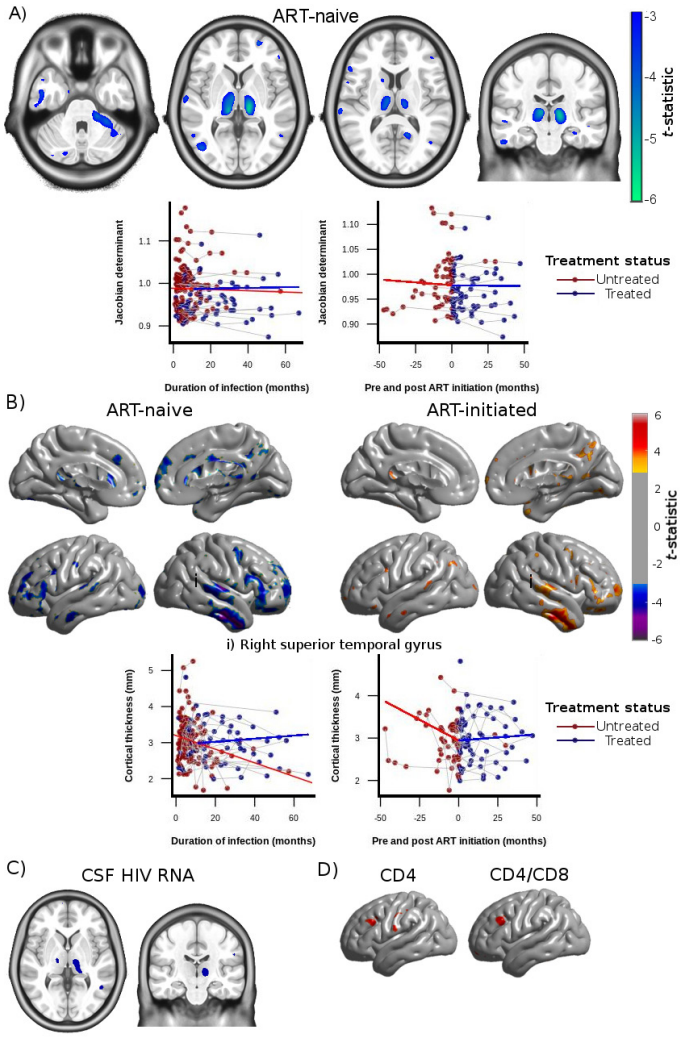
Ryan Sanford[1], Beau M. Ances[2], Richard W. Price[3], Dieter Meyerhoff[3], Serena S. Spudich[4], Louis Collins[1]
[1]Montreal Neurological Institute, Montreal, QC, Canada, [2]Washington University St Louis, St Louis, MO, USA, [3]University of California San Francisco, San Francisco, CA, USA, [4]Yale University, New Haven, CT, USA

Background: HIV penetrates the brain early in infection. However, brain volume changes that occur during this period and the effect antiretroviral therapy (ART) has on these changes are unclear. To explore this issue, we used tensor-based morphometry (TBM) and cortical modeling to examine the longitudinal trajectory of regional brain volumes and cortical thickness in treated and untreated primary HIV-infected (PHI) participants.

Methods: PHI participants (<1 year after exposure) in the PISCES cohort from San Francisco underwent longitudinal MRI. Several participants commenced ART during follow-up. TBM and cortical modeling estimated regional brain volumes and cortical thickness, respectively. A two-phase mixed-effect model assessed the trajectory of our MRI measures before and after ART. This involved fitting a linear model at time points before ART initiation and a different linear model at time points after ART. Both models were constrained to meet at the time of ART initiation. Additional mixed-effect models assessed correlations of regional MRI measures with CD4+ and CD8+ cell counts, CD4/CD8 ratio, and CSF and blood HIV RNA at time points before ART.

Results: 65 male PHI participants enrolled ((mean±SD) age 36.8±9 year, education 15.4±2.3 year, duration of infection 4.2±2.5 month, MRI per participant 2.5±1.5). Prior to ART initiation, we observed that longer duration of infection was correlated with brain volume loss in the thalamus, caudate, temporal lobe and cerebellum as shown by TBM (see Fig 1 for voxel-wise statistics), and with cortical thinning in the frontal and temporal lobes, as well as middle cingulate cortex (p<.05) (Fig 1B). After ART initiation, no further significant brain volume changes were found by TBM (Fig 1A). However, small but statistically significant increases of cortical thickness in the right frontal and temporal lobes correlated with longer ART duration (p<.05) (Fig 1B). Before ART, increased CSF HIV RNA was related with volume reductions in the thalamus (p<0.1) (Fig 1C). CD4+ cell count and CD4/CD8 ratio were positively correlated with cortical thickness in the left frontal lobe (p<.05) (Fig 1D).

Conclusion: Regional subcortical volume loss and cortical thinning occur before ART initiation. However, initiating ART can halt further structural deterioration. These findings support the hypothesis that brain injury due to HIV occurs during untreated infection and worsens in the absence of ART. This suggests that early initiation of ART preserves long-term brain health.



121 HIV AND BRAIN ATROPHIC SIGNATURE IN ASYMPTOMATIC NEUROCOGNITIVE IMPAIRMENT

Lucette Cysique[1], Madeline Nichols[1], Thomas Gates[2], James Soares[1], Kirsten Moffat[2], Caroline Rae[1], Bruce J. Brew[1]

[1]University of New South Wales, Sydney, NSW, Australia, [2]St. Vincent's Hosp, Sydney, NSW, Australia

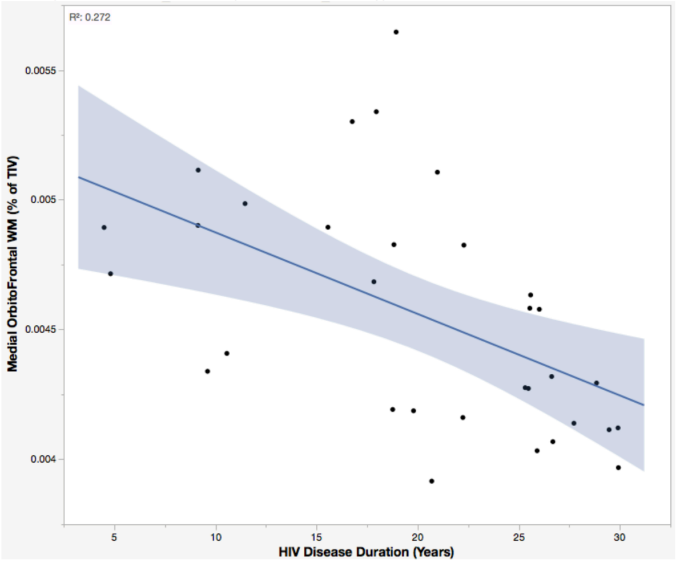
Background: There is controversy as to whether Asymptomatic Neurocognitive Impairment (ANI) in HIV-Associated Neurocognitive Disorders (HAND) solely represents a statistical neuropsychological entity with no neurobiological underpinning and no HIV causation. We hypothesized that in a sample of non-confounded virally suppressed HIV+ persons versus demographically comparable controls, HIV-related grey and white matter (WM) atrophy could be observed in ANI.

Methods: 85 HIV+ (plasma & CSF HIV RNA <50cp/mL, median nadir CD4=180, CD4=528) and 44 demographically comparable HIV- men (mean age=55; mean education=14.5 years; 90% men who have sex with men, 95% White Australian) underwent anatomical MRI, neuropsychological evaluation, and HIV laboratory tests. Volumes of interest (VOI) from MR images were extracted using Freesurfer to yield grey and WM in regions linked to HIV-related brain injury (total cortical volume, basal ganglia, lateral ventricles, fronto-striatal and fronto-parietal WM, all relative to Total Intracranial Volume, TIV). HAND status was ANI=38%, MND=13%, HAD= 3% based on the Global Deficit Score (GDS≥0.5) and functional decline; others were neuropsychologically (NP)-normal. A history of HAND occurred in 17.6%. We used multivariate analyses controlling for family-wise error rate to assess the effects of HIV status group on VOI. Next, ANI (N=32), MND (N=10) vs. NP-normal (N=40) and HIV biomarker (HIV duration, nadir CD4, current CD4 & CD8) effects on VOI were assessed with multiple regression controlling for a history of HAND.

Results: Relative to the HIV- group, the HIV+ group demonstrated subcortical grey (d=0.50-0.60) and WM (d=0.43-0.69) atrophy, with relative cortical sparing (d=0.23). ANI showed reduced medial-orbitofrontal WM compared to NP-normal cases (p=.04, β=-.31). MND showed enlarged lateral ventricles (p=.02, β=.34), reduced caudal-middle-frontal WM (p=.04, β=-.32), reduced caudal-anterior-cingulate WM (p=.006, β=-.42), and reduced inferior-parietal WM (p=.04, β=-.33) compared to NP-normal cases. HIV disease duration predicted greater medial-orbitofrontal WM atrophy only in ANI (p=.002, β=-.51; Fig.1). Higher CD8 were independently associated with atrophy in the inferior-parietal WM (p=.003, β=-.41).

Conclusion: ANI is associated with specific frontal WM atrophy. HIV disease duration is a unique contributor to ANI related brain atrophy. These findings give neurobiological validity to ANI and may serve as an ANI biomarker.

Figure 1: HIV disease duration is associated with atrophy of the medial-orbitofrontal WM in ANI (univariate correlation is presented for clarity)



122 LONGITUDINAL COGNITIVE OUTCOMES AFTER TREATMENT IN ACUTE HIV INFECTION

Phillip Chan[1], Umit Tokac[2], Joanna Hellmuth[3], Eugène Kroon[1], Donn Colby[1], Carlo Sacdalan[1], James L. Fletcher[1], Somporn Tipsuk[1], Suteeraporn Pinyakorn[4], Merlin L. Robb[5], Jintanat Ananworanich[4], Victor Valcour[3], Serena S. Spudich[6], Robert Paul[2]

[1]SEARCH, Bangkok, Thailand, [2]University of Missouri St Louis, St Louis, MO, USA, [3]University of California San Francisco, San Francisco, CA, USA, [4]US Military HIV Research Program, Bethesda, MD, USA, [5]US Military HIV Research Program, Silver Spring, MD, USA, [6]Yale University, New Haven, CT, USA

Background: HIV-infected individuals continue to exhibit cognitive dysfunction despite achieving viral suppression with antiretroviral therapy (ART). It remains unclear if initiation of ART during acute HIV (AHI) results in more favorable long-term cognitive outcomes.

Methods: Participants included 445 AHI individuals (Fiebig stages I-V) who initiated ART within 30 days after diagnosis and maintained virologic control over the study period. They completed a brief cognitive battery that measured fine motor speed and dexterity, psychomotor speed, and executive functioning at baseline before ART and then at 2 years (n=262) and 6 years (n=47) after ART with sustained viral suppression. Global cognitive performance (NPZ-4) and frequency of cognitive impairment (performance < -1 SD on ≥ 2 tests, or <-2 SD on ≥ 1 test) were determined at baseline and follow-up. Group-based trajectory analysis (GBTA) compared longitudinal test performance of the AHI group to performance obtained from 99 HIV-negative healthy Thai individuals. Meaningful cognitive change was defined as performance differences ≥ 0.5 SD or > 1 standard error of measurement. Multiple regression models examined the co-variance between test performance and demographic/clinical variables.

Results: Most participants were male (>90%), with a mean age of 26 years (Table). Cognitive impairment was identified in 26% at baseline, 10% at 2

years, and 15% at 6 years. Baseline plasma HIV RNA correlated with baseline NPZ-4 (p=0.005, adjusted β=-0.103, 95% CI -0.176 to -0.031). GBTA revealed significant improvement in cognitive test performance in all participants from baseline to year 2, and from year 2 to year 6 (all p<0.001). In addition, the time effect analysis showed that individuals' NP performance significantly changed overtime (F(32,2) ≥21.36, p<0.001). The average degree of improvement (Δz-score=1.22) exceeded that estimated from practice effects alone. In addition, the average degree of improvement was more pronounced for individuals who had z-score <-1 at baseline (Δz-score=2.61).

Conclusion: Our findings reveal favorable long-term cognitive performance in the context of ART-induced viral suppression initiated during early infection. Improvement occurs in the cohort over the course of treatment and exceeds that expected from practice effect. The results suggest the need of proactive identification and health care system readiness for this unique group of patients.

Characteristics	Baseline (N=445)	Two-Year Follow-Up (N=262)#	Six-Year Follow-Up (N=47)#
Age, year	26 (9)	28 (9)	32 (10)
Gender at birth, male, n (%)	432 (97)	250 (96)	42 (90)
Education, bachelor degree or above, n (%)	261 (59)	162 (62)	31 (66)
Fiebig stage, n (%) I & II III – V	 177 (40) 268 (60)	 122 (47) 140 (53)	 23 (49) 24 (51)
Plasma HIV RNA (Log10 copies/ml)	5.90 (1.50)	-	-
CD4 lymphocytes count	365 (239)	637 (263)	676 (334)
CD8 lymphocytes count	515 (548)	580 (325)	590 (341)
CD4/CD8 ratio	0.706 (0.618)	1.11 (0.550)	1.12 (0.520)
ARS presentation at baseline, n (%)	340 (76)	195 (74)	37 (79)
Cognitive impairment, n (%)	115 (26)	26 (10)	7 (15)

Median and IQR are presented unless specified. ARS = acute retroviral syndrome, HIV blips below 400 copies/ml and no longer than 12 weeks were included
Only participants with sustained viral suppression are included.

123 IMPACT OF ART REGIMENS ON CSF VIRAL ESCAPE IN HIV-1 INFECTED ADULTS

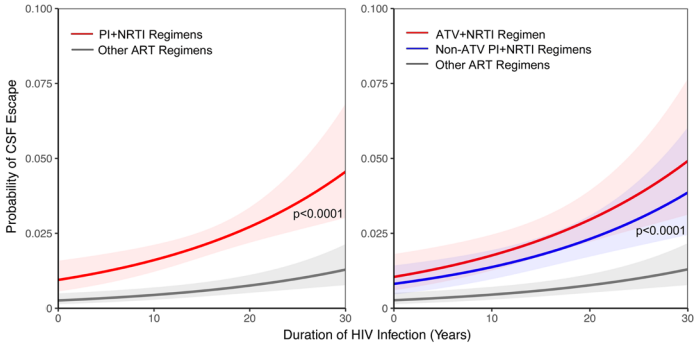
Shibani S. Mukerji[1], Vikas Misra[1], David Lorenz[1], Hajime Uno[1], Susan Morgello[2], Donald Franklin[3], Ronald J. Ellis[3], Scott L. Letendre[3], Dana H. Gabuzda[1]
[1]Dana–Farber Cancer Institute, Boston, MA, USA, [2]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [3]University of California San Diego, La Jolla, CA, USA

Background: Cerebrospinal fluid (CSF) viral escape occurs in 4-20% HIV-infected adults on antiretroviral therapy (ART), yet the impact of ART regimens on CSF escape in HIV infection is unclear.

Methods: Prospective study of 1063 participants on ART from the NNTC, CHARTER, and HNRC cohorts (age ≥18, baseline plasma viral load (VL) ≤400 copies/ml between 2005-2016). CSF escape was defined as paired CSF VL ≥ plasma VL, or CSF VL >50 copies if plasma VL was undetectable. Odds ratio for ART regimens (PI with nucleoside reverse transcriptase inhibitor [PI+NRTI] versus other ART [excluding monotherapy]) and CSF escape was estimated using mixed-effects models, adjusting for age at HIV diagnosis, duration of infection, CD4 nadir, plasma VL≤50 copies/mL, and number of CSF exams. Drug resistance mutation frequencies in plasma and CSF were calculated using a merged dataset from cohort participants and published studies (n=99).

Results: Baseline mean age was 46 years; median plasma VL, CD4 nadir, and CD4 count was 50 copies/mL, 88 cells/μL, and 424 cells/μL, respectively. Forty-eight percent were on PI+NRTI, 33% on non-NRTI, and 6% on integrase inhibitors. During 4,785 total person-years of follow up, CSF escape occurred in 77 participants (7.2%, n=127 events). PI+NRTI use was an independent predictor of CSF escape (OR 3.1 [95% CI: 1.8-5.0]) in adjusted analyses and models restricted to plasma VL ≤50 copies/ml (p<0.001). Regimens containing atazanavir (ATV) were a stronger predictor of CSF viral escape [OR 3.2 [95% CI: 1.8-5.5]) than non-ATV PI+NRTI regimens [OR 2.7 [95% CI: 1.5-4.8]) when compared to other ART regimens. Plasma and CSF M184V/I along with thymidine-analog mutations (TAMs) were more frequent in CSF escape compared to those without escape (23% vs. 2.3%), while accessory resistance mutation frequencies were similar. CNS penetration-effectiveness (CPE), genotypic susceptibility scores (GSS), and GSS-adjusted CPE scores were calculated for CSF escape patients with M184V/I mutations (n=34). The median unadjusted CPE score was 7 [IQR: 7-8], but adjusted CPE scores were low (<5) for CSF and plasma in 27 (79%) and 13 (38%) patients, respectively, indicating suboptimal CNS drug availability.

Conclusion: PI+NRTI regimens, in particular ATV-containing regimens, are independent predictors of CSF escape in HIV+ patients. Reduced CNS ART bioavailability may predispose to CSF escape in patients with M184V/I mutations. These findings suggest optimizing ART regimens may reduce risk of asymptomatic CSF escape.



Probability of CSF Viral Escape over 30 Years of HIV Infection by ART Regimen

124 SIV REBOUND IN THE SPINAL CORD AFTER STOPPING ART: A NOVEL CNS RESERVOIR

Megan E. McCarron, Lisa Mangus, Samuel A. Brill, Sarah E. Beck, Kelly A. Metcalf Pate, Suzanne E. Queen, **Joseph Mankowski**
Johns Hopkins University, Baltimore, MD, USA

Background: Growing evidence implicates the brain as a long-term latent HIV reservoir. The spinal cord, like the brain, contains HIV-infected microglia, but has not been evaluated as a potential HIV reservoir. This SIV/macaque study compared brain versus spinal cord by quantitating SIV DNA after long-term ART suppression, and by measuring SIV RNA tissue levels after release from ART to test if the spinal cord serves as a source of rebound virus.

Methods: 10 SIV-infected pigtailed macaques were treated with PMPA, FTC, and dolutegravir for 4 months. Plasma and CSF SIV RNA became undetectable within 40 days of starting ART. 4 of the 10 SIV-infected treated animals were euthanized after 3 months of suppression; the other 6 animals were euthanized after stopping ART (post 3 months suppression) when rebound plasma SIV RNA reached set-point levels. SIV DNA and RNA were measured in brain and spinal cord by qPCR. Spinal cord microglia were cultured from the ART release group to evaluate production of SIV by qRTPCR.

Results: In animals euthanized after 3 months of suppressive ART, SIV DNA levels were significantly higher in lumbar spinal cord than basal ganglia (31.2 versus 0.46 median SIV copies/10x5 cells; p = 0.029, Mann-Whitney). After stopping ART and tracking rebound SIV RNA in paired plasma and CSF samples, time to initial detection of SIV RNA in plasma after stopping ART was 4 days (group median) while CSF time to first rebound was 12 days. Animals reached plasma viral load set-point (10x5-10x6 SIV copies/mL) at an average of 20 days after ART withdrawal. CSF viral loads were lower at this time-point (10x4 SIV copies/mL). To establish the source of CSF SIV RNA, qRTPCR was performed on basal ganglia and spinal cord. Whereas SIV RNA was present in spinal cord of 5 of the 6 animals (median = 1,211 SIV copy eq/ug of tissue RNA), low level SIV RNA was only detected in the brain of one animal (10 copy eq/ug tissue RNA) To identify the cellular source of SIV RNA, spinal cord microglia were cultured; culture supernatants from all 6 animals were positive for SIV RNA by qRTPCR.

Conclusion: This study shows the spinal cord serves as a substantial SIV reservoir in the setting of ART. Our findings of higher levels of SIV DNA and RNA in spinal cord than brain suggest rebound SIV RNA in CSF may arise predominantly from SIV-infected spinal cord microglia rather than brain. The spinal cord merits consideration as a HIV reservoir that could challenge HIV cure efforts.

125 IDENTIFICATION OF BRAIN INJURY USING A NOVEL DEFINITION OF COGNITIVE IMPAIRMENT

Jonathan Underwood[1], James H. Cole[1], Davide De Francesco[2], Caroline Sabin[2], Alan Winston[1]
[1]Imperial College London, London, UK, [2]University College London, London, UK

Background: Despite the reportedly high prevalence of HIV-associated cognitive impairment in the antiretroviral era, the relationships with neuroimaging measures of brain injury have been inconsistent. This lack of consistency may be explained by recent modelling data which has suggested that the two common methods of defining impairment, the HAND or 'Frascati' criteria and the global deficit score (GDS), have specificities below 80%. Here, we tested the hypothesis that a novel, multivariate method (NMM) of defining cognitive impairment would be more reliably associated with brain injury.

Methods: Cognitive function was tested across seven domains and T1-weighted MRI data were obtained from virally suppressed people living with HIV (PLWH) from the CHARTER cohort (n=139, mean [SD] age 45.2 [7.45], 79.1% male, 46.0% white ethnicity). Cognitive impairment was defined using the Frascati criteria and GDS as well as a NMM based on the Mahalanobis distance, with a priori specificity of 85% based on modelling data. Associations with brain volumes were assessed using multiple linear regression adjusting for age, intracranial volume, scanner and comorbidity status. In addition, a multivariate, machine learning model of healthy brain ageing using volumetric neuroimaging data (training dataset n=2001, age range 18-90 years, model R^2=0.88) was used to quantify the difference between apparent and chronological brain age and the associations with different definitions of cognitive impairment were determined.

Results: The prevalence of cognitive impairment was 53.2% using the Frascati criteria, 37.4% using the GDS and 20.9% using the NMM, despite similar median global T-scores between the groups (table). There were no associations between Frascati or GDS defined cognitive impairment and grey matter volume (p>0.5 for both). However, PLWH with cognitive impairment defined using NMM had 21.0 (3.51-69.2) mL less grey matter than PLWH without impairment (p<0.01). White matter volume did not differ between PLWH with and without cognitive impairment, regardless of the definition used (p>0.2 for all). Compared to PLWH without NMM defined cognitive impairment, PLWH with NMM impairment had older appearing brains (3.43 [0.17-6.68] years, p=0.04, others p>0.4).

Conclusion: The prevalence of cognitive impairment in virally suppressed PLWH varies depending on the definition used. The NMM method, where specificity can be set a priori, was associated with brain injury more consistently than the Frascati and GDS methods.

Table. Characteristics of HIV-positive individuals with cognitive impairment defined using different methodologies.

		Method of defining cognitive impairment					
	Cognitive status	Frascati	p-value	GDS	p-value	NMM	p-value
Prevalence of impairment, n (%)		74 (53.2%)		52 (37.4%)		29 (20.9%)	
Global T-score, median (IQR)	Impaired	42.7 (38.7-45.1)	<0.001	41.1 (37.8-44.3)	<0.001	43.7 (36.4-45.6)	<0.001
	Not impaired	50.7 (48.2-53.5)		49.8 (47.0-53.2)		48.2 (44.5-53.3)	
Grey matter volume, mean† (95% CI) mL	Impaired	641 (631-651)	0.72	640 (630-650)	0.53	627 (614-640)	<0.01
	Not impaired	643 (633-654)		644 (634-654)		648 (639-657)	
White matter volume, mean† (95% CI) mL	Impaired	462 (451-473)	0.50	460 (449-471)	0.22	458 (443-473)	0.31
	Not impaired	467 (455-478)		469 (457-480)		467 (457-477)	
Brain-PAD, mean‡ (95% CI) mL	Impaired	3.13 (0.95-5.31)	0.55	3.64 (1.31-5.97)	0.87	5.97 (3.03-8.92)	0.04
	Not impaired	4.03 (1.64-6.42)		3.40 (1.08-5.73)		2.54 (0.51-4.57)	

p-values calculated for the comparison between those with and without cognitive impairment for each classification method
†least-squares means adjusted for age, intracranial volume, scanner and comorbidity status
‡least-squares means adjusted for scanner and comorbidity status

Abbreviations: GDS – global deficit score; NMM – novel multivariate method; PAD – predicted age difference = brain predicted age – chronological age (i.e. positive values indicate brains that are older appearing than expected).

126 HEME OXYGENASE-1 POLYMORPHISM ASSOCIATES WITH NEUROIMMUNE ACTIVATION IN HIV SUBJECTS

Alexander J. Gill[1], Rolando Garza[1], Suren A. Ambegaokar[2], Patricia J. Vance[1], Benjamin B. Gelman[3], Dennis L. Kolson[1]
[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Ohio Wesleyan University, Delaware, OH, USA, [3]University of Texas at Galveston, Galveston, TX, USA

Background: Heme oxygenase-1 (HO-1) is a critical cytoprotective enzyme that limits oxidative stress, inflammation, and cellular injury within the central nervous system (CNS) and other tissues. We previously demonstrated that HO-1 protein expression is decreased within the brains of HIV+ subjects and that this HO-1 reduction correlates with CNS immune activation and neurocognitive dysfunction. To define a potential CNS protective role for HO-1 against HIV, we analyzed a common HO-1 promoter region (GT)n dinucleotide repeat polymorphism implicated in regulating HO-1 promoter transcriptional activity (shorter repeats associate with greater transcription), in an expanded version of this HIV autopsy cohort.

Methods: HO-1 (GT)n polymorphism allele lengths were determined by PCR and capillary electrophoresis, and brain prefrontal cortex RNA expression was analyzed by qPCR from an autopsy cohort of HIV-, HIV+, and HIV encephalitis (HIVE) subjects (n=554). Statistical analyses were performed by chi-square, Kruskal-Wallis, and multivariate linear regression.

Results: The HO-1 (GT)n polymorphism allele repeat lengths ranged from 13 to 44 repeats with a trimodal distribution of peaks at 23, 30, and 39, as in previous reports. Based on this allele repeat length distribution, we assigned genotypes as short (< 27), medium (27-34) and long (> 34) HO-1 alleles. HIV+ subjects with short alleles had a significantly lower risk of HIVE (p=0.04, odds ratio=0.62). In HIV+ subjects without HIVE, the presence of a short allele correlated significantly with lower brain type I interferon responses (ISG15 p<0.001, MX1 p<0.001, IRF1 p=0.007) and T-lymphocyte activation markers (CD38 p=0.008, GZMB p=0.01, CD8A p=0.07). No correlations were found with macrophage markers (CD163, CD68), endothelial markers (PECAM, VWF), or the B-lymphocyte maker CD19. Also the presence of a short allele did not correlate with plasma or CNS viral loads or CD4 T-cell counts or nadirs.

Conclusion: Our data suggest unique modifying risk effects for HIV- induced CNS neuroinflammation and associated neuropathogenesis that are driven by an individual's HO-1 promoter (GT)n polymorphism allele repeat length. The presence of shorter HO-1 alleles might provide neuroprotection through decreased neuroimmune activation and neuroinflammation as a result of increased HO-1 promoter activity. Therapeutic strategies that induce HO-1 expression may further decrease HIV-associated CNS neuroinflammation and decrease the risk for development of HIV neurological disease.

127 RETREATMENT OF HEPATITIS C INFECTION IN PATIENTS WHO FAILED GLECAPREVIR/PIBRENTASVIR

David L. Wyles[1], Ola Weiland[2], Betty Yao[3], Robert Reindollar[4], Frank Weilert[5], Jean-Francois Dufour[6], Stuart Gordon[7], Fred Poordad[8], Albrecht Stoehr[9], Ashley Brown[10], Stefan Mauss[11], Suvajit Samanta[3], Tami Pilot-Matias[3], Lino Rodrigues[3], Roger Trinh[3]
[1]Denver Health Medical Center, Denver, CO, USA, [2]Karolinska University Hospital, Stockholm, Sweden, [3]AbbVie, Inc, North Chicago, IL, USA, [4]Piedmont Healthcare, Statesville, NC, USA, [5]Waikato Hospital, Hamilton, New Zealand, [6]University Hospital of Bern, Bern, Switzerland, [7]Henry Ford Hospital, Detroit, MI, USA, [8]University of Texas at San Antonio, San Antonio, TX, USA, [9]Institute for Interdisciplinary Medicine, Hamburg, Germany, [10]Imperial College London, London, UK, [11]Center for HIV and Hepatogastroenterology, Düsseldorf, Germany

Background: Glecaprevir*/pibrentasvir (G/P; *identified by AbbVie and Enanta) is a next-generation Hepatitis C virus (HCV) treatment regimen that has demonstrated high sustained virologic response (SVR) regardless of HCV genotype (GT) or baseline patient or viral characteristics. Approximately 1% of patients treated in the G/P clinical trial program to date had virologic failure (VF) and no data have been presented on their outcomes following retreatment. These patients were enrolled into a retreatment study, MAGELLAN-3 (NCT02939989).

Methods: MAGELLAN-3 is an ongoing phase 3b, open-label trial, in which patients who had VF following G/P were retreated with the combination of G/P 300 mg/120 mg once daily (QD) + sofosbuvir (SOF) 400 mg QD + ribavirin (RBV) 1,000–1,200 mg (weight based, twice daily). Patients who were non-GT3-infected, non-cirrhotic, and naïve to protease inhibitor and/or NS5A inhibitor prior to VF with the G/P regimen received 12-week (Arm A) treatment with the combination regimen; all other enrolled patients who did not meet any of these criteria received the same regimen for 16 weeks (Arm B). Efficacy (primary outcome is SVR at post-treatment (PT) Week 12 [SVR12]), safety, and baseline resistance were assessed. Preliminary SVR at PT Week 4 (SVR4) results, safety, and baseline resistance are reported here.

Results: As of 15 September 2017, 24 patients were enrolled (3 in Arm A; 21 in Arm B). Baseline characteristics are presented in the table. To date, 12 of 13 patients who completed PT Week 4 achieved SVR4. One patient in Arm B who had a GT1 infection and prior treatment experience with protease inhibitor and/or NS5A inhibitor before failing the G/P regiment experienced relapse at PT Week 4. Adverse events (AEs) reported in ≥10% of patients overall were headache (25.0%), pruritus (25.0%), dizziness (16.7%), and irritability

(16.7%). One patient had a serious AE of cholelithiasis considered unrelated to the treatment by the investigator. There were no study discontinuations. No significant laboratory abnormalities were observed.

Conclusion: Preliminary data show that the combination of direct-acting antiviral agents G/P + SOF + RBV yielded a high rate of SVR4 in patients who had VF with G/P treatment. The retreatment regimen was well tolerated. Study enrollment is ongoing and updated results, including the SVR12 rate for this subset of patients, will be reported at the conference.

Table. Patient Characteristics (N=24)

Parameter	Arm A (n=3)	Arm B (n=21)	Total (N=24)
Mean Age, years (SD)	54 (3.5)	55 (7.9)	55 (7.5)
Male, n (%)	2 (66.7)	17 (81.0)	19 (79.2)
White, n (%)	3 (100.0)	18 (85.7)	21 (87.5)
Hepatitis C Virus Genotype, n (%)			
1	1 (33.3)	7 (33.3)	8 (33.3)
2	2 (66.7)	0	2 (8.3)
3	0	14 (66.7)	14 (58.3)
Resistance-associated Substitutions, n (%)			
NS3 alone	0	0	0
NS5A alone	1 (33.3)	11 (52.4)	12 (50.0)
Both NS3 and NS5A	1 (33.3)	6 (28.6)	7 (29.2)
Missing	1 (33.3)	4 (19.0)	5 (20.8)
Compensated Cirrhosis, n (%)	0	7 (33.3)	7 (29.2)

128 8 WEEKS OF GRAZOPREVIR/ELBASVIR FOR ACUTE HCV: A MULTICENTER CLINICAL TRIAL (DAHHS 2)

Anne Boerekamps[1], Anja De Weggheleire[2], Guido van den Berk[3], Fanny Lauw[4], Mark Claassen[5], Dirk Posthouwer[6], Wouter Bierman[7], Sebastiaan Hullegie[1], Eric Florence[2], Anton Dofferhoff[8], Joop E. Arends[9], Bart Rijnders[1]

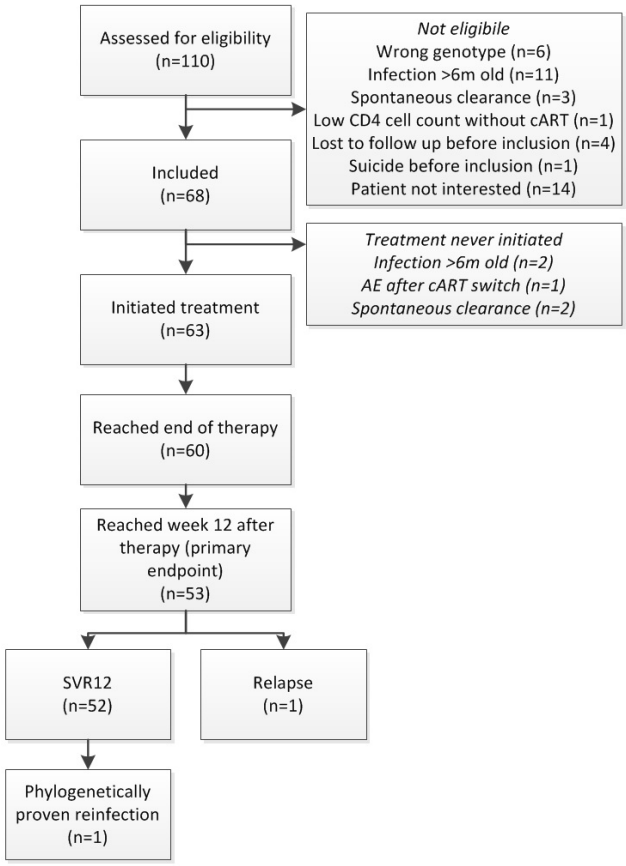
[1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]Institute of Tropical Medicine, Antwerp, Belgium, [3]OLVG, Amsterdam, Netherlands, [4]Slotervaart MC, Amsterdam, Netherlands, [5]Rijnstate Hospital, Arnhem, Netherlands, [6]Maastricht University Medical Center+, Maastricht, Netherlands, [7]University Medical Center Groningen, Groningen, Netherlands, [8]Radboud University Medical Center, Nijmegen, Netherlands, [9]University Medical Center Utrecht, Utrecht, Netherlands

Background: The arrival of direct acting antiviral (DAA) therapy for chronic hepatitis C (HCV) infection has led to speculations about HCV elimination. Modeling and real-life data on HCV elimination in well-defined risk groups like HIV-positive MSM have been promising (CROI 2017 LB137/136). However, high reinfection rates and increased sexual risk behavior may become significant obstacles. Another obstacle is the lack of approval of DAA for the treatment of acute HCV. Indeed, few studies evaluated DAA as acute HCV therapy and included a small numbers of patients (n=17 to 26). Sustained virological response (SVR) rates in these studies varied between 32-59% for sofosbuvir/ribavirin and 77-100% for sofosbuvir/ledipasvir. The Dutch Acute HCV in HIV study no. 2 (DAHHS2; NCT02600325) was designed to prove that 1. grazoprevir/elbasvir are effective when given during the acute phase of HCV and 2. treatment can be shortened during acute HCV.

Methods: Single-arm prospective open-label multicenter trial in patients with acute HCV genotype 1 or 4. Fifteen hospitals referred patients diagnosed with an acute HCV to 1 of the 9 DAHHS study centers spread across the Netherlands and Belgium. Patients received 8 weeks of grazoprevir/elbasvir 100/50mg QD. Therapy was initiated no later than 26 weeks after the estimated day of infection. The primary endpoint was SVR 12 weeks post-treatment in the intention to treat population.

Results: From 02/2016 and ongoing, 110 patients with a recently acquired HCV were evaluated for eligibility. 68 were enrolled, 5 patients never initiated therapy (Fig1). Of the 63 patients that started therapy, 53 reached the primary endpoint at the time of abstract submission. All subjects were MSM with a mean age of 47 years and all but 3 were HIV-infected. CD4 at baseline in HIV-infected patients was 600/µl (IQR 474-760) and HIV viral load was <50 c/ml in 97%. The genotype 1a/1b/4 distribution was 62/0/38%. Median HCV viral load at study entry was 3.67E5 IU/ml (IQR 1.95E4-2.00E6) and 16% (n=10/63) of HCV infections were a reinfection. SVR12 was observed in 52 of 53 patients (98%; 95%CI 90-100%). One patient relapsed, but without new NS5a/NS3 compared to his baseline virus. One of the 52 patients had a phylogenetically proven new infection. All 13 patients with a baseline viral load >10E6 IU/ml reached SVR12.

Conclusion: An 8 week course of grazoprevir/elbasvir (a NS3/NS5a combination) is highly effective for the treatment of acute HCV. The results of all 63 patients will be presented.



129 FUELING THE EPIDEMIC: LOW RATES OF SPONTANEOUS CLEARANCE OF ACUTE HCV COINFECTION

Christoph Boesecke[1], Elena Müller Martinez[1], Mark Nelson[2], Patrick Ingiliz[3], Thomas Lutz[4], Stefan H. Scholten[5], Christiane Cordes[6], Heribert Knechten[7], Maria Martínez-Rebollar[8], Christoph D. Spinner[9], Michael Rausch[10], Thomas Reiberger[11], Stefan Mauss[12], Jürgen K. Rockstroh[1]

[1]Bonn University Hospital, Bonn, Germany, [2]Chelsea and Westminster Hospital, London, UK, [3]Center for Infectiology, Berlin, Germany, [4]Infektiologikum, Frankfurt, Germany, [5]Praxis Hohenstaufenring, Cologne, Germany, [6]Praxis Cordes, Berlin, Germany, [7]Praxenzentrum Blondelstrasse, Aachen, Germany, [8]Hospital Clinic of Barcelona, Barcelona, Spain, [9]Klinikum rechts der Isar, Munich, Germany, [10]Ärztezentrum Nollendorfplatz, Berlin, Germany, [11]Medical University of Vienna, Vienna, Austria, [12]Center for HIV and Hepatogastroenterology, Düsseldorf, Germany

Background: Several clinical trials have shown comparable SVR rates in the treatment of acute hepatitis C (AHC) coinfection with direct acting antivirals (DAA) compared with chronic hepatitis C (HCV) coinfection. In addition, data from modelling and real life cohorts have shown a reduction in AHC incidence when DAA are used to treat acute HCV coinfection. However, with no DAA currently being licensed for the treatment of AHC and with the high drug prices the question becomes eminent which patients will resolve their AHC infection spontaneously and which patients should be offered timely treatment. Here we evaluate rates of spontaneous clearance of acute HCV coinfection in a large European cohort.

Methods: The PROBE-C study is an observational European cohort on AHC in HIV coinfection. Between 2007 and 2016 465 AHC episodes were documented in HIV-infected patients with at least 12 months of follow-up from Austria, Denmark, France, Germany, Great Britain and Spain. Fisher's exact, chi-square and Mann-Whitney U test were used for statistical analysis.

Results: 457/465 (98%) patients were male, median age was 41 years (IQR 38-46). Main routes of HCV transmission were MSM (98.9%) and IVDU (1.1%). 78.3% of patients were infected with HCV genotype (GT) 1, 2.6% with GT3 and 18.6% with GT4. Median baseline HCV-RNA was 230,000 IU/mL (135,000-474,432) and median CD4+ T cell count 574 cells/µL (547-604). 92% of all patients received cART, 91% had baseline suppressed HIV-RNA (<200 copies/mL). Median maximum ALT was 445 U/l (402-522). Overall, in 55/465 (11.8%) AHC resolved spontaneously. In 325/465 (69.9%) treatment was initiated within 48 weeks of AHC diagnosis, in 61 cases with interferon-free DAA regimen 24 weeks after acute HCV diagnosis. SVR rate was 75.7%. 51/465 (11%) patients were HCV reinfected. 85/465 (18.3%) developed chronic HCV infection. There was no statistically significant association between spontaneous clearance and HCV transmission risk, HCV GT, HCV RNA levels nor baseline ALT or HIV parameters.

Conclusion: Spontaneous clearance of acute HCV infection in the setting of HIV coinfection is a rare event. Almost 90% of acutely infected patients face a chronic course. Therefore treatment initiation needs to be considered early on to prevent onward transmission to sex partners. As a result DAA drug labels as well as clinical guidelines need to be amended to allow usage of DAA during the acute phase of HCV infection in a high-risk population.

130 INTERNATIONAL VERSUS DOMESTIC HCV TRANSMISSION IN MSM: A PERSPECTIVE FOR THE DAA ERA

Luisa Salazar-Vizcaya[1], Roger Kouyos[2], Karin Metzner[2], Kamila Caraballo[3], Cyril Shah[2], Jürg Böni[2], Manuel Battegay[4], Enos Bernasconi[5], Alexandra Calmy[6], Matthias Cavassini[7], Herbert A. Mbunkah[2], Olivia Keiser[8], Andri Rauch[1]
[1]University Hospital of Bern, Bern, Switzerland, [2]University Hospital Zurich, Zurich, Switzerland, [3]Medical University of Warsaw, Warsaw, Poland, [4]University Hospital Basel, Basel, Switzerland, [5]Servizio di Malattie Infettive, Lugano, Switzerland, [6]University Hospitals of Geneva, Geneva, Switzerland, [7]Lausanne University Hospital, Lausanne, Switzerland, [8]University of Geneva, Geneva, Switzerland

Background: Rapid scale-up of early direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) in HIV-positive men who have sex with men (MSM) is ongoing in many European countries. It is expected to abate the high incidence of HCV associated with sexual practices. But isolated public health strategies in neighbouring countries might boost or hinder each other if international transmission is frequent. Switzerland is ideally placed to study international transmission due to its small population size and its high connectivity to international transmission networks. We used molecular epidemiology for estimating the contribution to the Swiss epidemic of HCV-infections acquired by contact with MSM from abroad, as a measure of potential vulnerability to foreign public health strategies.

Methods: HCV subtype 1a genomes from 29 HIV-positive MSM with incident HCV infections were sequenced using Illumina technology (study sequences). Subtype 1a accounts for 62% of replicating infections in this population. Sampling dates ranged between 1999 and 2013. We used RAxML to infer maximum-likelihood phylogenetic trees containing a 436-base-pairs fragment of the NB5B region of the study sequences and other circulating strains (including 84 from other HIV+ people in Switzerland and 220 from across Europe). We established the likely geographic origin of infection (Swiss-to-Swiss versus imported transmissions) by inferring transmission clusters and locating the study sequences in such clusters. Sufficient degree of certainty was defined as a bootstrap value above 70%.

Results: Ninety-seven percent of study sequences (28/29) were located in MSM clusters. Of those, ninety-six percent (27/28) were found amongst five transmission clusters within Europe (including Switzerland; Figure-A). Swiss-to-Swiss transmission was estimated to range between 38% and 76%. German-Swiss transmission was estimated to range between 7% and 41%. Transmissions linked to other European regions ranged between 0% and 28% (Figure-B).

Conclusion: Swiss-domestic transmission of HCV subtype 1a is ongoing and therefore national treatment scale-up is expected to reduce HCV-incidence. But at least a quarter of sequenced infections were likely acquired by contacts with MSM from other European countries, in particular the neighboring country Germany. Our findings suggest the need for joint European scale-up schemes. Time-updated phylogenies are valuable for assessing the impact of national DAA scale-up programs.

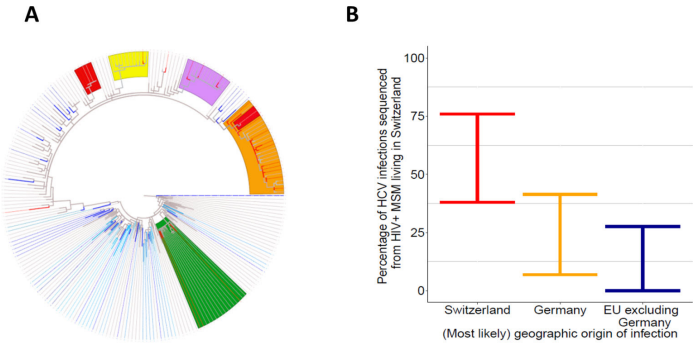


Figure
Panel A. NS5B fragment phylogenetic tree for HCV subtype 1a containing sequences from incident infections in MSM in Switzerland (study sequences, red branches and highlight) pooled with other circulating sequences. Color code: Swiss MSM outside study population: Pink; Swiss people who inject drugs (PWID): dark blue. Swiss but neither PWID nor MSM classification available: light blue. Transmission clusters (>70% bootstrap value) are highlighted to indicate dominant geographic locations. Color code: Switzerland: red; Mixed Switzerland & Germany: orange; Yellow: Holland; green: UK, mixed Europe: violet). Identical NS5B sequences were assumed to share ancestor. This tree displays only one sequence per each of these pairs. **Panel B.** Estimated ranges for the percentage of study sequences strongly associated with different geographic locations.

131 ITAP TRIAL: MATERNAL AND INFANT EFFICACY AND SAFETY RESULTS 12 MONTHS AFTER DELIVERY

Gonzague Jourdain[1], Linda J. Harrison[2], Nicole Ngo-Giang-Huong[1], Tim R. Cressey[1], Luc Decker[1], Camlin Tierney[2], Jullapong Achalapong[3], Prateep Kanjanavikai[3], Anita Luvira[3], Ussanee Srirompotong[3], Trudy V. Murphy[4], Noele Nelson[4], George K. Siberry[5], Stanislas Pol[6]
[1]IRD, Chiang Mai, Thailand, [2]Harvard University, Cambridge, MA, USA, [3]Ministry of Pubic Health, Nonthaburi, Thailand, [4]CDC, Atlanta, GA, USA, [5]NIH, Bethesda, MD, USA, [6]Cochin Hospital, Paris, France

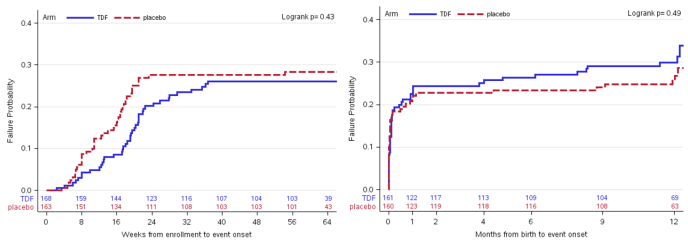
Background: iTAP was a double-blind randomized clinical trial assessing the efficacy and safety of tenofovir disoproxil fumarate (TDF) to prevent perinatal HBV transmission in hepatitis B virus (HBV) chronically infected pregnant women with HBeAg (NCT01745822). We report secondary endpoints through 12 months after delivery.

Methods: HBsAg and HBeAg positive women (age ≥18 years, ALT ≤60 IU/L, negative HIV and hepatitis C serology, creatinine clearance >50 mL/min) were randomized to receive TDF 300mg or placebo, once daily from 28 weeks gestation through 2 months postpartum in 17 hospitals in Thailand. Infants received HBIg at birth, and HB vaccine at birth, 1, 2, 4 and 6 months of age. After their 6-month visit, mothers were seen at 12 months and infants at 9 and 12 months. Infant HBV DNA PCR was performed at 9 months and an HBsAg test at 12 months.

Results: Of the 331 (168 TDF, 163 placebo) enrolled pregnant women, 282 (85%) (140, 83% TDF; 142, 87% placebo) remained in follow-up to 12 months postpartum. Median follow-up was 63 weeks. Time to grade 3/4 or serious adverse event in women was not different by arm (Figure). At scheduled study visits, ALT was >60IU/L for 76 women on 160 occasions in TDF and 86 women on 199 occasions in placebo. Nine women of 155 on TDF and 9 of 157 on placebo had ALT >300IU/L during follow up; with 9 (6%) and 6 (4%), respectively, after study treatment discontinuation (Fisher's exact p=0.44). All ALT elevations were asymptomatic. Of 323 live births, 286 (89%) (146, 90% TDF; 140, 88% placebo) remained on follow-up until 12 months. One infant died (placebo) shortly after birth with multiple abnormalities. No other deaths occurred. Three infants (all placebo) were HBV infected by 6 months of age. No additional HBV infections were detected between 6 and 12 months. Of 275 infants evaluated for anti-HB antibodies at 12 months, 4 (all placebo) were <10 IU/L; including the 3 with HBV infection and one without HBV infection but a declining antibody level. The proportion of infants experiencing a grade 3/4 or serious adverse event was similar by arm (see Figure). Infants' weight, height and head circumference Z-scores at 12 months did not differ by arm.

Conclusion: Results were similar to those of the primary 6-month analysis. There were no statistically significant differences between the TDF and placebo arms in infant HBV infection or any secondary safety endpoints up to 12 months postpartum.

Figure: Time to first Grade 3/4 or Serious Adverse Event (Left=Women, Right=Infants)



132 STATIN EXPOSURE IS ASSOCIATED WITH DECREASED RISK OF CANCER

Roger Bedimo[1], Fatma Shebl[2], Keith M. Sigel[3], Sheldon T. Brown[4], Kristina Crothers[5], Matthew B. Goetz[6], Amy C. Justice[7], Janet Tate[7]
[1]VA North Texas Health Care Center, Dallas, TX, USA, [2]Yale University, New Haven, CT, USA, [3]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [4]James J. Peters VA Medical Center, Bronx, NY, USA, [5]University of Washington, Seattle, WA, USA, [6]VA Greater Los Angeles Health Care System, Los Angeles, CA, USA, [7]VA Connecticut Healthcare System, West Haven, CT, USA

Background: Beyond inhibition of cholesterol biosynthesis, statins appear to have pleiotropic effects, including modulation of cell growth, apoptosis, and inflammation. Statins may also reduce cancer risk, particularly among HIV-infected (HIV+) subjects who experience chronic inflammation and immune activation. Small observational studies have suggested an association between statin use and lower cancer risk in HIV+ but small sample sizes limited cancer type-specific analyses. Comparison of the association of statin exposure with cancer in HIV+ and HIV-uninfected comparators (HIV-) is also lacking. We used the Veterans Aging Cohort Study (VACS), a large observational cohort with cancer registry linkage and detailed pharmacy data to address these questions
Methods: We followed statin users identified between 2000-2012, beginning 180 days after an index date defined as first statin prescription for users and a random visit date in the same year for non-users. To account for known and potential confounders we fit a propensity score (PS) model for statin use including age, calendar year, smoking, chronic diseases (e.g., diabetes, hypertension, HCV co-infection, alcohol use disorder), and laboratory values (e.g., LDL, albumin). We matched each statin user to up to four non-users by PS. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CI) associated with statin use for all cancers, individual cancers, infection-related cancers (anal, colorectal, head and neck, liver, lymphoma, and stomach) and notinfection-related cancers.
Results: The PS-matched sample included 48,214 participants, of whom 23,512 (48.8%) were incident statin users. Incident cancers were diagnosed in 940 (9.7%) of 9,649 HIV+ and 3,079 (8.0%) in 38,565 uninfected. Overall, statin use was associated with ~20% reduced risk of any cancer [HR 0.82 (95% CI 0.77 – 0.88)] and ~40% lower risk for infection-related cancers [HR 0.62 (95% CI 0.55 – 0.70)]. In general, the association was stronger in HIV+, but the interaction did not reach statistical significance except for non-Hodgkin lymphoma
Conclusion: Statin exposure is associated with lower risk of cancer independent of HIV status. This protective effect appears to be stronger for infection-related cancers.

Table: Statin exposure and risk of cancer in US Veterans, 2000 - 2012

	All		HIV -	HIV +	
Cancer type	**HR (95% CI)**	**P**	**HR (95% CI)**	**HR (95% CI)**	**P for interaction**
Any Cancer	0.82 (0.77 – 0.88)	<.0001	0.85 (0.79 – 0.91)	0.75 (0.66 - 0.85)	0.086
Infection-related					
All	0.62 (0.55 – 0.70)	<.0001	0.66 (0.57 – 0.77)	0.52 (0.41 - 0.66)	0.088
Anal	0.82 (0.52 – 1.28)	0.383	1.17 (0.37 - 3.70)	0.77 (0.47 - 1.25)	0.505
Oropharynx	0.50 (0.38 – 0.66)	<0.001	0.58 (0.43 - 0.80)	0.30 (0.15 - 0.58)	0.074
Liver	0.50 (0.38 – 0.65)	<0.001	0.50 (0.37 - 0.69)	0.55 (0.33 - 0.91)	0.770
Colorectal	0.67 (0.52 – 0.87)	0.002	0.74 (0.56 - 0.97)	0.39 (0.20 - 0.79)	0.096
Hodgkin's Lymphoma	0.99 (0.46 – 2.13)	0.983	0.73 (0.19 – 2.79)	1.17 (0.45 – 3.03)	0.577
NHL	0.59 (0.42 – 0.83)	0.003	0.79 (0.51 - 1.22)	0.36 (0.20 - 0.66)	0.043
Not Infection-related					
All	0.91 (0.85 – 0.98)	.014	0.92 (0.85-1.00)	0.89 (0.76 – 1.04)	0.679
Lung and Bronchus	0.95 (0.82 – 1.11)	0.534	0.95 (0.79 - 1.14)	0.95 (0.71 - 1.28)	0.997
Prostate	0.96 (0.86 – 1.07)	0.447	0.96 (0.85 - 1.09)	0.94 (0.71 - 1.24)	0.875

133 PREDICTORS OF KS-IRIS IN MILD/MODERATE AIDS-KS DURING ART IN LOW-RESOURCE SETTINGS

Thomas Campbell[1], Minhee Kang[2], Trijn Umbleja[2], Susan E. Krown[3], Agrey Bukuru[4], Jeffrey N. Martin[5], Catherine Godfrey[6], Mulinda Nyirenda[7], Naftali Busakhala[8], Margaret Borok[9], Deborah Langat[10], Brenda Hoagland[11], Noluthando Mwelase[12], Mina C. Hosseinipour[13]
[1]University of Colorado, Aurora, CO, USA, [2]Harvard University, Cambridge, MA, USA, [3]AIDS Malignancy Consortium, New York, NY, USA, [4]Joint Clinical Research Centre, Kampala, Uganda, [5]University of California San Francisco, San Francisco, CA, USA, [6]DAIDS, NIAID, Rockville, MD, USA, [7]Malawi College of Medicine-Johns Hopkins University Research Project, Blantyre, Malawi, [8]Moi University, Eldoret, Kenya, [9]University of Zimbabwe, Harare, Zimbabwe, [10]Kenya Medical Research Institute/ Walter Reed Project, Kericho, Kenya, [11]Institute de Pesquisa Clinica Evandro Chagas, Rio de Janeiro, Brazil, [12]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [13]University of North Carolina Project–Malawi, Lilongwe, Malawi

Background: Kaposi sarcoma-associated immune reconstitution inflammatory syndrome (KS-IRIS) is characterized by abrupt worsening of KS after antiretroviral therapy (ART) initiation. Incidence and risks for KS-IRIS are not well-established, particularly in resource-limited settings, and well-defined diagnostic criteria have rarely been applied. In a planned secondary analysis, we evaluated the incidence and baseline factors associated with KS-IRIS in a multinational clinical trial.
Methods: 190 chemotherapy and ART-naïve, HIV-1-infected adults with mild-to-moderate KS in Africa and South America were randomized 1:1 to ART (TDF/FTC/EFV) alone or with delayed oral etoposide (ET; As-Needed) vs ART plus up to 8 cycles of ET (Immediate). KS-IRIS was prospectively defined as clinical progression of KS (PD) within 12 weeks of ART initiation associated with CD4+ increase ≥50 cells/uL and/or decreased plasma HIV RNA ≥0.5 $\log_{10}$ c/mL. KS response criteria were strictly defined and PD confirmed by an Independent Endpoint Review Committee. Analysis was restricted to participants who had week 48 data potential. Cumulative incidence was calculated using Kaplan-Meier methods and Gray's approach to compare between arms was used to account for competing risks, with censoring at wk 12. Wk 48 outcome was compared between participants with/without KS-IRIS in the As-Needed arm. Potential baseline characteristics associated with time to KS-IRIS were assessed using cause-specific Cox regression models and all subsets variable selection.
Results: The cumulative incidence of KS-IRIS was 21/94 (23.1%; 95%CI 15.0, 32.3) in the As-Needed arm vs 7/96 in the Immediate arm (7.4%; 95%CI 3.2, 13.9; P=0.003); among KS-IRIS median baseline CD4+ 217 vs 268 cells/uL and plasma HIV RNA 5.09 vs 5.54 $\log_{10}$ c/mL. Covariates associated with increased hazards of KS-IRIS in the final model are provided in the Table. Among evaluable participants in the As-Needed arm who did not initiate alternate KS treatment), there were trends toward more wk 48 PD (73% vs 28%) and less response (27% vs 45%) among 11 participants with KS-IRIS compared to 55 without KS-IRIS. Death by wk 48 among evaluable participants was 11% with KS-IRIS vs 7% without KS-IRIS.
Conclusion: KS-IRIS was common among persons with AIDS-KS initiating ART in low-resource settings; early ET reduced KS-IRIS risk. The presence of raised skin lesions, low albumin and low performance status should be considered as markers for higher risk of KS-IRIS during ART.

Associations with Time to KS-IRIS in the Final Model (Cause-specific Hazards)

Covariate	Effect level	Hazard Ratio (95% CI)	P-value
Study arm	As-Needed	3.45 (1.46, 8.15)	0.005
W0: ALB grade, categorized	Grade ≥1	2.40 (1.14, 5.06)	0.022
Scr: Karnofsky score, categorized	<90	2.33 (1.10, 4.91)	0.027
W0: Raised cutaneous lesions present	Yes	3.94 (1.18, 13.17)	0.026

134 ACTG 5282: HPV TEST & TREAT VS CYTOLOGY-BASED CERVICAL CANCER PREVENTION IN HIV+ WOMEN

Timothy Wilkin[1], Roy Matining[2], Vikrant Sahasrabuddhe[3], Huichao Chen[2], Reena Masih[4], Rosie Mngqibisa[5], Mohammed Rassool[6], Yamikani Mbilizi[7], Tsitsi M. Magure[8], Cynthia Riviere[9], Aida Asmelash[10], Ramesh Bhosale[11], Pamela Michelow[12], Catherine Godfrey[13], Cindy Firnhaber[14]
[1]Weill Cornell Medicine, New York, NY, USA, [2]Harvard University, Boston, MA, USA, [3]National Cancer Institute, Frederick, MD, USA, [4]Social &Scientific Systems, Silver Spring, MD, USA, [5]Epicentre, Mbarara, Uganda, [6]Clinical HIV Research Unit,

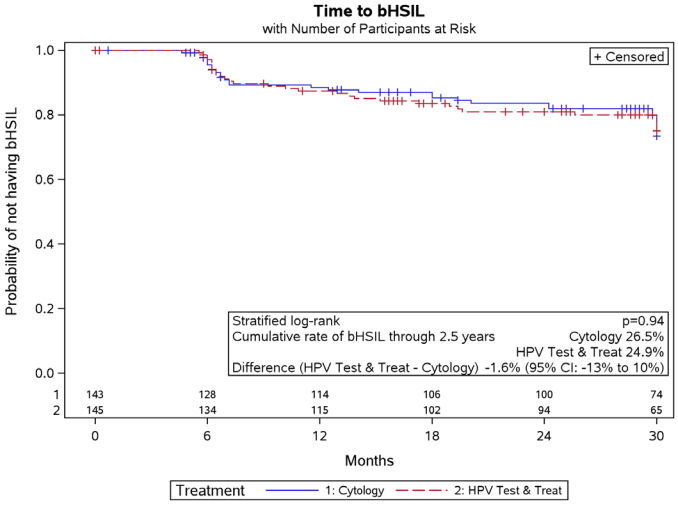
Johannesburg, South Africa, [7]Malawi Coll of Med–Johns Hopkins Univ Rsr Proj, Blantyre, Malawi, [8]University of Zimbabwe, Harare, Zimbabwe, [9]GHESKIO, Port-au-Prince, Haiti, [10]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [11]Byramjee Jeejeebhoy Government Medical College, Pune, India, [12]National Health Laboratory Service, Johannesburg, South Africa, [13]DAIDS, NIAID, Bethesda, MD, USA, [14]University of Witwatersrand, Johannesburg, South Africa

Background: Cytology-based cervical cancer screening, confirmation of high-grade squamous intraepithelial lesions by colposcopic biopsy (bHSIL), and loop electrosurgical excision (LEEP) treatment are difficult to implement in resource-constrained settings. We hypothesized that screening with high-risk human papillomavirus (hrHPV) testing followed by immediate cryotherapy of HPV positive women (HPV Test&Treat) may improve outcomes measured by reduction in bHSIL during follow-up.

Methods: A5282 is a randomized, open-label, phase 2, multinational clinical trial enrolling HIV-infected women age 18 or older with cervical hrHPV detected and having no cervical lesions or limited lesions appropriate for cryotherapy. Women were randomized to HPV Test&Treat or Cytology-based screening. For HPV Test&Treat, cervical biopsies were obtained followed by treatment with cervical cryotherapy, and in the Cytology Arm, women with abnormal cytology underwent colposcopy and directed biopsies followed by LEEP if bHSIL was detected. Women were followed every 6 months through 30 months. The primary endpoint was time to bHSIL detected at Month 6 through study completion and compared using log-rank test. The cumulative rate of bHSIL was estimated by the Kaplan-Meier method.

Results: HIV+ women (N=288, HPV Test&Treat 145, Cytology-based 143) were randomized: median age 35 years, 84% on antiretroviral therapy, median CD4 501 cells/mm^3. In the HPV Test&Treat Arm, 39 (27%) of women had bHSIL at entry and 142 (98%) underwent cryotherapy; in the Cytology Arm, 88 (62%) had abnormal cytology, 22 (15%) were diagnosed with bHSIL, and LEEP was performed on 12 (8%). In follow-up, time to bHSIL was similar between arms (see Figure, log-rank test p=0.92): 30 (21%) and 31 (22%) developed bHSIL and time to bHSIL was similar between arms (Figure, p=0.94). The prevalence of hrHPV at Month 6 was similar between arms (61% and 70%, p=0.13). There were no statistically significant differences in prevalence of abnormal cytology results at any follow-up visit (p≥0.16); bHSIL during study follow-up in the HPV Test&Treat arm were independently predicted by the presence of hrHPV (p=.014) and abnormal cytology (p=.03) at Month 6.

Conclusion: HPV test-and-treat was not associated with improved bHSIL outcomes as compared to a single round of cytology-based screening. This may be due to a poorer than expected response to cryotherapy in this population. More effective treatment options are required to improve outcomes from screen-and-treat programs.



135 ARV PROPHYLAXIS/ART INITIATION AT BIRTH LIMITS THE SIZE OF THE RESERVOIR IN CHILDREN

Marta Massanella[1], Jintanat Ananworanich[2], Louise Leyre[1], Thidarat Jupimai[3], Panadda Sawangsinth[3], Mark de Souza[4], Suteeraporn Pinyakorn[2], Piyarat Suntarattiwong[5], Pope Kosalaraksa[6], Thitiporn Borkird[7], Kulkanya Chokephaibulkit[8], Suparat Kanjanavanit[9], Thanyawee Puthanakit[10], Nicolas Chomont[1]

[1]Centre de Research du Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada, [2]US Military HIV Research Program, Bethesda, MD, USA, [3]HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [4]SEARCH, Bangkok, Thailand, [5]Queen Sirikit National Institute of Child Health, Bangkok, Thailand, [6]Khon Kaen University, Khon Kaen, Thailand, [7]Hat Yai Hospital, Songkhla, Thailand, [8]Mahidol University, Bangkok, Thailand, [9]Nakornping Hosp, Chiang Mai, Thailand, [10]Chulalongkorn University, Bangkok, Thailand

Background: Early antiretroviral therapy (ART) limits the size of the HIV reservoir in adults; however pediatric data are limited. We assessed the impact of age of ARV prophylaxis (proARV)/ART initiation on the size of the HIV reservoir in early-treated vertically infected infants.

Methods: We measured markers of HIV persistence in infants (4-23 weeks of age) who received uninterrupted triple proARV since birth (n=9) and those who did not receive proARV or interrupted either triple or AZT prophylaxis (n=17). In addition, samples from suppressed children (median 2.7 years of age) who initiated continuous ART/proARV at birth (n=12) or later (range 3-26 weeks, n=63) were also studied. Total and integrated HIV DNA in CD4 T-cells were quantified by real-time PCR and we used TILDA to measure the frequency of CD4 T cells producing multiply spliced RNA (msRNA) as a proxy for virus production, with and without stimulation.

Results: Viral loads were significantly lower in infants who received continuous proARV from birth compared to those who interrupted or never received prophylactic treatment (p<0.001). Similarly, levels of integrated HIV DNA tended to be lower in infants receiving uninterrupted proARV compared to those in whom proARV was interrupted or not initiated (p=0.08). The frequencies of cells producing msRNA spontaneously and after stimulation were significantly lower in infants who received uninterrupted proARV (p=0.003 and p=0.005, respectively). Importantly, the frequency of latently infected cells was significantly lower in infants who received uninterrupted proARV since birth (p=0.048). After ART initiation, children who received proARV/ART since birth had significantly lower total and integrated HIV DNA than children starting treatment later (p=0.01 and p=0.03, respectively). Although TILDA values were equally low and often below the limit of detection in both treated groups (43% and 47% samples with detectable TILDA, in the immediate and deferred groups, respectively), the size of the inducible reservoir correlated with age at which continuous proARV/ART was initiated for the first time (r=0.28, p=0.04).

Conclusion: Neonatal proARV without complete viral suppression significantly limits the size of the reservoir. Notably, uninterrupted ART dramatically restricts the pool of cells harboring total and integrated HIV DNA. Importantly, the age at which continuous proARV /ART is initiated for the first time impacts the size of the inducible reservoir.

136 LOW HIV RESERVOIR AT 84 WEEKS IN VERY EARLY TREATED HIV-INFECTED CHILDREN IN BOTSWANA

Roger L. Shapiro[1], Mathias Lichterfeld[2], Michael D. Hughes[1], Kara Bennett[3], Kenneth Maswabi[4], Gbolahan Ajibola[4], Pilar Garcia-Broncano[5], Sikhulile Moyo[4], Terence Mohammed[4], Patrick Jean-Philippe[6], Maureen Sakoi[4], Oganne Batlang[4], Shahin Lockman[2], Joseph Makhema[4], Daniel R. Kuritzkes[2]

[1]Harvard University, Boston, MA, USA, [2]Brigham and Women's Hospital, Boston, MA, USA, [3]Bennett Statistical Consulting, Inc, New York, NY, USA, [4]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [5]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [6]NIH, Rockville, MD, USA

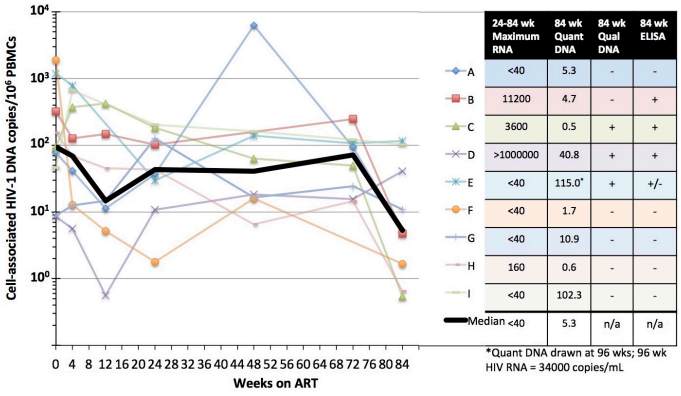
Background: Markers of HIV-1 reservoir size and immune responses are poorly described in HIV-infected infants treated very early in life.

Methods: The Early Infant Treatment Study (EIT) screens HIV-exposed children in Botswana by Roche TaqMan qualitative DNA PCR, and offers antiretroviral treatment (ART) for HIV-infected infants < 7 days of age. Nevirapine, zidovudine (ZDV), lamivudine (3TC) are provided as initial ART, and changed to lopinavir/ritonavir, ZDV, 3TC at 2+ weeks. Study visits and HIV RNA testing occur at enrollment, weeks 1, 2, 4, 8, 12, 24, then every 3 months. At least 1 million

PBMCs for quantitative HIV DNA are collected at most visits. At 84 weeks, qualitative DNA PCR testing is repeated on PBMCs from a 3mL sample, and dual enzyme linked immunosorbent assay (ELISA) is performed (Bio-Rad GS HIV 1/2, Murex HIV 1.2.0). Children starting ART at age 30-365 days in the Botswana ART program and sampled 24-36 months of age served as controls.

Results: Between April 2015 and September 2017, 27 HIV+ children enrolled in EIT; 9 had reached 84 weeks on ART. Among these 9 children, median age at ART start was 2 days after birth (range 1, 5), and median baseline HIV RNA was 3145 copies/mL (range < 40, > 10,000,000). By 24 weeks, 6 (67%) had HIV RNA < 40 copies/mL; 5 (56%) remained < 40 copies/mL at all subsequent visits through 84 weeks. At the 84-week visit, 8 (89%) were < 40 copies/mL. HIV ELISA was negative in 5 (56%) children at week 84 (all were children with low or undetectable HIV RNA from 24-84 weeks); indeterminate in a child with subsequent viral rebound at week 96; and positive in 3 children with high HIV RNA at ≥ 24 weeks. Qualitative HIV DNA PCR at 84 weeks had reverted to negative for 6 (67%) of the early treated children, but only 2 (12%) of 17 controls. Figure 1 shows quantitative HIV DNA levels in PBMCs from enrollment through 84 weeks, with a median of 94.5 copies/million PBMCs at enrollment and 5.3 copies/million PBMCs at the week 84 visit. In the 6 children with negative qualitative DNA PCRs, 4 (67%) had quantitative HIV DNA PCR ≤ 5 copies/million PBMCs, and 5 (83%) were ELISA negative.

Conclusion: Children treated in the first week of life had low HIV viral reservoir at enrollment and after 84 weeks of ART. Negative qualitative HIV DNA PCR at week 84 was accompanied by negative HIV ELISA in 5 of 6 children.



137 TIME TO VIRAL REBOUND AFTER STOPPING ART IN CHILDREN TREATED FROM INFANCY IN CHER

Avy Violari[1], **Man Chan**[2], Kennedy N. Otwombe[1], Ravindre Panchia[1], Patrick Jean-Philippe[3], Diana Gibb[2], Mark Cotton[4], Abdel Babiker[2]
[1]Perinatal HIV Research Unit, Soweto, South Africa, [2]University College London, London, UK, [3]NIAID, Bethesda, MD, USA, [4]Stellenbosch University, Cape Town, South Africa

Background: We investigated factors associated with time to viral rebound in children in CHER who started ART at age <12 weeks and received 40 (ART-40W) or 96 weeks (ART-96W) of primary therapy.

Methods: HIV RNA viral load (VL) from stored samples was assessed 8 weeks after interruption and 12 weekly thereafter. Included were children with VL<400 c/ml at interruption and ≥1 VL measurement within 12 months. Multivariable stepwise Cox regression models (backwards elimination, exit probability p=0.05) were used to identify factors associated with time to viral rebound (confirmed VL≥400 c/ml). Follow-up was censored at ART reinitiation (if VL had not rebounded) or last VL measurement.

Results: Of 183 children virally suppressed (VL<400) at interruption, 54% were from ART-40W and 61% were female. At enrolment, 81% received PMTCT, 81% had CDC stage N; median [IQR] birth weight was 3 [2.7,3.3]Kg. At ART start, median [IQR] age was 1.8 [1.5,2.1] months, CD4% 34 [29,40]%, CD4 count 1982 [1445,2745], CD8% 28 [22,34]% and VL 750000 [376000,750000] copies/ml. Median VL at rebound was 354615 [91040,750000] copies/ml, not significantly different between arms [ART-40W=418760; ART-96W=325000 copies/ml; P=0.19]. 86% of children suppressed within 40 weeks of ART start [88% ART-40W; 83% ART-96W; P=0.38]. Overall estimated cumulative probability of rebound (95% CI) at 2, 4, 6 and 8 months were 70% (63,76)%, 80% (74, 85)%, 94% (90,97)% and 99% (96,100)%, respectively. Median time to rebound was 1.8 (range: 0.9-13.1) months. One child (ART-40W) maintained viral suppression until last VL available. Five children were censored due to ART restart. In univariable analysis, among baseline demographic and clinical factors, CD4% was the strongest predictor of longer time to rebound based on the log likelihood ratio. In multivariable analysis, longer time to rebound was associated with higher birth weight, baseline CD4% and viral suppression within 40 weeks of ART start (Table). There was no evidence of significant effect of gender, baseline VL and CD8%, CDC stage, PMTCT, age at ART initiation (6-12weeks) and length of therapy (arm) or site. Sensitivity analyses produced similar results.

Conclusion: Most children rebounded by 13 months while one remained suppressed until the end of follow up. Age at ART initiation ranging from 6 to 12 weeks and length of therapy were not associated with longer time to rebound. Our findings may inform the design of clinical trials involving analytic treatment interruption in paediatric HIV.

Table: Factors associated with time to rebound

	Univariable models		Multivariable model[b]	
	Hazard ratio [95% CI]	P-value	Hazard ratio[a] [95% CI]	P-value
CD4% at baseline[c] (per 10% increase)	0.83 [0.70 , 0.99]	0.037	0.83 [0.70 , 0.98]	0.030
Birthweight (per 1 Kg increase)	0.75 [0.53 , 1.06]	0.104	0.67 [0.47 , 0.97]	0.032
Viral suppression ≤40 weeks after ART start (vs >40 weeks)	0.68 [0.45 , 1.03]	0.070	0.61 [0.39 , 0.95]	0.028
#Duration of ART (96 vs 40 weeks)	1.12 [0.83 , 1.50]	0.468	1.14 [0.84, 1.54]	0.407

[a]Hazard ratio, adjusted for the listed factors in addition to clinical site
[b]Criteria for inclusion into the multivariable model: univariable model p-value<0.15 or defined *a priori*#
[c]Baseline = ART start date

138 SIMILAR CLINICAL OUTCOMES BETWEEN FORMULA AND BREASTFEEDING WOMEN IN PROMISE

Risa M. Hoffman[1], Konstantia Angelidou[2], Sean Brummel[2], Friday Saidi[3], Dingase E. Dula[4], Vidya Mave[5], Lee Fairlie[6], Gerhard Theron[7], Moreen Kamateeka[8], Tsungai Chipato[9], Avy Violari[10], Nahida Chakhtoura[11], Judith S. Currier[1], Mary Glenn Fowler[12]
[1]University of California Los Angeles, Los Angeles, CA, USA, [2]Harvard University, Boston, MA, USA, [3]University of North Carolina Project–Malawi, Lilongwe, Malawi, [4]Malawi College of Medicine-Johns Hopkins University Research Project, Blantyre, Malawi, [5]BJGMC Clinical Trials Unit, Pune, India, [6]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [7]Stellenbosch University, Cape Town, South Africa, [8]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, [9]University of Zimbabwe, Harare, Zimbabwe, [10]Perinatal HIV Research Unit, Soweto, South Africa, [11]NIH, Bethesda, MD, USA, [12]The Johns Hopkins University, Baltimore, MD, USA

Background: There are mixed data on the relationship between breastfeeding (BF) and disease progression in HIV-infected women. PROMISE 1077HS showed low rates of serious clinical events in formula-feeding (FF) women regardless of whether they continued or discontinued ART postpartum. We present clinical outcomes of predominately BF women in PROMISE 1077BF/FF and examine disease progression rates in light of those previously reported in FF women in 1077HS.

Methods: In PROMISE 1077BF/FF, HIV-infected women with pre-ART CD4 cell counts 350 cells/mm^3 who started ART during pregnancy were randomized to continue (cART) or discontinue (dART) treatment after delivery. Women were enrolled from India, Malawi, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe. LPV/RTV with TDF/FTC or ZDV/3TC were the preferred study regimens. The primary efficacy endpoint was a composite of progression to AIDS-defining illness (WHO Stage 4 clinical event) or death. Log-rank tests and Cox regression models estimated treatment effects. Incidence rates were calculated per 100 person-years (PYs). A post-hoc analysis evaluated WHO Stage 2 and 3 events. All analyses were intent to treat.

Results: 1612 women from 15 sites were enrolled (June 2011-October 2014) and 95% were breastfeeding. Median age at entry was 26 years, CD4 count 698 cells/mm^3 and the majority of women were Black African (97%) and enrolled from South Africa (32%), Malawi (28%), and Zimbabwe (19%). After a median follow-up of 1.6 years, there was no statistically significant difference in disease progression between arms (HR: 0.55; 95%CI 0.14, 2.08, p=0.37). WHO Stage 2 and 3 events were reduced with continued ART (HR: 0.60; 95%CI 0.39, 0.90, p=0.01). The arms did not differ with respect to the rate that women experienced a grade 2, 3 or 4 safety event (p=0.61). Rates of the primary

endpoint, the safety endpoint, and WHO 2 and 3 events were similar to those previously reported in both arms of the FF women in 1077HS (Table).

Conclusion: In the largest multi-site, perinatal, randomized trial to date evaluating postpartum ART, serious clinical events were rare among women with high CD4 cell counts over 18 months after delivery, regardless of whether they received postpartum ART. Outcomes appear similar between a cohort of predominately BF women compared to FF women, suggesting no adverse impact of prolonged BF on health outcomes in women with high CD4 counts.

Table. Clinical outcomes in women enrolled in PROMISE 1077BF/FF and PROMISE 1077HS

Outcome	*1077BF/FF (N=1612)			%1077HS (N=1652)		
	cART Rate per 100 PYs** (Number of events)	dART Rate per 100 PYs (Number of events)	#Hazard Ratio (95%CI)	cART Rate per 100 PYs (Number of events)	dART Rate per 100 PYs (Number of events)	#Hazard Ratio (95%CI)
Primary Efficacy Endpoint#	0.24 (3)	0.49 (8)	0.55 (0.14, 2.08)	0.21 (4)	0.31 (6)	0.68 (0.19, 2.40)
AIDS Defining illness	0.08 (1)	0.25 (4)	0.36 (0.04, 3.30)	0.10 (2)	0.15 (3)	0.67 (0.11, 4.01)
Death	0.24 (3)	0.43 (7)	0.65 (.017, 2.53)	0.10 (2)	0.20 (4)	0.52 (0.09, 2.81)
Primary Safety Endpoint^	15.3 (160)	13.9 (189)	1.03 (0.82, 1.28)	18.4 (260)	15.4 (232)	1.16 (0.97, 1.38)
WHO Stage 2 or 3 Event	2.70 (33)	4.66 (72)	0.60 (0.39, 0.90)	2.02 (39)	4.36 (80)	0.48 (0.33, 0.70)

*95% of women were breastfeeding; **PY: person-years
%1077HS was performed among non-breastfeeding women in Argentina, Botswana, Brazil, China, Haiti, Peru, Thailand, and the United States (Jan 2010 – Nov 2014). In 1077HS, the primary efficacy endpoint also included serious non-AIDS-defining cardiovascular, renal, or hepatic events. None of these events occurred during 1077HS follow-up
#Hazard Ratio is for the continue ART (cART) arm as compared to the discontinue ART (dART) arm
#Composite of progression to AIDS-defining illness (WHO Stage 4 clinical event) or death
^Composite of time to the first grade 3 or 4 sign or symptom, or grade, 2, 3, or 4 hematology or chemistry events

139 PROMISE TRIAL: RESULTS OF CONTINUED VS DISCONTINUED ART AFTER END OF BREASTFEEDING

Taha E. Taha[1], Sean Brummel[2], Konstantia Angelidou[2], Mary Glenn Fowler[1], Patricia M. Flynn[3], Cornelius Mukuzunga[4], Dingase E. Dula[5], Maxensia Owor[6], Dhayendre Moodley[7], Tsungai Chipato[8], Amy J. Loftis[9], Nahida Chakhtoura[10], Katie McCarthy[11], Judith S. Currier[12]

[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Harvard University, Cambridge, MA, USA, [3]St. Jude Children's Research Hospital, Memphis, TN, USA, [4]University of North Carolina Project–Malawi, Lilongwe, Malawi, [5]Malawi Coll of Med–Johns Hopkins Univ Rsr Proj, Blantyre, Malawi, [6]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, [7]KwaZulu-Natal Research Institute for TB and HIV, Durban, South Africa, [8]University of Zimbabwe, Harare, Zimbabwe, [9]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [10]National Institute of Child Health and Human Development, Bethesda, MD, USA, [11]FHI 360, Durham, NC, USA, [12]University of California Los Angeles, Los Angeles, CA, USA

Background: As use of lifetime ART becomes universal, longer term safety evaluation of extended treatment remains important. This analysis compares rates of clinical and safety events between women randomized to continue or discontinue ART after cessation of breastfeeding (BF) in the PROMISE multi-site PMTCT trial. At the time, lifelong ART was recommended only for symptomatic HIV-infected women with lower CD4 counts.

Methods: Women with CD4 counts >350 cells on ART for PMTCT were randomized after cessation of BF to 1 of 2 arms: continue ART or discontinue ART and resume when needed for their own health. Lopinavir-ritonavir + Emtricitabine-Tenofovir was the preferred regimen. Data collected from November 2011 to July 2015 were analyzed. The primary efficacy endpoint was a composite measure of progression to AIDS-defining illness (WHO stage IV clinical event) and/or death. Secondary endpoints included selected clinical and laboratory adverse events (AEs). Analyses used the intent-to-treat principle, according to the randomized arm. The log-rank test compared the two arms. Incidence rates were calculated per 100 person-years (PYs) using a quasi-Poisson model with person time as an offset.

Results: 557 women [Malawi (33%), Zimbabwe (25%), South Africa (21%), Uganda (13%), India (6%), Tanzania (1%) and Zambia (one woman)] were randomized at end of BF: 289 to continue and 268 to discontinue ART. At time of randomization, median age was 28 years, mean BMI was 23.1 kg/m2, 93% were WHO clinical stage I, and 95% had CD4 >500 cells/mm^3. Median follow-up was 84 weeks (range: 4-171) and did not differ between arms. The primary and secondary endpoint rates are shown in Table. There were two deaths, one per arm, and no AIDS-defining illnesses. There were higher rates of Grade 3 or 4 AEs in women who continued ART compared to those who discontinued ART ($p<0.05$). Grade 2 or higher AEs were also higher in women who continued ART ($p=0.08$). This difference was mostly driven by signs and symptoms (p-value=0.01) with more frequent Grade 3 weight loss in the continue ART arm (13 Grade 3 weight loss and 1 Grade 4 weight loss) compared to discontinue arm (5 Grade 3 weight loss and no Grade 4 weight loss).

Conclusion: AIDS-defining illness, death, or clinical events were rare in both arms (0.23% per 100 person-years overall). However, rates of several AEs were higher in the continue ART arm compared to the discontinue ART arm.

Table: Rates of adverse events in the two study arms

Adverse Event	Rate per 100 PY (# cumulative events/PY of observation); 95% Confidence interval		P-value (Log-rank test; time to occurrence of first event)
	Continue ART	Discontinue ART	
Primary			
AIDS-defining illness or death*	0.23 (1/435.1); 0.15-0.34	0.23 (1/430.5); 0.16, 0.35	0.98
Secondary			
Composite Grade 2, 3 or 4 Adverse Events**	21.7 (78/359.1); 17.1, 27.7	16.0 (57/356.1); 12.1, 21.3	0.08
Composite Grade 3 or 4 Serious Adverse Events***	9.7 (38/391.4) 7.5, 12.5	5.5 (22/400.3) 3.9, 7.7	0.03
Grade 3 or 4: Signs or symptoms***	4.9 (20/408.9) 3.8, 6.3	1.7 (7/411.3) 1.1, 2.6	0.01
Grade 2, 3, 4 Hematology or Chemistry***	15.4 (57/370.9) 11.8, 20.1	12.3 (45/365.1) 9.1, 16.7	0.28
Composite endpoint of HIV/AIDS-related event or WHO stage II/III event**	4.28 (18/420.2); 3.21, 5.72	2.37(10/422.8); 1.61, 3.49	0.12

* Pre-specified analysis; only two deaths; no AIDS defining illness. Reported cause of death: Continue ART - ruptured ectopic pregnancy; Discontinue ART - chronic renal insufficiency.
** Pre-specified secondary outcome
*** Post-hoc analysis

140 ART DETECTION AND RESISTANCE DURING VIRAEMIC EPISODES IN PREGNANCY AND BREASTFEEDING

Landon Myer[1], Andrew D. Redd[2], Elton Mukonda[1], Briana Lynch[2], Tamsin K. Phillips[1], Anna Eisenberg[2], Allison Zerbe[3], Autumn Breaud[4], Nei-Yuan M. Hsiao[5], Craig Martens[2], Maia Lesosky[1], James A. McIntyre[6], William Clarke[4], Elaine J. Abrams[3], Steven J. Reynolds[2]

[1]University of Cape Town, Cape Town, South Africa, [2]NIAID, Bethesda, MD, USA, [3]ICAP at Columbia University, New York, NY, USA, [4]Johns Hopkins University, Baltimore, MD, USA, [5]National Health Laboratory Service, Cape Town, South Africa, [6]Anova Health Institute, Johannesburg, South Africa

Background: Viremic episodes (VE) following initial viral suppression (VS) occur frequently in HIV+ women initiating ART in pregnancy, particularly postpartum. However the contribution of ART non-adherence vs pre-existing drug resistance mutations (DRM) to VEs in African settings is unknown.

Methods: In a South African cohort recruited during routine primary care, HIV+ women initiated TDF+FTC+EFV regardless of clinical stage or CD4 and were followed with intensified VL testing from first antenatal visit through 12m postpartum. In women who achieved VS<50 cps/mL, we conducted a nested case-control study comparing antiretroviral (ARV) drug levels and DRM in: (i) women with VE>1000 cps/mL after initial VS (cases), versus (ii) women who maintained VS (controls; matched on duration of ART use). Plasma from cases (both at time of VE and preceding specimen with VS) and controls were analyzed for the presence of ARV using high-performance liquid chromatography with high-resolution mass spectrometry (Q Exactive; Thermo Scientific; lower limit, 10ng/mL). Viral RNA from VE (cases only) and pre-ART specimens (cases and controls) was amplified and sequenced in the Pol region using next-generation sequencing; consensus sequences encompassing a cluster of at least 0.2% of the total sequences for that sample were included (Illumina Inc). DRM were defined for sequences found in >5% of total consensus sequences.

Results: By 12m postpartum 30% of women in the cohort experienced VE after VS. In 107 cases and 124 controls, median duration on ART was 42w. Cases were younger with greater previous ARV exposure and higher pre-ART VL. At the time of VE, ARVs were detected in 17% of cases, compared to 89% of preceding samples from the same women when VS, and 94% of VS controls sampled at the corresponding time on ART (both adjusted p<0.001). Pre-ART DRM were detected in 11% of cases and 5% of controls, all NNRTI-related. At the time of VE, 45% of cases had DRM (almost all major NNRTI mutations). Of 12 women with pre-ART DRM, most (92%, n=11) experienced VE, and of these, most (82% n=9) had the same DRM detected again during VE. However these 9 women were a minority (19%) of all women with DRM during VE (n=48) most of whom had no DRM detected pre-ART and no previous ARV exposure.
Conclusion: The vast majority of VE in this setting are explained by ART non-adherence; the frequency of early VE and rapid emergence of NNRTI DRM during VE have implications for long-term maternal outcomes and choice of optimal ART regimens.

Table. Comparison of **cases** [experiencing viral episode (VE) >1000 copies/mL after initial viral suppression (VS) <50 copies/mL] to **controls** (persistent VS)

	Cases n=107	Controls n=124	p-value
At ART initiation			
Mean age (years)	26.9	29.3	<0.001
Any previous ARV use	34%	21%	0.035
Mean viral load (log_{10} copies/mL)	4.11	3.77	0.002
DRM detected [1]	11%	5%	0.145
NNRTI: major	9%	5%	
NNRTI: minor	2%	-	
NRTI: major	-	-	
NRTI: minor	-	-	
Cases: last VS before first VE			
Median duration on ART (weeks)	28.1		
Any ARV detected [2]	89%		<0.001 *vs case VE*
Cases: at first VE			
Median duration on ART (weeks)	43.9		
Any ARV detected	18%		
Viral load (log_{10} copies/mL)	4.11		
Any DRM detected [1]	45%		
NNRTI: major	44%		
NNRTI: minor	9%		
NRTI: major	-		
NRTI: minor	1%		
Controls: VS (matched to case duration on ART)			
Median duration on ART (weeks)		41.8	
Any ARV detected [2]		94%	<0.001 *vs case VE*

1. Major mutations defined as those detected in >20% of consensus sequences; minor mutations were detected in 5-20% of consensus sequences; mutations in <5% of consensus sequences were excluded from analysis.
2. ARVs detected by this assay include TDF, FTC, EFV (routine first line regimen in this setting used by all participants) as well as other NNRTI (NVP), NRTI (AZT, 3TC, D4T, ABC) and PI (LPV/r, ATV) used in the public sector in South Africa.

141 VAGINAL CONTRACEPTIVE HORMONE EXPOSURE PROFOUNDLY ALTERED BY EFV- AND ATV/R-BASED ART

Kimberly K. Scarsi[1], Yoninah S. Cramer[2], David Gingrich[3], Susan L. Rosenkranz[2], Francesca Aweeka[3], Robert Coombs[4], Carmen D. Zorrilla[5], Kristine Coughlin[6], Laura E. Moran[7], Baiba Berzins[8], Catherine Godfrey[9], Susan E. Cohn[8]
[1]University of Nebraska Medical Center, Omaha, NE, USA, [2]Harvard University, Cambridge, MA, USA, [3]University of California San Francisco, San Francisco, CA, USA, [4]University of Washington, Seattle, WA, USA, [5]University of Puerto Rico, San Juan, Puerto Rico, [6]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [7]Social &Scientific Systems, Silver Spring, MD, USA, [8]Northwestern University, Chicago, IL, USA, [9]DAIDS, NIAID, Bethesda, MD, USA

Background: Contraceptive hormones delivered by a vaginal ring result in stable systemic hormone exposure over 21 days of use, with concentrations that are lower than those observed with oral or injectable contraceptives. Drug-drug interactions (DDI) exist between oral hormonal contraceptives and some antiretroviral therapy (ART), but the impact of ART on hormone exposure when released from a vaginal ring is not known. We hypothesized that efavirenz (EFV)-based ART and atazanavir/ritonavir (ATV/r)-based ART would alter plasma concentrations of vaginally administered etonogestrel/ethinyl estradiol (ENG/EE).
Methods: A5316 was an international, multicenter, longitudinal, parallel group, pharmacokinetic (PK) evaluation of HIV-positive women ≥ 16 years old. A vaginal ring releasing ENG/EE 120/15 mcg/day was inserted at entry in three groups of participants: (1) not yet receiving ART (control group; n=25); (2) ART containing EFV 600mg daily (EFV group; n=25); (3) ART containing ATV/r 300/100mg daily (ATV/r group; n=24). Participants returned on days 7, 14, and 21 for single measurements of ENG and EE PK, assessed by a validated LC/MS/MS method. Plasma hormone PK exposure was compared between each ART group and the control group at each visit by geometric mean ratio (GMR) with 90% CI, and by Wilcoxon-rank sum at the primary endpoint (day 21). Demographics are summarized as mean (standard deviation) or frequency (%).
Results: Overall, 74 evaluable women were 35 (7.6) years of age, 72.5 (24.2) kg, 37 (50%) Black, and 26 (35%) Hispanic. ENG and EE PK results are described and compared between groups in the Table. Compared to the control group, participants in the EFV group had 76-79% lower ENG and 53-57% lower EE over 21 days (all p<0.001). In contrast, participants in the ATV/r group had 71-79% higher ENG (all p<0.001), yet 29-35% lower EE (p=0.066, 0.032 and 0.004 for days 7, 14 and 21, respectively) over 21 days compared to the control group.
Conclusion: Both EFV- and ATV/r-based ART altered systemic hormone exposure delivered via a vaginal ring; these changes were similar or greater to prior DDI studies with oral hormonal contraceptives. Women on EFV- or ATV/r-based ART should consider an alternative contraception method or barrier contraception in addition to the vaginal ring until the clinical relevance of these PK changes is better understood. These data highlight the importance of evaluating DDIs between ART and non-oral hormone contraceptive methods during novel drug product development.

Table: ENG and EE concentrations at days 7, 14, and 21 during continuous administration of a vaginal ring alone (Control Group) or in combination with EFV- or ATV/r-containing ART

	Median (Interquartile Range)			Geometric Mean Ratio (90% CI)	
	Control Group pg/mL (n=25)	EFV Group; pg/mL (n=25)	ATV/r Group; pg/mL (n=24)	EFV: Control Groups	ATV/r: Control Groups
Etonogestrel (ENG)					
Day 7	1970 (1310, 2400)	427 (282, 509)	3250 (2480, 4040)	0.21 (0.17, 0.27)	1.71 (1.41, 2.06)
Day 14	2070 (1600, 2620)	437 (292, 550)	3530 (2950, 4360)	0.22 (0.17, 0.29)	1.79 (1.44, 2.23)
Day 21	1860 (1530, 2330)	429 (311, 577)	3290 (2690, 3900)	0.24 (0.18, 0.32)	1.74 (1.38, 2.20)
Ethinyl Estradiol (EE)					
Day 7	18.1 (12.6, 31.0)	10.0 (7.3, 12.7)	15.7 (11.3, 19.3)	0.47 (0.35, 0.63)	0.68 (0.54, 0.87)
Day 14	19.7 (16.1, 28.3)	10.5 (7.8, 12.7)	16.6 (11.2, 20.6)	0.45 (0.34, 0.60)	0.71 (0.57, 0.89)
Day 21	21.3 (15.9, 30.3)	11.4 (6.5, 13.0)	16.1 (9.8, 19.7)	0.43 (0.33, 0.57)	0.65 (0.50, 0.84)

142LB RANDOMIZED TRIAL OF SAFETY OF ISONIAZID PREVENTIVE THERAPY DURING OR AFTER PREGNANCY

Amita Gupta[1], Grace Montepiedra[2], Lisa Aaron[2], Gerhard Theron[3], Katie McCarthy[4], Carolyne Onyango-Makumbi[5], Tsungai Chipato[6], Gaerolwe Masheto[7], Katherine Shin[8], Bonnie Zimmer[9], Timothy R. Sterling[10], Nahida Chakhtoura[11], Patrick Jean-Philippe[8], Adriana Weinberg[12]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]Harvard University, Boston, MA, USA, [3]Stellenbosch University, Cape Town, South Africa, [4]FHI 360, Durham, NC, USA, [5]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, [6]University of Zimbabwe, Harare, Zimbabwe, [7]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [8]NIAID, Bethesda, MD, USA, [9]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [10]Vanderbilt University, Nashville, TN, USA, [11]National Institute of Child Health and Human Development, Bethesda, MD, USA, [12]University of Colorado Denver, Denver, CO, USA

Background: The safety, efficacy, and optimal timing of isoniazid preventive therapy (IPT) for HIV-positive pregnant women on antiretroviral therapy (ART) is unknown. We hypothesized that IPT can be safely initiated during pregnancy.
Methods: A Phase IV randomized, double-blind, placebo-controlled trial compared initiation of 28 weeks of IPT in antepartum (AP; immediate) (arm A) versus at 12 weeks postpartum (PP; deferred) (arm B) in HIV-positive women from TB-endemic areas in Africa, Asia, and Haiti. Randomization 1:1 was stratified by gestational age [GA] (14-<24 weeks, 24-34 weeks); mother-infant pairs were followed to week 48 PP, with safety evaluations performed every 4 weeks. The primary safety endpoint was treatment-related maternal adverse events (AE) ≥ grade 3 or permanent drug discontinuation due to toxicity. The non-inferiority margin (NIM) was an incidence rate (IR) of 5/100 person-years

(PY), assuming a 5/100 PY IR in arm B based on reports in non-pregnant HIV-positive adults. Secondary outcomes were maternal hepatotoxicity, maternal/infant death, TB, adverse pregnancy outcomes, and infant AE.

Results: Among 956 enrolled, 93% were black, median age was 29 years, median CD4 was 493 cells/μL, 30% were IGRA+, 955 (>99%) were on ART (85% efavirenz-based), 63% had undetectable HIV-1 RNA, and 34% were 14-<24 weeks GA. Median follow-up was 58.6 weeks. 147 (15%) reached the primary outcome (74 in arm A, 73 in arm B), with IRs 15.4 and 14.9/100 PY, respectively (IR difference=0.5/100 PY, [95%CI: -4.4, 5.4]; Table).171 women discontinued the study prematurely; 6 died (2 in arm A, 4 in arm B), with 3 deaths due to treatment-related hepatotoxicity (1 in arm A, 2 in arm B) and one non-treatment-related hepatotoxicity in arm B; 77 withdrew consent (most after DSMB and sponsor-required safety memo about risk of death from IPT); 75 were lost to follow-up. There were no statistical differences in IRs of any maternal grade ≥3 AE, all-cause hepatotoxicity, or infant grade ≥3 AE between arms. There was no difference in maternal TB or infant TB by study arm. Adverse pregnancy outcomes however were significantly higher in arm A vs. B (23% vs 17%; p=0.009).

Conclusion: IR for the primary safety outcome was higher than expected and similar for immediate vs. deferred IPT, but did not meet the pre-specified NIM. TB incidence was low. Of note, immediate IPT was associated with excess adverse pregnancy outcomes. The recommendation to initiate IPT during pregnancy in HIV-positive women on ART needs re-evaluation.

Table: Key Maternal, Pregnancy, and Infant Outcomes by 48 Weeks Postpartum

Outcomes	Treatment Arm: Arm A Immediate INH	Treatment Arm: Arm B Deferred INH	Treatment Arm: Arm A Immediate INH	Treatment Arm: Arm B Deferred INH	
	n / Total n (%)		*IR/100 PY*		*IRD (95% CI)*
Maternal Safety					
Primary safety endpoint	74/477 (16%)	73/479 (15%)	15.4	14.9	0.5 (-4.4, 5.4)
Any grade 3 or 4 adverse event	145/477 (30%)	136/479 (28%)	35.2	31.3	3.9 (-3.8, 11.7)
All-cause hepatotoxicity	29/477 (6%)	34/479 (7%)	5.8	6.7	-0.9 (-4.0, 2.2)
Death	2/477 (<1%)	4/479 (<1%)	0.4	0.8	-0.4 (-1.3, 0.5)
Permanent discontinuation of study treatment due to toxicity	17/477 (4%)	28/479 (6%)	3.4	5.5	-2.1 (-4.7, 0.5)
Infant Safety					
Any grade 3 or 4 adverse event	191/445 (43%)	189/464 (41%)	70.7	64.7	6 (-7.6, 19.6)
Infant death	11/445 (2%)	17/464 (4%)	2.9	4.2	-1.4 (-4, 1.3)
TB					
Maternal TB	3/477 (<1%)	3/478 (<1%)	0.6	0.6	0 (-0.9, 0.9)
Infant TB	0/445 (0%)	1/464 (<1%)	0.5	0.5	0 (-1.0, 1.0)
Pregnancy					*P value*
Any adverse pregnancy outcome	106/459 (23%)	77/466 (17%)			0.009
Fetal demise	17/459 (4%)	9/466 (2%)			0.09
Low birth weight: <2500 g	62/442 (14%)	46/458 (10%)			0.07
Preterm delivery: <37 wk	48/442 (11%)	40/458 (9%)			0.29
Congenital anomaly	10/442 (2%)	6/458 (1%)			0.26

143LB HIGH UPTAKE AND REDUCED HIV-1 INCIDENCE IN AN OPEN-LABEL TRIAL OF THE DAPIVIRINE RING

Jared Baeten[1], Thesla Palanee-Phillips[2], Nyaradzo Mgodi[3], Ashley Mayo[4], Annalene Nel[5], Zeda Rosenberg[5], Sharon L. Hillier[6], Elizabeth Brown[7]
[1]University of Washington, Seattle, WA, USA, [2]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [3]University of Zimbabwe, Harare, Zimbabwe, [4]FHI 360, Durham, NC, USA, [5]International Partnership for Microbicides, Paarl, South Africa, [6]University of Pittsburgh, Pittsburgh, PA, USA, [7]Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: Two phase III clinical trials (MTN-020/ASPIRE & IPM 027/The Ring Study) demonstrated that a monthly vaginal ring containing dapivirine was safe and reduced HIV-1 incidence by approximately 30% compared to placebo. For tenofovir pre-exposure prophylaxis (PrEP), adherence and HIV-1 prevention effectiveness have often been greater in open-label studies than in earlier placebo-controlled trials. We are conducting MTN-025/HOPE, a phase IIIb open-label extension trial of the dapivirine vaginal ring; a planned interim analysis of data was conducted in October 2017.

Methods: HIV-1 uninfected women who had participated in ASPIRE are offered 12 months of access to the dapivirine vaginal ring in HOPE at 14 sites in Malawi, South Africa, Uganda, and Zimbabwe. Used rings are returned at each study visit (monthly for 3 months, then quarterly) and are tested for residual levels of dapivirine. HIV-1 incidence in HOPE was compared to that expected by weighted bootstrap sampling of the placebo arm of ASPIRE, selecting 10,000 times for a subset of women matched on trial site, age, and presence of a curable sexually transmitted infection at trial entry.

Results: Between August 2016 and October 2017, 1407 women enrolled into HOPE, 57% of those HIV-1 uninfected at completion of ASPIRE. The median age was 31 years (IQR 27-37), with 13% aged 20-24 and 28% 25-29 years; 16% had a curable sexually transmitted infection. Of 1407 enrollees, 1299 (92%) accepted the dapivirine vaginal ring. 89% of returned rings had residual dapivirine levels consistent with some use during the prior month. A total of 12 HIV-1 infections in 616 person-years of follow-up have been observed (incidence 1.9 per 100 person-years, 95% CI 1.0-3.4). Given the site, age, and sexually transmitted infection distribution of the population enrolled, HIV-1 incidence was expected to be 4.1 per 100 person-years (95% CI 3.2-5.1) in the absence of access to the dapivirine vaginal ring, and an incidence of 1.9 would be expected to occur with a frequency of less than 1 in 10,000 samplings.

Conclusion: Interim results from this open-label extension trial of the dapivirine ring demonstrate high uptake and adherence, and HIV-1 incidence has been half of the expected rate. These findings are limited by the lack of a contemporaneous placebo group and prior participation of the study population in ASPIRE, but they suggest important HIV-1 prevention effectiveness of the dapivirine vaginal ring when used by African women in an open-label setting.

144LB HIV INCIDENCE AND ADHERENCE IN DREAM: AN OPEN-LABEL TRIAL OF DAPIVIRINE VAGINAL RING

Annalene Nel[1], Neliette Van Niekerk[1], Ben Van Baelen[2], Zeda Rosenberg[3]
[1]International Partnership for Microbicides, Paarl, South Africa, [2]BVB Clin Consult, Herent, Belgium, [3]International Partnership for Microbicides, Silver Spring, MD, USA

Background: The monthly Dapivirine Vaginal Ring (DVR; 25 mg) was evaluated for safety and efficacy in two Phase III clinical trials, The Ring Study and ASPIRE. The trials demonstrated that the ring was safe and reduced the risk of HIV-1 infection in women, 18 to 45 years, by ≈ 30% relative to placebo. DREAM is an ongoing Phase IIIb, multi-center, open-label follow-on trial to The Ring Study to evaluate continued safety and adherence to ring use. The preliminary results are presented.

Methods: Women who participated in The Ring Study and who were HIV-negative at screening for DREAM were eligible for enrolment at 5 Research Centers (RCs) in South Africa and 1 in Uganda. Monthly RC visits take place up to 3 months after enrolment, whereafter participants continue on a quarterly visit schedule. HIV testing and safety evaluations are conducted at each visit, and used rings are returned for analysis of dapivirine residual levels. HIV-1 incidence was compared descriptively to the rate expected by bootstrap sampling, based on the placebo arm of The Ring Study, selecting 10,000 times for a subset of women matched for RC, age, and presence of a curable sexually transmitted infection (STI) at enrolment.

Results: By September 2017, 900 women were enrolled in DREAM. The median age was 29 years (range: 20-50); 3% were ≤21, 24% were >21 and ≤25; 33% were >25 and ≤30; 21% were >30 and ≤35; and 19% were >35 years. A total of 11 HIV-1 seroconversions in 623 person-years (PY) of follow-up was observed on product: an incidence rate of 1.8 per 100 PY (95% CI: 0.9-3.2). Based on RC, age, and STI distribution of the population enrolled, HIV-1 incidence was expected to be 3.9 per 100 PY (95% CI: 2.9-4.9) in the absence of DVR use. An incidence of 1.8 per 100 PY would be expected to occur with a frequency of less than 1 in 10,000 samplings. Only 4% of returned rings had a residual level >23.5 mg, indicative of non-adherence to ring use, compared to 17% in The Ring Study. Eleven serious adverse events were reported, all unrelated to ring use.

Conclusion: Preliminary results from DREAM indicate a similar safety profile of DVR to that observed in Phase III. Based on dapivirine ring residual levels, adherence to ring use is higher. Although interpretation is limited by the lack of a placebo arm, the observed HIV-1 incidence rate is ≈ 54% lower than the expected rate in the absence of access to DVR, supporting the hypothesis that increased efficacy would occur when participants knew the DVR's safety and efficacy from Phase III.

145 WHO REMAINS UNTESTED FOLLOWING NEAR-UNIVERSAL (>95%) POPULATION HIV TESTING?

Dalsone Kwarisiima[1], Jane Kabami[2], Norton Sang[3], Kevin Kadede[3], Atukunda Mucunguzi[4], Katherine Snyman[5], Tamara D. Clark[5], Elizabeth A. Bukusi[6], Teri Liegler[5], Edwin D. Charlebois[5], Laura B. Balzer[7], Maya L. Petersen[8], Moses R. Kamya[9], Diane V. Havlir[5], Gabriel Chamie[5]

[1]Makerere University Joint AIDS Program, Kampala, Uganda, [2]Makerere Univ and Univ of California San Francisco Rsr Collab, Mbarara, Uganda, [3]Kenya Medical Research Institute, Kisumu, Kenya, [4]Makerere University–University of California San Francisco Research Collaboration, Kampala, Uganda, [5]University of California San Francisco, San Francisco, CA, USA, [6]Kenya Medical Research Institute, Nairobi, Kenya, [7]University of Massachusetts Amherst, Amherst, MA, USA, [8]University of California Berkeley, Berkeley, CA, USA, [9]Makerere University College of Health Sciences, Kampala, Uganda

Background: As HIV testing uptake increases in sub-Saharan Africa, with some settings exceeding the UNAIDS 90% target, HIV+ persons who remain unaware of their status are likely to contribute disproportionately to HIV-associated morbidity and transmission. We sought to characterize adults that remain untested for HIV despite living in communities with near universal testing coverage.

Methods: Over 2 years, the SEARCH trial (NCT01864683) achieved 95.6% adult HIV testing coverage among 77,788 stable (≥6 months in community), adult (≥15) residents in 16 intervention communities in Kenya and Uganda with annual multidisease health campaigns followed by home-based testing for non-attendees, as previously described. We also ascertained vital status of residents. We sought to characterize stable adult residents enumerated by baseline census that remained alive and residing in community, but did not test with SEARCH over 2 years. We compared characteristics of non-tester residents to adults who tested at least once. Multivariate logistic regression was used to evaluate factors associated with never testing in adjusted analyses, accounting for clustering by household.

Results: After 2 years, 74,342 (95.6%) tested for HIV at least once and 3,446 (4.4%) never tested. Of tested adults, 8720 (12%) out-migrated and 1203 (1.6%) died. Of non-testers, 1515 (44%) out-migrated and 126 (3.7%) died. Overall, 66,224 adult residents were alive, in-community after 2 years, of whom 1805 (2.7%) never tested. Of non-testers alive, in community, 1201/1805 (67%) were men, 678 (38%) were <25 years, and 159 (10%) lived alone. Of 1646 non-testers who did not live alone, 312 (19%) lived with an HIV+ household member. In multivariate models stratified by sex, odds of never testing among men were significantly increased in middle age (25-44), single men, greater months out of community at baseline, those with higher educational attainment, and those with no job or high-risk informal sector jobs. Among women, we observed similar associations, except the likelihood of never testing for women was greatest in 15-24 year olds, and greater among women with no job or formal jobs (Table).

Conclusion: Following a 2-year testing intervention in the SEARCH trial, 2.7% of adult residents who were alive and living in the community remained untested. Among these non-testers, risk of never testing was significantly greater in middle-aged men and adolescent women, calling for continued outreach to these important populations at risk of HIV infection.

Table: Factors associated with never testing for HIV at three annual testing campaigns followed by home-based testing, among adults who remained alive and residing in community in the SEARCH trial in Kenya and Uganda.

		Men				Women			
			95% CI				95% CI		
		OR	Low	High	P-value	OR	Low	High	P-value
Age in years	15-24	*ref*				ref			
	25-34	1.85	1.487	2.305	<.0001	1.35	1.016	1.799	0.038
	35-44	1.90	1.469	2.446	<.0001	1.28	0.911	1.798	0.154
	>44	1.15	0.882	1.507	0.297	0.98	0.676	1.411	0.901
Marital status	Single	*ref*				*ref*			
	Married	0.53	0.433	0.654	<.0001	0.18	0.136	0.245	<.0001
	Widowed	0.56	0.275	1.142	0.111	0.22	0.144	0.322	<.0001
	Divorced	1.17	0.495	2.785	0.717	0.63	0.272	1.476	0.290
	Separated	0.26	0.118	0.556	0.001	0.76	0.483	1.191	0.230
Months out of community at baseline	0	*ref*				*ref*			
	1	1.95	1.499	2.541	<.0001	2.07	1.399	3.058	0.000
	2	2.84	2.184	3.685	<.0001	1.97	1.181	3.273	0.009
	3	3.03	2.391	3.837	<.0001	2.50	1.693	3.692	<.0001
	4	3.45	2.454	4.863	<.0001	3.55	1.989	6.331	<.0001
	5	5.40	3.495	8.333	<.0001	7.46	3.716	14.972	<.0001
	6	3.58	2.469	5.194	<.0001	3.65	2.256	5.893	<.0001
Occupation	No job								
	Formal[a]	0.73	0.538	0.993	0.045	0.64	0.442	0.937	0.021
	Informal high-risk[b]	1.55	1.082	2.217	0.017	1.00	0.543	1.829	0.992
	Informal low-risk[c]	0.92	0.684	1.244	0.597	0.88	0.617	1.255	0.478
	Other	1.26	0.881	1.812	0.203	1.83	1.025	3.254	0.041
Education	No school	*ref*				*ref*			
	Any primary	0.85	0.653	1.098	0.210	1.37	0.963	1.935	0.080
	Any secondary	1.41	1.069	1.858	0.015	2.29	1.529	3.426	<.0001
	Tertiary/University	1.95	1.422	2.674	<.0001	6.08	3.887	9.516	<.0001
HIV+ Household Members?	No	*ref*			0.808	*ref*			0.745
	Yes	0.98	0.818	1.170		0.96	0.757	1.220	

[a]Defined as teacher, student, government worker, military worker, health worker, or factory worker.
[b]Defined as fishmonger, fisherman, bar owner, bar worker, transport, or tourism.
[c]Defined as farmer, shopkeeper, market vendor, hotel worker, homemaker, household worker, construction worker, or mining
OR: odds ratio. CI: Confidence Interval.

146 EXPANDED HIV TESTING ELIGIBILITY INCREASES DETECTION OF HIV INFECTIONS, WESTERN KENYA

Rachel Joseph[1], Paul K. Musingila[1], Fredrick Miruka[1], Lucy Ng'ang'a[2], Hellen Muttai[1], Kevin M. De Cock[2], Felix M. Mulama[3], Caroline O. Dande[4], Polycarp Musee[5], Stella Wanjohi[6]

[1]US CDC Kisumu, Kisumu, Kenya, [2]US CDC Nairobi, Nairobi, Kenya, [3]ICAP at Columbia University–Kenya, Kisumu, Kenya, [4]KEMRI-UCSF, Kisumu, Kenya, [5]Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA, [6]Centre for Health Solutions, Siaya, Kenya

Background: Homa Bay, Siaya, and Kisumu counties in western Kenya have the highest estimated HIV prevalence (20–26%) in the country, and struggle to meet targets for HIV testing services (HTS). The Kenya Ministry of Health (MOH) recommends annual HIV testing for the general population. To increase access to HTS, seven high-volume facilities in western Kenya expanded HIV testing eligibility in March, 2017 to include those reporting a negative HIV test in the past 3–12 months, or in the past <3 months if unverified by records. We quantified HIV infections detected among clients meeting MOH and expanded eligibility criteria for HIV testing.

Methods: We conducted a retrospective analysis of routinely collected program data from March to July, 2017. Data from clients >10 years of age who received HTS in outpatient (OPD) and inpatient settings at the seven health facilities were included. Outcomes were meeting specific MOH and expanded HIV test eligibility criteria, and HIV test result. STATA version 14.2 was used to explore the data, and to test for differences in outcomes by client characteristics using bivariate analysis.

Results: During the 15-week period 88,641 clients received HTS, of whom 79% (70,065) were screened in OPD, and 59% (52,475) were women. A total of 70,493 (80%) were eligible for testing and 97% (68,513) received a test. Overall, 26% (18,456) of clients tested met MOH eligibility criteria: 7% (4,921) had never been tested, 15% (10,247) reported a negative HIV test in the past >12 months, and 5% (3,288) met other criteria. The remaining 74% (52,037) met expanded criteria: 52% (35,274) reported a negative test in the past 3–12 months, and 23% (15,913) had an unverified negative test in the past <3 months. In total, 1.1% (740) of clients had a positive HIV test. Although the yield of positive tests was 2.4-fold higher among those meeting MOH criteria (1.9% vs. 0.8%; p<0.001), more than half of all infections (406) were found among clients meeting expanded criteria, the majority (77%) reporting a negative test in the past 3–12 months.

Conclusion: The majority of HIV infections detected at facilities with expanded testing occurred among clients reporting a negative HIV test in the past 12 months, clients ineligible for testing under the current MOH guidelines. Expanding MOH HTS eligibility in high HIV-burden areas to include clients tested in the past 3–12 months could increase access to HTS and timely diagnosis, and accelerate epidemic control.

147 OPTIMAL HIV TESTING STRATEGIES TO INCREASE HIV DIAGNOSIS IN SOUTH AFRICA

Leigh F. Johnson[1], Gesine Meyer-Rath[2], Craig Van Rensburg[3], Caroline Govathson[3]

[1]University of Cape Town, Cape Town, South Africa, [2]Boston University, Boston, MA, USA, [3]University of the Witwatersrand, Johannesburg, South Africa

Background: The UNAIDS goal of a 90% rate of HIV diagnosis by 2020 has prompted much innovation in community-based testing and self-testing strategies. However, it remains unclear which strategies are likely to have the greatest population-level impact and which strategies are likely to be most cost-effective.

Methods: A mathematical model was developed to simulate the impact and cost-effectiveness of different HIV testing strategies in South Africa. The model is calibrated to historic data on levels of HIV prevalence and testing in South Africa. Existing strategies include general testing, partner testing and testing in antenatal clinics, STI clinics, patients with OIs, prisons, men seeking MMC and sex workers using PrEP. Potential new strategies include home-based testing, mobile testing, testing targeted to sex workers and MSM, testing partners of pregnant women and testing in family planning clinics, schools and workplaces. Self-testing is modelled in the context of home-based and antenatal partner testing.

Results: Over the 2019-39 period, the strategies with the highest yield (numbers on new diagnoses per test) are expected to include testing partners of newly-diagnosed individuals, sex workers, OI patients, PrEP users and MSM,

while the strategies with the lowest yield are expected to include home-based and school-based testing (Figure). Considering only testing costs associated with the potential new strategies, the incremental cost per life year saved is lowest for MSM testing ($182) and highest for self-testing scenarios ($1935 for partners of pregnant women and $1108 for home-based testing). Incremental costs dropped substantially when considering the impact on the cost of the entire HIV programme, rendering a number of strategies marginally cost saving over 20 years. In the absence of any change to current strategies, levels of HIV diagnosis in adults are expected to increase from 84.8% in 2016 to 93.3% in 2025. Biennial home-based testing including a self-testing kit offer would have the greatest impact, increasing this fraction to 96.7% in 2025, while home-based testing without the self-test kit offer would increase the fraction to 96.2%.

Conclusion: There is a trade-off between achieving substantial population-level increases in diagnosis rates and pursuing the most cost-effective HIV testing modalities. Community-based testing and self-testing are likely to be important in reaching diagnosis targets but may be relatively inefficient.

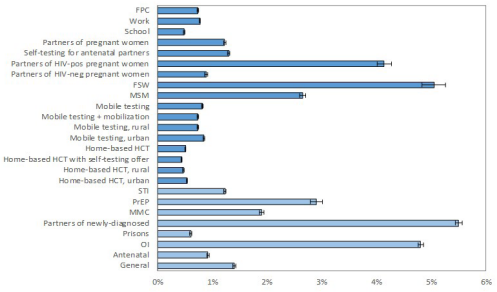


Figure: Number of new diagnoses per test, over 2019-2039 period, by HIV testing modality

Current testing strategies are in light blue; potential new strategies are in dark blue. Error bars represent 95% confidence intervals.

148 EFFECT OF HIV SELF-TESTING ON SEXUAL PARTNER NUMBERS FOR ZAMBIAN FEMALE SEX WORKERS

Catherine E. Oldenburg[1], Michael M. Chanda[2], Katrina F. Ortblad[3], Magdalene Mwale[2], Steven Chongo[2], Nyambe Kamungoma[2], Catherine Kanchele[2], Andrew Fullem[4], Guy Harling[5], Till Bärnighausen[6]
[1]University of California San Francisco, San Francisco, CA, USA, [2]John Snow, Inc, Lusaka, Zambia, [3]Harvard University, Cambridge, MA, USA, [4]John Snow, Inc, Boston, MA, USA, [5]University College London, London, UK, [6]Heidelberg University, Heidelberg, Germany

Background: HIV self-testing is a promising HIV testing technology that may reduce some traditional barriers to HIV testing among female sex workers (FSW). However there are concerns that self-testing may lead to behavioral compensation amongst those who test negative. Here, we assess the effect HIV self-tests distribution modalities on the number of FSW client and non-client sexual partners in a randomized controlled trial of HIV self-testing among FSW in Zambia.

Methods: Peer educators recruited participants via their social networks. Peer educator-participant groups were randomized in a 1:1:1 fashion to one of three arms: 1) delivery of HIV self-tests directly from a peer educator, 2) free facility-based delivery of HV-self tests in exchange for coupons, or 3) referral to standard HIV testing (standard of care). All participants also completed four peer educator intervention sessions, including condom distribution. Quantitative assessments were completed at baseline, one, and four months. Participants were asked their average number of client partners per night at baseline, one and four months, and their number of non-client partners in the past 12 months at baseline and in the past month at one and four months. The mean change in number of client and non-client partners was calculated separately using a mixed effects generalized linear model, with fixed effects for study arm, study site, and baseline average number of client or non-client partners and a random effect for peer educator group.

Results: From September-October 2016, 965 women were enrolled and randomized in 160 peer educator groups. Participants were a median of 25 years of age (interquartile range 21 to 30). The majority of participants (89.3% at one month and 79.6% at four months) reported testing for HIV during the study period. At four months, participants reported significantly fewer clients per night in the direct peer delivery arm (mean difference -0.78 clients, 95% CI -1.28 to -0.28, P=0.002) and facility-based coupon arm (-0.71, 95% CI -1.21 to -0.21, P=0.005) compared to standard-of-care. Similarly, they reported fewer non-client partners in the direct peer delivery arm (-3.19, 95% CI -5.18 to -1.21, P=0.002) and in the facility-based coupon arm (-1.84, 95% CI -3.81 to 0.14, P=0.07) compared to standard-of-care.

Conclusion: In contrast to previous concerns, expansion of HIV self-testing may have positive spillover effects on HIV prevention efforts among FSW in Zambia.

149 HIV SELF-TEST DISTRIBUTION INCREASES TEST FREQUENCY IN SOUTH AFRICAN MSM

Sheri A. Lippman[1], Tim Lane[1], Oscar Rabede[2], Hailey Gilmore[1], Yea-Hung Chen[3], Nkuli Mlotshwa[2], Kabelo Maleke[2], Alexander Marr[1], James A. McIntyre[2]
[1]University of California San Francisco, San Francisco, CA, USA, [2]Anova Health Institute, Johannesburg, South Africa, [3]San Francisco Department of Public Health, San Francisco, CA, USA

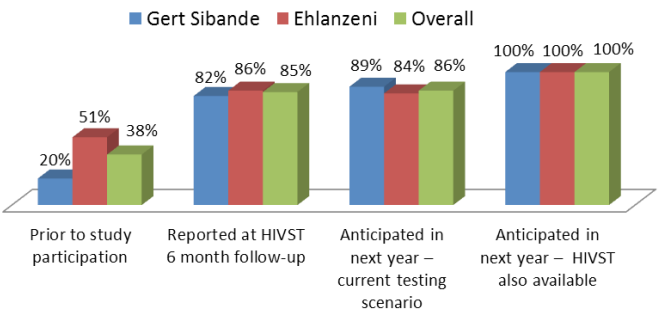
Background: South African men who have sex with men (MSM) have a high burden of undiagnosed HIV infection and HIV-testing rates incommensurate with their risk. HIV self-testing (HIVST) may increase testing uptake, frequency, and earlier HIV detection and treatment. We implemented a longitudinal HIVST study among South African MSM in Mpumalanga Province, in order to explore acceptability, feasibility, utilization and distribution patterns, and to understand how HIVST might expand testing frequency in this high prevalence area.

Methods: We recruited 127 HIV-negative MSM between June 2015 and May 2017 in Gert Sibande and Ehlanzeni districts. Participants received 5 self-test kits of their choice - oral fluid or blood fingerstick – at baseline and an additional 4 kits at a three month visit. Participants were asked to use the kits themselves at least one time and to distribute the other kits to their networks. Surveys were conducted at baseline, three months, and six months post-enrollment to elicit information on HIVST experiences, preferences, acceptability, utilization of HIVST and clinic-based testing, and test distribution to others. We used generalized estimating equations to assess changes in regular (every six months or more frequent) testing.

Results: Ninety-one percent of all participants self-tested, all of whom reported being likely to self-test again, with over 80% preferring HIVST to clinic-based testing. Fingerstick tests were preferred: 45% ever choose oral fluid tests and 80% ever choose blood. Returning participants distributed 728 tests to sexual partners (18.5% of kits), friends (51.6%), and family (29.8%). Among those testing, 32% of the cohort reported testing with someone else present and 24% reported concurrent testing (testing at the same time as another). Six participants (5% of those returning for follow-up) seroconverted during the study; 40 new diagnoses were reported among network test recipients. Regular testing increased from 37.8% prior to the study to 84.5% at follow-up ($p<0.1$), and participants reported anticipated regular testing of 100% if HIVST were available compared to 84% if only clinic-testing were available in the coming year ($p<.01$). (Figure 1)

Conclusion: HIVST is highly acceptable and feasible to distribute through MSM networks in South Africa. Newly quarterly testing guidelines are unlikely feasible in a clinic-based environment alone, however our data suggest that HIVST is key to meeting regular testing goals and improving early detection.

Figure 1: Regular HIV Testing over time



150LB LINKAGE TO CARE AFTER HIV SELF-TESTING IN ZIMBABWE: A CLUSTER-RANDOMISED TRIAL

Euphemia Sibanda[1], Melissa Neuman[2], Mary Tumushime[1], Karin Hatzold[3], Constancia Watadzaushe[1], Miriam N. Mutseta[4], Jeffrey Dirawo[1], Sue Napierala[5], Getrude Ncube[6], Miriam Taegtmeyer[7], Cheryl Johnson[8], Katherine Fielding[2], Helen A. Weiss[2], Elizabeth L. Corbett[2], Frances Cowan[7]
[1]Centre for Sexual Health and HIV/AIDS Research Zimbabwe, Harare, Zimbabwe, [2]London School of Hygiene & Tropical Medicine, London, UK, [3]Population Services International, Washington, DC, USA, [4]Population Services International, Harare, Zimbabwe, [5]RTI International, San Francisco, CA, USA, [6]Ministry of Health and Child Welfare, Harare, Zimbabwe, [7]Liverpool School of Tropical Medicine, Liverpool, UK, [8]WHO, Geneva, Switzerland

Background: HIV self-testing (HIVST) enables novel strategies, but needs new approaches to maximise linkage to care. We investigated: 1) whether financial incentives for community-selected volunteers (CVs) who distributed HIVST-kits improved timely linkage, and 2) if community-based HIVST increased facility-based ART initiation.
Methods: Trained CVs distributed HIVST kits door-to-door for 4-6 weeks in 38 rural wards in Zimbabwe. Using a cluster-randomised design with 1:1 randomisation of wards, CVs were allocated to receive stipend-only (one-off payment of US$50) or stipend-plus: US$50 + US$0.20 incentive per client linked to confirmatory HIV testing, non-communicable disease screen, family planning or male circumcision. Client self-report of HIVST uptake and linkage was assessed 6 weeks later by population survey. The primary outcome was linkage to any post-HIVST service, analysed with random-effects logistic regression, adjusted for imbalance between arms. We used a difference-in-differences quasi-experiment to investigate trends in ART initiation at public facilities in both HIVST and non-HIVST communities, from 6 months before to 3 months after HIVST distribution. Generalised estimation equations (GEE) were used to analyse the relationship between campaign period and trial arm on ART initiation. .
Results: A total of 39,205 HIVST kits were distributed by 445 CVs in the stipend-plus arm (mean/CV 88; 95%CI 85-92) and 41,173 by 447 CVs in the stipend-only arm (mean/CV 93; 95%CI 89-96). Overall 7,146/ 8,566 (83.4%) household members responded at 6 weeks; 50.3% had self-tested, 46.5% in males and 46.2% in young people <25 years old. Self-test HIV prevalence was 8.0%; 36.3% of self-testers were first-time testers. Incentives had no effect on the primary outcome, but confirmatory testing by newly diagnosed/untreated HIVST+ clients was significantly higher in the stipend-plus arm, 25/33 (75.8%) versus 20/40 (50.0%), adjusted risk ratio 1.59, 95%CI 1.05-2.39 (Table). GEE modelling of 12,808 ART initiations from 168 clinics (1192 clinic-months) showed a 27% increase in ART initiation in HIVST versus non-HIVST communities (95%CI 14-43%), with no difference by incentive arm (Table).
Conclusion: Community-based HIVST campaigns achieved high uptake, including among youth, men and first-time testers, and increased demand for ART. A small linkage incentive to distributors may have increased timely linkage to care in HIV-positive participants not already on ART. Funding: UNITAID-PSI STAR, PACTR20160700170178

Table: HIVST and linkage outcomes

	Stipend plus incentive arm n/N (%)	Stipend only arm n/N (%)	Crude PR (95% CI)	Adjusted PR (95% CI)
Uptake of self-testing	1,770/3,698 (47.9)	1,823/3,448 (52.9)	0.90 (0.80-1.02)	0.91 (0.80-1.02)
Linkage to any services: primary outcome	1,062/3,698 (28.7	1,075/3,448 (31.2)	0.92 (0.84-1.01)	0.94 (0.86-1.03)
Linkage to confirmatory testing in HIVST+ves (includes retesting on ART): secondary outcome	88/157 (56.1)	72/132 (54.5)	1.03 (0.83-1.27)	1.02 (0.82 - 1.28)
Linkage to confirmatory testing in newly diagnosed/untreated HIVST+ve*	25/33 (75.8)	20/40 (50.0)	1.52 (0.79-2.90)	1.59 (1.05-2.39)
Linkage to male circumcision	19/854 (2.2)	12/853 (1.4)	1.55 (0.67- 3.57)	1.76 (0.77-4.03)
DIFFERENCE-IN-DIFFERENCE IN ART UPTAKE BY STUDY PERIOD				
No self-test distribution (ref)	**Adjusted initiation rate ratio (95%CI)**		**p-value**	
Before HIVST distributed (reference)	1			
HIVST community during kit distribution	1.27 (1.14-1.43)		<0.001	
HIVST community after kit distribution	1.0 (0.87-1.15)		0.99	

*Posthoc analysis restricted to people not previously on ART

151 NOVEL PARADIGM FOR MEASURING HIV-1 RESERVOIR ALLOWS QUANTITATION OF INTACT PROVIRUSES

Katherine Bruner[1], Alexandra J. Murray[1], Ya-Chi Ho[2], Gregory Laird[1], Zheng Wang[1], Kyungyoon J. Kwon[1], Subul A. Beg[1], Andrew Timmons[1], Sarah B. Laskey[1], Janice E. Clements[1], Janet Siliciano[1], Robert Siliciano[1]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]Yale University, New Haven, CT, USA

Background: HIV-1 establishes latency in resting memory CD4+ T cells, creating a major barrier to eradication. Assessing the efficacy of HIV-1 cure strategies is hindered by the lack of an accurate and scalable assay for latent HIV-1. Standard DNA PCR assays overestimate the latent reservoir by 10-100 fold and mainly measure defective proviruses. The quantitative viral outgrowth assay (QVOA) does not capture all proviruses with potential to cause rebound. To address these issues, we developed an entirely novel approach to reservoir measurement that is rapid and scalable.
Methods: Defective proviruses make up over 93% of all proviruses; the most common defects are large internal genome deletions and APOBEC-mediated G to A hypermutation. We analyzed 338 sequences containing large deletions obtained via full-genome sequencing from 28 ART-suppressed individuals. Our analysis indicated that simultaneously probing the HIV-1 genome with two selected amplicons correctly identifies 90% of deleted proviruses as defective. To address hypermutation, we incorporated a pair of probes in one amplicon that distinguish between hypermutated and intact proviruses. Employing both of these features using droplet digital PCR (ddPCR) to analyze proviruses on an individual level, we developed an intact proviral DNA assay (IPDA) which eliminates 95% of all defective proviruses and is predicted to overestimate the reservoir by only 1.9 fold.
Results: Extensive plasmid controls and HIV-1 cell lines validated the specificity and linearity of the IPDA. We assessed the reservoir size in 29 HIV-1 infected, ART suppressed individuals using the IPDA and compared to QVOA and total DNA measurements. The median frequency of cells with intact proviruses (IPDA) was 56.23 per million CD4+ T cells. The frequencies measured by the IPDA were a median of 52-fold higher than those measured by QVOA and 19-fold lower than total DNA measurements. For 13 of the HIV-1 infected individuals, we assessed the correlation between the fraction of intact proviruses as measured by IPDA and by full-length, single genome sequencing and found a significant correlation.
Conclusion: The IPDA correctly distinguishes intact proviruses from most deleted or hypermutated proviruses by interrogating the HIV-1 genome in regions commonly deleted or mutated by APOBEC3G. By measuring primarily intact proviruses, we anticipate the IPDA will better assess the impact of eradication strategies on the true reservoir of virus that must be eliminated to achieve an HIV-1 cure.

152LB CLONES OF CD4 T CELLS WITH UNIQUE GENE SIGNATURE CONTRIBUTE TO HIV-1 PERSISTENCE

Lillian B. Cohn[1], Israel T. da Silva[2], Renan Valieris[2], Amy Huang[1], Julio C. Lorenzi[1], Yehuda Z. Cohen[1], Joy A. Pai[1], Allison Butler[1], Marina Caskey[1], Mila Jankovic[1], Michel Nussenzweig[1]
[1]The Rockefeller University, New York, NY, USA, [2]AC Camargo Cancer Center, São Paulo, Brazil

Background: Latently infected CD4+ T cells are the major barrier to HIV-1 cure. These cells have been difficult to study due to their scarcity in blood and lack of distinguishing surface markers. To investigate the cells that contribute to the latent reservoir, we developed a method to enrich and isolate reactivated latent cells from ART suppressed donors by combining antibody staining, magnetic enrichment, and flow cytometry (latent cell capture, or LURE).
Methods: Surface expression of viral Envelope protein was used to enrich reactivated latent T cells producing HIV-RNA by combining antibody staining, magnetic enrichment, and flow cytometry. Single cell RNA sequencing was performed to obtain a more comprehensive understanding of the nature of the captured reactivated primary latent cells.
Results: We obtain enrichment of reactivated latent T cells producing HIV-RNA. The degree of enrichment was found to be dependent in part on the size of the latent reservoir as measured by viral outgrowth assays in infectious units per million. We performed virus reconstruction from single cell RNA sequencing reads to identify intact, full length virus produced by single cells. Viruses reconstructed from single cells were identical to those found in viral outgrowth cultures. These captured cells represent clones of in vivo expanded T cells as determined by the sequence of their T cell receptors. Comparison of gene expression data from reactivated latent cells to autologous activated uninfected cells or to productively in vitro infected cells revealed a specific gene signature that prominently includes genes implicated in silencing the virus.
Conclusion: We conclude that reactivated latent T cells share a gene expression program that may allow for cell division without activation of the cell death pathways that are normally triggered by HIV-1 replication. We speculate

that active HIV-1 suppression during CD4+ T cell division could be one of the mechanisms that maintains the latent reservoir and that interfering with these cellular safeguards could contribute to accelerating latent HIV-1 clearance.

153 IDENTIFICATION OF INTEGRATION SITES OF INDUCIBLE HIV-1 USING HIV-1 RNA SORTSEQ

Ales Varabyou[1], C. Conover Talbot[1], Hao Zhang[1], Subul A. Beg[1], Ross Pollack[1], Haiping Hao[1], Joseph B. Margolick[1], Robert Siliciano[1], Mihaela Pertea[1], **Ya-Chi Ho**[2]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]Yale University, New Haven, CT, USA

Background: HIV-1-infected cells may undergo clonal expansion through integration into cancer-related genes. A significant proportion of the clonally expanded HIV-1-infected cells are replication competent. However, given the technical barrier to identify full-length HIV-1 proviral genome (requiring nested PCR spanning the HIV-1 genome) and integration site (requiring shearing of the HIV-1 genome) at the same time, it remains unclear whether HIV-1 proviruses which are integrated into cancer-related genes are intact or defective.
Methods: To identify the integration sites of inducible HIV-1 proviruses, we developed a novel assay, HIV-1 RNA SortSeq, which can identify HIV-1-infected cells containing inducible HIV-1 proviruses for RNAseq analysis. Resting CD4+ T cells from HIV-1-infected individuals on suppressive antiretroviral therapy were activated with PMA/ionomycin in the presence of antiretroviral therapy for 18 hours to induce HIV-1 RNA expression. HIV-1 RNA expression serves as a surrogate to identify cells containing inducible HIV-1 proviruses. Cells were then fixed, permeabilized, and hybridized with HIV-1 RNA-specific fluorescent probes. Cells expressing HIV-1 RNA were isolated by flow cytometric sorting for subsequent RNAseq. We designed bioinformatic pipelines to identify the HIV-1-host genome junctions and the HIV-1 RNA genome.
Results: Using HIV-1 RNA SortSeq, we identified HIV-1-host genome chimeric RNA from cells containing inducible HIV-1 from virally suppressed HIV-1-infected individuals. We found that some of the read-through transcripts contain both HIV-1 LTR and the host genomic RNA in cancer-related genes, indicating that HIV-1 proviruses which are integrated into cancer-related genes are actually inducible, producing readily detectable cell-associated HIV-1 RNA. Strikingly, we found that some of the HIV-1-host chimeric RNAs contain host exons of cancer-related genes splicing into canonical splice acceptors of HIV-1, indicating that HIV-1 integrated into cancer-related genes can produce aberrant HIV-1-host chimeric RNA encoding novel open reading frames.
Conclusion: The novel HIV-1 RNA SortSeq assay allows identification of the integration sites of inducible HIV-1 proviruses and overcomes the technical barrier of simultaneous identification of the integration sites and the HIV-1 genome. We showed that HIV-1 proviruses which are integrated into cancer-related genes can not only be induced but also produce novel HIV-1-host chimeric RNAs through aberrant splicing.

154LB HERITABLE CLONE-SPECIFIC DIFFERENCES IN HIV-1 GENE EXPRESSION

Edmond A. Atindaana, David Read, Kalyani Pyaram, Sarah Emery, Cheong-Hee Chang, Jeffrey Kidd, Alice Telesnitsky
University of Michigan, Ann Arbor, MI, USA

Background: Because host genes are regulated by a complex interplay of epigenetic and non-epigenetic mechanisms, it seems possible that integrated proviruses might be subject to host locus-specific regulation despite HIV-1's independent promoter. Here, we studied how the genetic neighborhoods of integrated HIV-1 proviruses affected their expression patterns and whether clonal expression phenotypes were heritable.
Methods: We developed a system for ensemble analysis of single-cycle replication outcomes and persistence properties of thousands of HIV-1 Env- proviruses. Proviruses marked with "zipcodes"-sequence tags within viral sequences that identify clonal progeny of individual integration events--were quantified by high-throughput sequencing. The system was benchmarked using selectably marked proviruses using adherent cells, which allowed informatics to be developed and optimized for a known number of integrants. These studies confirmed our ability to analyze zipcodes from both cell DNA and viral RNA, and to address the fidelity of one round of replication by analyzing the remobilization of first-round integrants on fresh cells. In a second experiment, Jurkat cells were infected with an Env-Vpr-PuroR virus harboring gfp in the nef ORF and were used to study the stability of HIV-1 gene expression.
Results: Over 90% of proviruses maintained infectivity through one cycle of replication in low-restriction cells, which is on the upper end of previous fidelity estimates. Surprisingly, based on virion-to-cell zip code ratios, many first-round integrants' second-round success appeared limited by clonal differences in gene expression. Separately sorting pool halves into GFP-positive and GFP-negative subpopulations revealed reproducible large differences among zipcodes in GFP+ cell proportions that persisted through an additional week of separately propagating in subculture. In contrast, first sort GFP- cells largely remained silent through subsequent cell passaging, likely reflecting epigenetic proviral silencing. When analyzed by integration site, no strong correlation to any known genome features was observed.
Conclusion: This new zipcoding system, shows that in transformed cells, provirus inactivation by replication-induced mutagenesis is lower than that estimated in earlier studies. However, individual proviruses' expression phenotypes, as monitored by GFP+/total cell levels within integrant clones, differed reproducibly and fairly stably across over three logs of magnitude.

155 CD32+PD-1+ TFH CELLS ARE THE MAJOR HIV RESERVOIR IN LONG-TERM ART-TREATED INDIVIDUALS

Alessandra Noto, Francesco Procopio, Jean-Marc Corpataux, Giuseppe Pantaleo
Lausanne University Hospital, Lausanne, Switzerland

Background: HIV-1 persists after many years of suppressive antiretroviral therapy (ART). It is well established that lymphoid tissues serve as primary anatomic sites for HIV-1 replication. We have previously shown that PD-1+/Tfh cells serve as primary cell compartment for HIV-1 replication in viremic patients and for persistent HIV transcription in long-term treated aviremic individuals. Recently, CD32 has been identified as a marker of HIV reservoir in blood memory CD4 T cells. We therefore investigated the distribution of the HIV reservoir in lymph nodes (LNs) memory CD4 T cell populations defined by the expression of CD32 and PD-1.
Methods: LN biopsies were obtained from 10 HIV-1 infected viremic individuals naive to ART and 13 aviremic long-term treated individuals. Expression of CD32, PD-1 and a large panel of cell lineage, activation and migration markers was assessed in memory CD4 T cells using flow- and mass cytometry that included 30 isotope conjugated antibodies. HIV-DNA was measured in total CD32+ and PD-1+ cell populations and cell associated HIV-RNA in memory CD4 T cells isolated on the basis of PD-1 and CD32 expression (PD-1-CD32-, PD-1-CD32+, PD-1+CD32-, PD-1+CD32+).
Results: Similar to what previously shown for PD-1+ CD4 T cells, the frequency of CD32+ CD4 T cells was increased in viremic as compared to treated individuals (3% vs 1.2% $p<0.0001$) and positively correlated with viremia while negatively with years of suppressive ART and CD4 cell count. CD32+ CD4 T cells were enriched for total HIV DNA as compared to CD32- cells in both viremic and treated individuals (average 210 fold, $n=6$, $p=0.01$, and 1.9 fold, $n=7$, $p=0.03$ respectively) but no difference was found as compared to PD-1+ cells. In both viremics and ART treated individuals CD32+ CD4 T cells were found predominantly within the PD-1+ and Tfh cell populations. Double positive CD32+ PD-1+ cells were phenotypically similar to CD32-PD-1+ cells and Tfh cells as indicated by the expression of ICOS, CD57, CD38, CXCR5, CD40L, CCR5 and CXCR4. CD32+PD-1+ CD4 T cells were enriched in cell associated HIV RNA as compared to CD32-PD-1- (average 7.6 fold), to CD32+ PD-1- (5.2 fold) and to CD32-PD-1+ cell populations (average 7.6 fold) ($n=4$ ART treated).
Conclusion: Co-expression of CD32 and PD-1 defines a population of Tfh cells serving as the major HIV cell reservoir in HIV long-term ART treated individuals.

156 MAJORITY OF THE LATENT RESERVOIR RESIDES IN CD32A NEGATIVE CD4 T CELLS

Lynn N. Bertagnolli[1], Jennifer White[1], Subul A. Beg[1], Gregory Laird[1], Francesco R. Simonetti[1], Jun Lai[1], Costin Tomescu[2], Alexandra J. Murray[1], Annukka Antar[1], Hao Zhang[1], Joseph B. Margolick[1], Luis Montaner[2], Robert Siliciano[1], Janet Siliciano[1]
[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Wistar Institute, Philadelphia, PA, USA

Background: The persistence of HIV-1 in a stable reservoir in resting CD4+ T cells is the major barrier to curing HIV-1 infection. Cell surface biomarkers that could distinguish cells comprising this latent reservoir from uninfected cells have been lacking. If identified, these biomarkers could significantly enhance the progress towards an HIV cure. A recent study (Descours et al., 2017) identified the cell-surface protein CD32a, a low-affinity Fc receptor for IgG that

is commonly found on B cells and cells of the myeloid lineage, as a potential marker for the latent reservoir.
Methods: To explore this biomarker, CD4+ T cells were isolated from 6 HIV-1 infected patients virally suppressed on cART for at least 6 months and sorted for the expression of CD32. CD4+CD32- and CD4+CD32+ T cells were plated and tested for the presence of infectious HIV-1 using the quantitative viral outgrowth assay (QVOA). Additional studies compared viral outgrowth and HIV-1 proviral DNA levels in CD4+ T cells isolated using differing selection methods in order to investigate the possibility that CD32+ CD4 T cells were being removed using the negative depletion method for purifying CD4+ T cells.
Results: In cultures from 6 aviremic patients in which CD32 sorting was performed, no viral outgrowth was detected in CD4+ T cells expressing CD32 using the standard ELISA assay for HIV-1 p24 antigen. In contrast, CD4+CD32- cultures showed viral outgrowth that was comparable in frequencies previously measured from the same patients as well as to historical controls. Since an ultrasensitive p24 assay was used in the original report, we also analyzed culture supernatants with this method. Using this assay, low levels of p24 slightly above the limit of detection were seen in CD32+ cultures, but levels did not increase exponentially over time. Studies using different modes of total CD4+ T cell isolation, including positive selection or negative depletion, showed no difference in viral outgrowth.
Conclusion: We conclude that an enrichment of HIV-1 infected cells is not observed in viral outgrowth cultures of CD32+ CD4+ T cells while CD32- CD4+ T cells from the same donors had expected levels of infected cells. Detection of p24 antigen using ultrasensitive methods may represent defective virus or assay artifacts. Our results demonstrate that the cell-surface molecule CD32a does not specifically mark the latent reservoir, and that additional efforts are needed to identify biomarkers for latently infected cells.

157 CD32 DOES NOT MARK THE HIV-1/SIV LATENT RESERVOIR

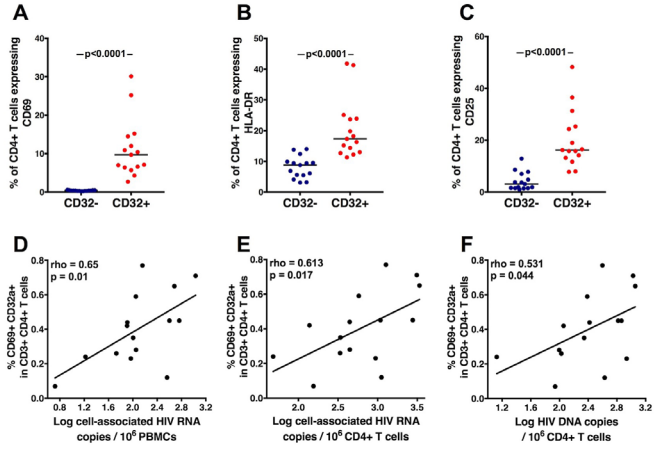
Christa E. Osuna[1], Richard Apps[2], So-Yon Lim[1], Jessica L. Kublin[1], Rasmi Thomas[3], Yanqin Ren[2], Nathaniel D. Bachtel[2], Margaret Ackerman[4], Jintanat Ananworanich[5], Dan Barouch[1], Nelson L. Michael[6], R. Brad Jones[2], Douglas Nixon[2], **James Whitney**[1]
[1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]The George Washington University, Washington, DC, USA, [3]Walter Reed Army Institute of Research, Silver Spring, MD, USA, [4]Dartmouth College, Hanover, NH, USA, [5]US Military HIV Research Program, Bethesda, MD, USA, [6]US Military HIV Research Program, Silver Spring, MD, USA

Background: A recent report by Descours et al., suggests that the cell surface expression of CD32a marks the replication-competent latent HIV reservoir in CD4+ T cells. However, after significant effort to replicate these findings, we found no evidence to suggest that CD32 marks a CD4+ T cell population enriched for replication-competent virus, in HIV-1 infected study participants, or SIV-infected macaques on ART.
Methods: The percent of CD32+ CD4+ T cells was measured in samples from ART-suppressed patients and macaques and was correlated with viral DNA. CD32+ and CD32- CD4+ T cells were sorted with or without exclusion of CD20+ and CD14+ cells and viral DNA was measured either by digital droplet PCR or qPCR. CD32-sorted rhesus cells were cultured with CEMx174 cells and virus production kinetics were measured over time by qRT-PCR.
Results: CD32-high CD4+ T were sorted from human PBL, rhesus PBMC, and rhesus LNMC and were found to not be enriched in viral DNA. Additionally, the frequency of CD32-high did not correlate with viral DNA content of sorted total CD4+ T cells in blood and tissue. Rhesus CD32-high CD4 cells were not enriched in replication-competent virus determined by virus production kinetics after co-culture with CEMx174 cells. We next examined CD32 expression in a cohort of macaques that began ART on the day of infection or 3 days post-infection. There was no difference in CD32 expression on the day of ART initiation, nor after 24 weeks on ART, despite differences in SIV DNA content. Next, we further investigated the phenotypes of CD32-high cells. We found that CD32-high cells had a greater frequency of being a memory cell than naïve and were also more activated than CD32-negative cells. We also observed that the CD32-high population is prone to contamination by non-T cells, due to rare expression on T cells. We found that sorting CD32-high cells without excluding CD14+ and CD20+ contaminants can have a significant impact on measurements of proviral DNA content.
Conclusion: Utilizing samples from HIV-infected participants and SIV-infected rhesus macaques on ART, we have assessed the hypothesis that CD32 is a marker of the replication-competent viral reservoir. While we did detect similar frequencies of CD4+ T cells expressing CD32, our findings contradict the notion that these populations are enriched in latent virus. We found no significant difference in total and replication-competent proviral DNA content between cell populations including, or excluding, CD32 fractions.

158 CD32+ CD4+ T CELLS ARE HIV TRANSCRIPTIONALLY ACTIVE RATHER THAN A RESTING RESERVOIR

Mohamed Abdel-Mohsen[1], Costin Tomescu[1], Surya Vadrevu[1], Adam M. Spivak[2], Leticia Kuri-Cervantes[3], Guoxin Wu[4], Kara Cox[4], María J. Buzón[5], Michael R. Betts[3], Vicente Planelles[2], Karam Mounzer[6], Bonnie J. Howell[4], Daria Hazuda[4], Pablo Tebas[3], Luis Montaner[1]
[1]Wistar Institute, Philadelphia, PA, USA, [2]University of Utah, Salt Lake City, UT, USA, [3]University of Pennsylvania, Philadelphia, PA, USA, [4]Merck & Co, Inc, Kenilworth, NJ, USA, [5]Vall d'Hebron Research Institute, Barcelona, Spain, [6]Philadelphia FIGHT, Philadephia, PA, USA

Background: CD32a was recently suggested as a marker of the replication-competent HIV reservoir. We aimed to comprehensively assess whether CD32 associates with latent or active HIV reservoir during antiretroviral therapy (ART).
Methods: CD4+ T cell-surface expression of CD32 and activation markers (CD69, HLA-DR, and CD25) were measured using flow cytometry on fresh blood from 15 ART-suppressed HIV+ individuals, and on cryopreserved PBMCs from 12 ART-suppressed HIV+ individuals. Levels of cell-associated HIV-1 RNA and total HIV-1 DNA were measured in negatively selected isolated CD4+ T cells and in total unfractionated PBMCs using qPCR and ddPCR. Added measurements of HIV DNA and HIV RNA were performed on either FACS sorted CD32+ and CD32- from total or resting CD4+ T cells (n= 9) or CD32 pull downs (n= 2) with Ab conjugated magnetic beads as compared to cell number normalized pre-IP pull-downs. PMA-induced p24 secretion was also measured using ultrasensitive HIV gag p24 ELISA assay. Non-parametric Wilcoxon signed rank and spearman's rank correlation tests were used for statistical analysis.
Results: The levels of CD32 on fresh CD4+ T cells (median 3.95%, IQR 1.3) were significantly higher than on frozen cells (median 0.41%, IQR 0.3). In both fresh and frozen samples, the percentages of CD69+, HLADR+, and CD25+ were significantly higher on CD32+ cells compared to CD32- cells ($p<0.0001$). Levels of CD32+CD4+ T cells correlated with levels of HLADR+CD4+ T cells and CD25+CD4+ T cells ($p<0.05$). Cell-associated HIV RNA correlated positively with frequency of CD69+CD32+CD4+ T cells in PBMC (rho=0.65, p=0.01), or isolated CD4+ T cells (rho=0.61, p=0.017). CD4+ T cell-associated HIV DNA correlated positively with the frequency of CD69+CD32+CD4+ T cells (rho=0.53, p=0.044). Enrichment of HIV RNA (total elongated, unspliced, poly-adenylated, and multispliced) was observed in the sorted CD32+CD4+ T cells (3.9 to 7.4 fold) with only a slight enrichment (~1.5 fold) in HIV DNA when compared to CD32-CD4+ T cells. No HIV DNA was detected in CD32+HLADR- CD4+ T cells. Accordingly, HIV DNA was only slightly enriched (≤1.5 fold) in CD4+CD32+ pull downs relative to controls; and we observed a partial but not exclusive inducible p24 signal with PMA-induced CD4+CD32+ cells when compared to CD4+CD32- cells.
Conclusion: Our data highlight that CD32 may be preferentially expressed on activated CD4+ T cells harboring a transcriptionally active HIV reservoir during ART rather than restricted to the resting latent HIV reservoir.



159 INTEGRATING NEW ANTIRETROVIRAL THERAPIES

Chloe Orkin, *Barts Health NHS Trust, London, UK*

The 'pipeline' of candidate anti-HIV drugs includes novel classes, novel mechanisms of action, biologics and broadly neutralizing monoclonal antibodies. Formulations under development include a diverse range of options such as long-acting oral weekly products and implants capable of providing treatment for several months. Patient acceptability survey outcomes of LA/ER injectable Cabotegravir-Rilpivirine in phase III trials have been very positive. Importantly, drugs are also being developed for patients with extensive anti-viral resistance. Moving towards the future, it is important to examine the efficacy of current ART regimes in first line therapy and beyond, including when switching virologically suppressed patients. In 2018, is efficacy driven mainly by virological factors (high baseline viral load and emergence of resistance) or by tolerability and simplicity? How do we address the data gaps in RCTs, which largely enroll well, young male patients and very few women, transgender, co-infected, complex or ethnically diverse patients? With a future moving towards reducing drug exposure can we 'simplify' ART? Near-normal life expectancy of people living with HIV makes it ever more important to use regimens that safeguard against future comorbidity. Advances in the triple therapy TAF-based backbone have reduced treatment-related discontinuations related to bone and renal toxicity, while maintaining efficacy rates of > 90% in treatment-naïve studies. Second generation integrase inhibitors, recommended in the first-line guidelines of ALL well-resourced settings, have reduced emergent resistance toward zero and offer options which avoid booster-related drug interactions. Successful ART simplification is determined by critical pharmacological, biological and behavioural factors including potency, the genetic barrier, adherence and duration of suppression. Attempts to reduce toxicity by using certain two-drug (2DR) combinations in first line therapy and in switch studies have produced unexpectedly disappointing results. However, other 2DR combinations (such as bPI+3TC and NNRTI+INSTI) have demonstrated efficacy similar to triple therapy in switch studies. Large first-line 2DR studies will soon report outcomes. Some data on the safety benefits of 2DR regimens vs TDF-containing regimes have been reported but more are needed. Improving simplicity, tolerability, acceptability while reducing toxicity will be key areas of focus for the ART regimes of the future.

160 BROADLY NEUTRALIZING ANTIBODIES FOR HIV PREVENTION AND TREATMENT: DREAM OR PIPE DREAM?

Daniel R. Kuritzkes, *Brigham and Women's Hospital, Boston, MA, USA*

Small molecule inhibitors of HIV-1 replication have transformed antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP). Despite these successes, for many persons living with or at risk of acquiring HIV infection, the burden of taking daily medication poses significant challenges. Monoclonal antibodies that neutralize a broad range of HIV-1 isolates (bNAbs) may provide a long-acting alternative to daily oral therapy. The antiviral activity and preventive efficacy of several bNAbs administered singly or in combination have been demonstrated in non-human primate models and pilot human clinical trials, and large-scale efficacy trials of one bNAb for PrEP are currently underway. Significant challenges remain, however, in translating these promising preliminary results into practical, scalable and affordable preventive and therapeutic agents. These include identifying suitable combinations, potential immunogenicity of modified or synthetic bNAbs, developing formulations that allow self-administration, and process improvements that reduce the costs of manufacture to make bNAbs cost-effective alternatives to daily oral single-tablet regimens.

161 ANTIRETROVIRAL THERAPY IN CHILDREN: PRESENT CHALLENGES, FUTURE OPPORTUNITIES

Helena Rabie, *Stellenbosch University, Cape Town, South Africa*

Despite the reduction in mother to child transmission each year 100000–220000 new HIV infections still occur in children below 14 years of age globally, with only 43% accessing antiretroviral therapy. The complexities of diagnosis, linkage to care and retention are known but all children have unique therapeutic challenges. High suppression rates in adults are not mirrored in children. In low-middle-income settings only 62.5% of children are suppressed after 12 months on therapy. Unsuitable formulations and poor access to protease inhibitors (PI) are contributory. Neonates, especially if premature or low birth weight, have unique dosing requirement and adolescents particular adherence challenges. As each developmental stage requires dosing information there are considerable delays (up to 9 years) between licensing in adults and children. Dosage for commonly used drugs are still lacking in neonates and young children, i.e. abacavir is only licensed from 3 months of age and P1093, a dosing study of dolutegravir is still in progress. Lack of data and appropriate formulations prevents harmonization of adult and pediatric guidelines. Strategies to accelerate development includes modeling of dosing and adapting study design to facilitate rapid enrollment, this includes addressing tuberculosis, still a common infection. Studies to compare regimens and drug sequencing are uncommon in children, careful extrapolation of adult data for efficacy will inform pediatric practice in planning standard regimens and placing new drugs in the therapy sequence. Most children are infected with drug resistant HIV. As adult treatment programs mature, infants of mothers failing to suppress on PI are particularly vulnerable. Despite lopinavir/ritonavir (the preferred first line therapy for young children) having a high resistance threshold, children develop resistance, where resistance testing is unavailable consideration should be given to what the appropriate third line should be. Using dolutegravir as a first line regimen in mothers may compromise this drug in first line therapy in some infants. Pediatricians share excitement for long acting injectable drugs, their best use may be to prevent HIV infection in infants. Under these circumstances, resistance should be studied in order to predict its effect on initial therapy. As new drugs and drug combinations are developed tolerability and ease of use should be actively studied as should its contribution to therapy success.

162 TRANSITIONING TO NEW GENERIC ANTIRETROVIRALS IN SUB-SAHARAN AFRICA

Tendani Gaolathe, *Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana*

The pricing of drugs has influenced national ARV treatment guidelines in many Sub Saharan countries. The new possibility of integrase inhibitors - mostly dolutegravir (DTG) as first line was becoming a reality. This development called for policy adoption and introduction into national treatment guidelines, planning for roll-out, streamlining, and strengthening supply chain systems; all in the context of the newly adopted 'treat all guidelines.' For most SSA countries, integrase inhibitor use has been limited to 3rd line and beyond treatment failures. However with the anticipation that the cost of the FDC containing TDF/FTC and DTG will be cheaper than the current price of TDF/FTC/EFV 600 in low and middle income African countries and the advantages conveyed by the resistance barrier of this regimen a move to first line therapy was proposed. The generic drug competition and large volumes anticipated, especially with the adoption of the Treat all program in many SSA countries would even lower the prices more. Botswana, Kenya, South Africa, Nigeria and Uganda have been noted as the early adopters of integrase inhibitors as first line in their national formularies. By end of November 2017, the integrase inhibitor DTG had made it as first line into the national formulary and procurements done. Similarly other countries have introduced first line integrase inhibitor-based therapy into the national guidelines but were at different stages of planning. According to WHO, by November 2017 more than 20 countries had included DTG as a first line option With all the excitement, there is also uncertainty with DTG as a first line option, as there is limited evidence on DTG and TB (a common OI in SSA) and outcomes in pregnancy. For other countries there remained concerns about low availability of the low cost generic drugs, and the time and effort needed for approvals and registration in countries until the latter part of 2017. For the HIV-infected clients who are initiating antiretroviral therapy the challenges are few, but for transitioning, or treatment switches (for cost savings), this process has to be managed carefully.

163 THE OPIOID EPIDEMIC AND INFECTIOUS DISEASES: A PUBLIC HEALTH CRISIS

Sally Hodder, *West Virginia Clinical and Translational Science Institute, Morgantown, WV, USA*

The accelerating death rate due to drug overdose has been widely publicized in the popular media, yet there lurks an underlying veiled scourge of death and morbidity due to emergent infectious disease epidemics that are a consequence of the opioid epidemic. In the United States in 2016, there were more than 60,000 drug overdose deaths. To that toll must be added the nearly 20,000 additional deaths from viral hepatitis. Deaths in the U.S. due to the opioid epidemic exceed those due to HIV at the height of the AIDS epidemic in the U.S. Reported cases of acute hepatitis C increased nearly 3-fold from 2010 to 2015, largely due to increases in injection drug use. There was a more than 20%

increase in acute hepatitis B, a vaccine preventable disease, from 2014 to 2015. The toll of opioid related death and morbidity is even greater if one considers the impact of bacterial endocarditis, septic arthritis, and other infectious complications of intravenous drug use. Opioid-associated infectious disease epidemics are emerging in areas of the United States that have historically not been infectious disease hotspots. Acute hepatitis C amongst persons < 30 years of age who inject drugs has been demonstrated to be greater in nonurban compared with urban areas and is occurring in predominantly white persons. The incendiary nature of injection drug use, viral hepatitis, and HIV, the emergence of these synergistic epidemics in rural America, and implications for stemming the tide will be discussed.

164 GLOBAL ELIMINATION OF HEPATITIS C

Jordan Feld, *Toronto General Hospital, Toronto, ON, Canada*

With the remarkable advances in therapy for hepatitis C virus (HCV) infection, almost all infected individuals can now be cured with short-course, well-tolerated therapy. The success of current treatment has raised the prospect that perhaps this chronic infection could actually be eliminated as a public health threat on a global scale. With this in mind, the World Health Organization (WHO) set out ambitious elimination goals, aiming to reduce new HCV infections by 90% and HCV-related mortality by 65% by the year 2030. As countries strive to meet these targets, it has become abundantly clear that elimination will take a lot more than effective medications. Although some challenges are common to all environments, the local epidemiology and health care system must be considered when developing HCV control strategies. Major improvements in the left side of the continuum of care including improved diagnostics, active case-finding and novel models of care will be required to allow the therapeutic advances to deliver a public health benefit. In addition, major innovations in prevention strategies will be required, which differ significantly across regions. In middle and high-income countries, harm reduction strategies to reduce drug-use-related transmission will be critical whereas in many low and some middle-income countries, needle safety will be paramount. Challenges and successes at every step in the continuum will be discussed with a focus on countries that are on target to meet the WHO elimination goals, particularly those that have used HCV as a tool to strengthen their health sector infrastructure. Remaining research challenges will also be highlighted, particularly the need for a protective vaccine if HCV is truly to be not just regionally eliminated, but actually globally eradicated.

165 THE RISING CHALLENGE OF LIVER CANCER

Massimo Colombo, *University of Milan, Milan, Italy*

In 2015 there have been 854,000 incident cases of liver cancer and 810,000 related deaths globally contributing to > 20 million disability-adjusted life-years (DALYs).Incident liver cancer increased by 75% between 1990-2015 : 47% explained by changing population age structures, 35% by population growth and 8% to changing age-specific incidence rates. Infection with the hepatitis B virus accounted for 33% liver cancer deaths, alcohol for 30%, hepatitis C (HCV) for 21%, and other causes for 16%,the latter including metabolic syndrome . HCC is on the raise in northern and central Europe, N America and English speaking Asia, mainly due to epidemics of viral hepatitis, alcohol abuse and metabolic syndrome. HCC is declining in several traditionally high risk countries of the Mediterranean Europe, Japan and Hong Kong following effective measures of sanitation, including vaccination. In HIV population HCC stands as a growing cause of end stage HCV infection and related mortality. Surveillance of patients with chronic liver disease allows for increased detection of small, potentially curable tumors via such radical therapies as liver transplantation, hepatic resection and local ablative therapies that in accurately selected populations result in survival rates up to 75% at 5 year. Survival benefits, were further extended following successful control/cure of viral hepatitis. Since the Milan criteria(MC) for liver transplantation(up to one 5 cm tumor or 3 nodules each 3 cm) are too restrictive and the prognosis is dismal for patients beyond MC treated with local ablative techniques, loosed criteria of listing are increasingly being adopted in patients beyond MC who are successfully downstaged with local ablative techniques. Patients with an intermediate burden of HCC not bridged to transplantation, can still have limited survival benefits from local tumor ablation through repeat courses of chemo embolization (TACE) whereas both patients failing TACE and those with advanced HCC may respond to first and second lines of systemic therapy with targeted agents sorafenib, regorafenib, lenvantinib and cabozantinib. In these patients, 2 RCT failed to show superiority of radio embolization with yttrium versus sorafenib immune therapy with PD1 check point inhibitors has been registered in the USA to treat experienced patients with advanced HCC.

166 EXPANDING HOPE: ORGAN TRANSPLANTS FROM DONORS WITH HIV OR HCV INFECTION

Christine Durand, *Johns Hopkins Hospital, Baltimore, MD, USA*

For those living with end-stage organ disease, transplantation provides a clear survival benefit. However, due to a critical shortage of donated organs, many individuals awaiting organ transplantation will die before every receiving an organ offer. As such, innovative strategies to expand the organ donor pool are needed. One such strategy is the use of organs from donors with chronic viral infections. More specifically, the use of organs from HIV-infected (HIV+) donors for HIV+ transplant candidates and the use of organs from hepatitis C virus-infected (HCV+) donors for HCV-uninfected transplant candidates is currently under investigation. HIV-to-HIV kidney transplantation was pioneered in South Africa in 2010 with good results in a small cohort. Inspired by this experience, in the United States the HIV Organ Policy Equity (HOPE) Act was enacted in 2013 and reverses the federal ban on HIV-to-HIV transplantation. Pursuant to the HOPE Act, HIV-to-HIV transplants have been allowed within research protocols since 2015. The first HIV-to-HIV kidney and liver transplants were performed at Johns Hopkins in March of 2016 and a national multicenter study of HIV-to-HIV kidney and liver transplantation is ongoing. This session will discuss the potential risks and benefits of HIV-to-HIV transplantation and transplant outcomes to date. Since HIV remain an incurable illness even with effective antiretroviral therapy, the use of HIV+ donors for those without HIV is not being considered. However, for chronic HCV infection, direct acting antivirals (DAAs) provide a definitive cure for HCV including for transplant recipients. Moreover, in the United States high-quality organs from HCV+ donors are currently underutilized and represent a neglected public health resource. Pilot studies have investigated the use of DAAs as pre-emptive or prophylactic treatment in combination with kidney transplantation from HCV+ donors for HCV- recipients. This session will also review the results of these trials and discuss the potential that HCV+ to HCV- transplantation has to expand organ options more broadly.

POSTER ABSTRACTS

167 RHESUS PRIMARY CELL IN VITRO SHIV INFECTION ASSAY CORRELATES WITH IN VIVO REPLICATION

Adrienne E. Swanstrom[1], Sean O'Brien[1], Paul Bieniasz[2], Theodora Hatziioannou[2], Mario Roederer[3], Brandon Keele[1], Gregory Q. Del Prete[1], Jeffrey D. Lifson[1]
[1]AIDS and Cancer Virus Program, Frederick, MD, USA, [2]The Rockefeller University, New York, NY, USA, [3]Vaccine Research Center, NIAID, Bethesda, MD, USA

Background: Chimeric simian-human immunodeficiency viruses (SHIVs) containing an HIV-1 Envelope (Env) in an SIV backbone allow direct assessments of HIV-1 Env-based antibody and vaccine strategies in nonhuman primates (NHP) that are not feasible in SIV infection systems. However, it has been difficult to identify SHIVs able to consistently replicate in NHP at levels comparable to HIV-1 in humans or pathogenic SIVs in NHP. Recent publications have shown enhancement of rhesus CD4 use by HIV-1 Envs through distinct mutations at two positions within Env - 281 and 375 - often lead to improved SHIV replication in NHPs. While alterations at these two sites have consistently enhanced RhCD4 engagement by HIV-1 Envs of various clades, there are multiple possible amino acid substitutions at each site. Data to date suggest that the amino acid substitution at either 281 or 375 that yields the highest level of in vivo replication is unpredictably specific to each Env clone, resulting in multiple candidate clones to screen for Env-SHIV development. Given the cost and time required for such in vivo studies, a more efficient process is needed to identify SHIVs with potentially good replicative fitness in rhesus macaques.
Methods: We have developed an in vitro infection assay that can be used to screen and downselect candidate SHIVs for in vivo studies. Enriched rhesus primary CD4+ T cells pooled from 3 naïve macaques were stimulated for 3 days with αCD2/CD3/CD28 beads and IL-2, then the beads were washed out and 1x10^6 cells were spinoculated with test SHIVs (MOI of 0.01). Input virus was washed out and cultures were maintained in IL-2 for up to 15 days with culture supernatants sampled every 2-4 days for p27 quantification by ELISA.
Results: Results from this in vitro assay and results from co-inoculation in vivo competition fitness studies in macaques showed comparable rank order performance of different mutant versions of multiple SHIVs tested, identifying variants exhibiting ≥ one log lower p27 production as less fit for in vivo replication.
Conclusion: As our understanding of how to manipulate HIV-1 Envs to enhance replication in NHPs improves, this assay will be useful to screen SHIVs for prioritization for in vivo studies.

168 FIRST REPORT OF A SUBTYPE B CONTAINING HIV-1 RECOMBINANT OF SUB-SAHARAN AFRICA ORIGIN

Gustavo Kijak[1], **Erik Billings**[1], Eric Sanders-Buell[1], Anne Marie O'Sullivan[1], Nicaise Ndembi[2], Sylvia Adebajo[3], Afoke Kokogho[4], Mark Milazzo[5], Merlin L. Robb[5], Nelson L. Michael[6], Sodsai Tovanabutra[1], Man Charurat[2], Trevor Crowell[5], Julie Ake[6]
[1]US Military HIV Research Program, Silver Spring, MD, USA, [2]Institute of Human Virology Nigeria, Abuja, Nigeria, [3]Population Council, New York, NY, USA, [4]Walter Reed Program–Nigeria, Abuja, Nigeria, [5]US Military HIV Research Program, Bethesda, MD, USA, [6]Walter Reed Army Institute of Research, Silver Spring, MD, USA

Background: Subtype B is the major HIV-1 subtype in Western Europe, the Americas, and Australia, and also circulates in Southeast Asia and China. In all of these regions, co-circulation with other subtypes has led to the emergence of unique recombinant forms (URFs) and circulating recombinant forms (CRFs). Data published to date indicates a limited dissemination of subtype B, and B-containing URFs and CRFs in sub-Saharan Africa. Here we describe the circulation of recombinant strains containing subtype B and CRF02_AG among a cohort of men who have sex with men (MSM) in Lagos, Nigeria.
Methods: Between 2013 and 2016, the Lagos arm of the RV368/TRUST study enrolled 672 Nigerian MSM. Within this group, the HIV-1 sero-prevalence was 59%. HIV-1 *pol* sequences (HXB2: 2273-3869) were obtained from 150 plasma samples with VL ≥ 1000 copies/mL. Samples with subtype B genetic material were further characterized by full–genome sequencing. HIV-1 subtype assignment and recombinant analysis were performed combining phylogenetic analysis, visual inspection, Simplot (v3.5.1), and subtyping tools (jpHMM, NCBI genotyping). A genetic distance of ≤ 1.5% and bootstrap supported maximum-likelihood branching were used to identify linked transmission networks.
Results: The predominant subtype was CRF02_AG (57%), followed by CRF02/B recombinants (15%), subtypes G (13%), A1 (3%), B (2%), and other recombinants containing CRF02, A1, or G. Transmission networks involved 24 participants in 9 clusters containing 2 to 5 participants per cluster. Within the main CRF02/B cluster, 5 strains were identified and subjected to near-full length sequence analysis. Three of the full-length genomes constitute the new CRF95_02B, containing *RT* and *int* genes from subtype B with the remainder comprised of CRF02_AG.
Conclusion: The newly isolated CRF95_02B and the large cluster of strains associated with it, demonstrate the need for increased epidemiological monitoring of all groups engaged in high-risk activities. With high HIV-1 prevalence, a new CRF, and multiple transmission networks, this cohort of Nigerian MSM represents a previously hidden reservoir of HIV-1 strains that will need to be considered during vaccine immunogen selection and development. The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.

169 PHYLOGENETIC CLUSTERS OF HIV-1 REVEAL POTENTIAL VIRAL GENETIC IMPACT ON COMORBIDITIES

Katharina Kusejko[1], Dominique L. Braun[1], Manuel Battegay[2], Enos Bernasconi[3], Alexandra Calmy[4], Matthias Cavassini[5], Matthias Hoffmann[6], Jürg Böni[7], Sabine Yerly[4], Thomas Klimkait[8], Matthieu Perreau[5], Andri Rauch[9], Roger Kouyos[1], Huldrych F. Günthard[1]
[1]University Hospital Zurich, Zurich, Switzerland, [2]University Hospital Basel, Basel, Switzerland, [3]Servizio di Malattie Infettive, Lugano, Switzerland, [4]University Hospitals of Geneva, Geneva, Switzerland, [5]Lausanne University Hospital, Lausanne, Switzerland, [6]St. Gallen Cantonal Hospital, St. Gallen, Switzerland, [7]University of Zurich, Zurich, Switzerland, [8]University of Basel, Basel, Switzerland, [9]University Hospital of Bern, Bern, Switzerland

Background: Understanding and addressing comorbidities, co-infections, and AIDS-defining illnesses in HIV-infected patients remains one of the major challenges in managing HIV-infection in the era of highly active antiretroviral therapy. Here we tested at the population level whether viral genetic data can be informative to discern the differences in occurrence of comorbidities respective co-infections based on similarity of viral genomes in addition to demographic and clinical parameters.
Methods: Using HIV-1 pol-sequences of ~11,000 patients of the drug resistance database of the Swiss HIV Cohort Study (SHCS) as well as 240,000 Los Alamos background sequences, we identified phylogenetic clusters of SHCS patients. The occurrence of comorbidities, co-infections and AIDS-defining illnesses in these patients was then analyzed with respect to those demographical and clinical confounders, which revealed a clustering pattern in the HIV-1 transmission network, by applying mixed effects logistic models.
Results: Overall, HIV-related thrombocytopenia, Kaposi's sarcoma and HIV-associated encephalopathy exhibited a significant (see **Table**) phylogenetic signal after adjusting for confounders suggesting a potential role of viral genetic factors for these diseases. In addition, the co-infections Hepatitis C, Hepatitis B and Cytomegalovirus revealed a strong phylogenetic clustering after adjusting for confounding suggesting shared transmission routes for these infectious conditions. The phylogenetic signal for diabetes mellitus, cardiovascular diseases, neoplasms, syphilis and candida stomatitis could be explained by the clustering of those demographical and clinical confounders which showed a high within-cluster similarity, such as age, sex, risk group, ethnicity, length of HIV infection and antiretroviral treatment.
Conclusion: This new type of analysis of combining viral sequences and well-defined clinical endpoints could be useful in triggering targeted pathogenesis

studies and inform about targeted screening: Most of the studied diseases were not randomly distributed on the HIV-1 transmission network, which is only partly due to the clustering of demographic properties and other well-known risk factors of comorbidities. Such analysis could hence be helpful in identifying additional pathogenesis traits for specific illnesses, such as HIV-associated encephalopathy as found in the current analysis or other comorbidities.

Disease	Number of patients included	Patients in cluster	Univariate cluster effect (p value)	Multivariate cluster effect (p value)
Non-infectious comorbidities:				
Osteoporosis	2,432	678	n.s	n.s
Diabetes mellitus	13,424	6,292	< 0.001	n.s
Cardiovascular diseases	13,629	6,378	0.0047	n.s
Thrombocytopenia	18,637	7,171	< 0.001	0.0095
Neoplasm	14,662	7,032	< 0.001	n.s
Co-infections:				
Hepatitis C	14,397	6,804	< 0.001	< 0.001
Hepatitis B	14,254	6,634	< 0.001	< 0.001
Syphilis	15,141	6,990	< 0.001	n.s
Cytomegalovirus	16,465	6,911	< 0.001	< 0.001
AIDS-defining diseases:				
Candida stomatitis	9,024	2,765	0.0035	n.s
Oral hairy leukoplakia	10,017	3,015	n.s	n.s
Pneumocystis pneumonia	9,738	2,934	n.s	n.s
Candidiasis esophageal	9,995	3,004	n.s	n.s
Herpes zoster multidermatomal	9,969	2,977	n.s	n.s
Kaposi's sarcoma	10,034	2,988	< 0.001	< 0.001
HIV-related encephalopathy	10,160	3,030	0.0012	0.0021

Table: Analysis of the most frequent comorbidities, co-infections and AIDS-defining diseases in the SHCS. The total study population for each disease consists of those patients with a clear diagnosis of the disease as well as controls, which clearly do not have the disease, matched by calendar year. The cluster analysis was then performed for the subset of patients, which clustered in the phylogenetic HIV-1 transmission network with other patients of the study population.

170 IS FITNESS RESPONSIBLE FOR POORER ART RESPONSE IN HIV-1 SUBTYPE F INFECTED PATIENTS?

Eva Poveda[1], Dane Winner[2], Samira Joussef[3], Berta Pernas[1], Marta Grandal[1], Antonio Aguilera[4], Angeles Castro[1], Alvaro Mena[1], Miguel E. Quinones-Nateu[3]
[1]Instituto de Investigación Biomédica de A Coruña, A Coruña, Spain, [2]University Hospitals Cleveland Medical Center, Cleveland, OH, USA, [3]Case Western Reserve University, Cleveland, OH, USA, [4]Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain

Background: Subtype F HIV-1 is highly prevalent in Northwestern (NW) Spain, having reached 36% of newly diagnosed HIV-infected individuals by the end of 2016. We have shown an impaired response to antiretroviral treatment (ART) in patients infected with HIV-1 subtype F viruses compared to those infected with subtype B. Here, we characterized a series of subtype F and B viruses from NW Spain patients to better understand the mechanism(s) associated with these findings.

Methods: Plasma samples from patients infected either with subtype F (n=10) or B (n=10) viruses, and clinical/virological data, were obtained from two hospitals in NW Spain. Two sets of recombinant viruses (3'Gag/PR/RT/INT and env) were constructed and used in drug susceptibility and neutralization assays, respectively, and also in viral growth kinetics (VGK) experiments. A deep sequencing-based HIV-1 genotyping assay was used to determine drug resistance and coreceptor tropism. Finally, we used deep sequencing to analyze near full-length HIV-1 genomes and determine intra-patient HIV-1 quasispecies diversity.

Results: No major differences in demographics/clinical characteristics were observed between both groups (F vs. B) with the exception of baseline plasma viral load (5.65 vs. 4.91 log c/ml, p = 0.013) and time to reach undetectable viremia (<50 log c/ml; 49 vs. 20 weeks, p=0.026). HIV-1 phenotypic/genotypic analysis showed that all 20 HIV-1 strains were susceptible to all antiretroviral drugs tested. All viruses were equally neutralized by the bNABs VRC01 and 10E8. Similar VGKs were observed in the 3'Gag/PR/RT/INT-recombinant viruses; however, although no significant, subtype F env-recombinant viruses showed slightly higher replication rates compared to subtype B viruses (median 0.036 vs. 0.015, p=0.119). Intrapatient HIV-1 quasispecies diversity was also slightly higher in subtype F vs. B viruses (1.08 vs. 0.89, p=0.37). Full HIV-1 genome analysis identified 39 polymorphisms present in subtype F but absent in all subtype B viruses, i.e., LTR (2), Gag (5), PR (5), RT (14), INT (3), Vif (3), gp120 (6), and gp41 (1).

Conclusion: The significant delay in initial response to ART in patients infected with subtype F viruses may be associated with higher viral replication capacity. Ongoing growth competition experiments, and further analysis of specific polymorphisms, are needed to corroborate the potential increase in replicative fitness of subtype F viruses compared to subtype B HIV-1 strains.

171 DETECTION OF ANTI-ASP ANTIBODIES IN SERA OF HIV+ INDIVIDUALS

Antonio Mancarella[1], Elisa De Crignis[2], Giampietro Corradin[3], Craig Fenwick[1], Matthieu Perreau[1], Giuseppe Pantaleo[1], Cecilia Graziosi[1]
[1]Lausanne University Hospital, Lausanne, Switzerland, [2]Erasmus University Medical Center, Rotterdam, Netherlands, [3]University of Lausanne, Lausanne, Switzerland

Background: HIV-1 Antisense protein (ASP) is an antisense open reading frame encoding for a highly hydrophobic protein of 20 kDa encompassing Env at the junction of gp120-gp41. Although initially suggested in 1988, existence of ASP remains controversial and its function has yet to be defined. A previous study shows that sera from HIV+ individuals can recognize ASP, suggesting actual production of this protein during infection. In these experiments however, the same sera were used for both immunoprecipitations and immunoblots. This, together with the fact that defective ribosome products with immune response have been reported for HIV-1, may have allowed for cross-reactivity leading to false positives. In this study we report the detection of anti-ASP antibodies in sera of HIV patients by ELISA assay using a panel of overlapping synthetic peptides spanning the whole length of the protein.

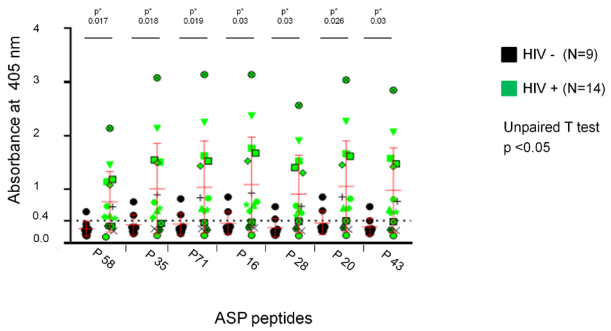
Methods: ASP-specific antibodies in sera of 14 HIV+ individuals and 9 healthy donors were determined by ELISA using 7 overlapping peptides spanning the whole ASP. 96-well flat-bottom plates were coated overnight with the synthetic peptides (1 peptide/well). Sera were diluted 1:200 prior to screening. Goat anti-human AP-conjugated secondary antibodies were diluted 1:2000. ELISA cut-off was calculated by adding 3 SDs to the mean OD from antigen-negative wells (healthy donors).

Results: Of the 14 patients analyzed, 5 (35.7%) had a positive ELISA result against each of the seven peptides tested (p<0.05) (Figure 1). Interestingly, the peptides characterized by the lowest OD values were P58, corresponding in the sense orientation to gp41, and P28 and P43, who corresponding to Env hypervariable regions V4 and V5. Two healthy donors were found to have OD values slightly above the cut-off, probably due to the low number of samples tested.

Conclusion: Our data show that anti-ASP antibodies are present in sera from HIV+ individuals. The use of overlapping fragments covering the entire length of the protein indicates that the antibody response is triggered by the whole protein and not by incomplete ribosome products. In addition, peptides derived from different regions of the protein appear to be more or less immunogenic depending on the Env region present in the opposite orientation. Unfortunately no clinical information is available for the patients tested. We are currently planning a large scale testing of sera from HIV-infected individuals before and after seroconversion and/or undergoing different therapeutic regimens.

Figure 1

Detection of anti-ASP antibodies in sera of HIV+ individuals by ELISA assay



172 STO-609 INHIBITS P24 RELEASE FROM GAG-EXPRESSING CELLS

Antonio Valentin, **Sue Crawford**
Baylor College of Medicine, Houston, TX, USA

Background: I recently discovered that a specific inhibitor of CaMKK2, STO-609 (7-Oxo-7H-benzimidazo[2,1-a]benz[de]isoquinoline-3-carboxylic acid acetate),

significantly decreased the extracellular production of p24 antigen from human PBMCs from two individuals infected with three different HIV-1 strains (X4, R5, X4R5). PBMC viability was high in the presence of STO-609 indicating that the reduction in virus infectivity was not due to STO-609 cytotoxicity. These results suggest CaMKK2 is critical for HIV replication. The goal of the proposed research is to determine at what step STO-609 inhibits HIV-1 replication.
Methods: Gag/Pol and Env were co-expressed in 293T cells. The levels of intracellular Gag expression and extracellular p24 release was assessed by western blot and p24 ELISA, respectively. To evaluate Gag intracellular trafficking, Gag interactions with the autophagy marker protein LC3, and the ESCRT (endosomal sorting complex required for transport) proteins Alix and Tsg101 required for Gag trafficking to and efficient release of virus particles from the plasma membrane, were evaluated by immunoprecipitation.
Results: The levels of intracellular Gag expression, p55 and the proteolytically processed p41 and p24, were similar in the absence or presence of STO-609. In contrast, p24 release and detection in the media of Gag-expressing cells were greatly reduced in cells cultured in the presence of STO-609 compared to cells cultured in the absence of STO-609. We next evaluated whether STO-609 inhibits Gag trafficking to the plasma membrane. In the absence or presence of STO-609, we identified that Gag interacts with the membrane-inserted LC3 II autophagy protein, and the ESCRT proteins Alix, and Tsg101 suggesting STO-609 does not inhibit Gag trafficking to the plasma membrane.
Conclusion: These results suggest that STO-609 does not affect Gag expression, trafficking to the plasma membrane, or proteolytic processing but inhibits p24 release from cells. This is an unexpected and potentially exciting finding, and we hypothesize that activation of HIV in latently-infected cells cultured in the presence of STO-609 will allow expression of HIV proteins while preventing HIV budding and release. We will focus our studies in the next year on testing this hypothesis in HIV-infected PBMCs. Proving our hypothesis may lead to strategies for enhanced detection of HIV-infected cells by the immune system and may be useful in the "kill" arm of the "shock and kill" strategy to cure HIV.

173 PROGRESS IN DEVELOPING HIGHLY POTENT SECOND-GENERATION MATURATION INHIBITORS

Phuong Pham[1], Emiko Urano[1], Sherimay Ablan[1], Justin A. Kaplan[1], T.J. Nitz[2], David E. Martin[3], Carl Wild[3], Ritu Gaur[2], Eric O. Freed[1]
[1]National Cancer Institute, Frederick, MD, USA, [2]South Asian University, Chanakyapuri, New Delhi, India, [3]DFH Pharma, Inc, Gaithersburg, MD, USA
Background: Maturation inhibitors (MIs) block HIV replication by disrupting conversion of CA-SP1 to mature CA resulting in the formation of non-infectious viral particles. MIs likely bind at or near the CA-SP1 cleavage site in the assembled immature Gag complex. Proof-of-concept for MIs was established with bevirimat (BVM), which was found safe and effective in reducing viral load. However, a single amino acid polymorphism in the SP1 region of Gag reduced susceptibility to BVM.
Methods: We identified a set of C-28 alkyl amine BVM analogs that exhibited enhanced activity against BVM-resistant polymorphs. The structure-activity relationship (SAR) of these analogs was determined. Variables included side chain length, amine substitution and heteroatom incorporation. Activity against BVM-sensitive and -resistant polymorphic viruses was determined by measuring CA-SP1 processing. Resistance selection studies were carried out against subtype B and C isolates.
Results: Effect of side-chain length was examined using aminoalkylamines with 2, 3 or 4 carbon atom linkers between amine moieties proximal to the triterpene template. Antiviral activity increased with linker length and was highest for the aminobutylamines. Amine substitution was examined using a series of N-substituted aminoalkylamines. Significant reduction in activity was observed on conversion of the C-28 proximal amine from secondary to tertiary. Alkyl substitution of the distal amine enhanced activity, with the dimethyl amine blocking CA-SP1 processing by 61%. Heteroatom incorporation was examined by substituting the terminal cyclohexyl group in the aminopropylalkyl side chain with piperidine, N-methylpiperidine, morpholine or N-methylpiperazine. Resistance mutations mapped to the major homology region of capsid and to positions in SP1 not previously observed in BVM selection experiments.
Conclusion: Side chain length and amine substitution had significant effects on activity against BVM-resistant polymorphs while heteroatom introduction did not. The amine proximal to the triterpene core plays a key role in activity, most likely by serving as a hydrogen bond donor that stabilizes compound/target interaction. The effect of side chain length could reflect the extended nature of the Gag target with a longer C-28 side chain positioning compound/target residues to better interact. These findings, coupled with the novel resistance mutations identified, provide new insights into the target and mechanism of action of MIs.

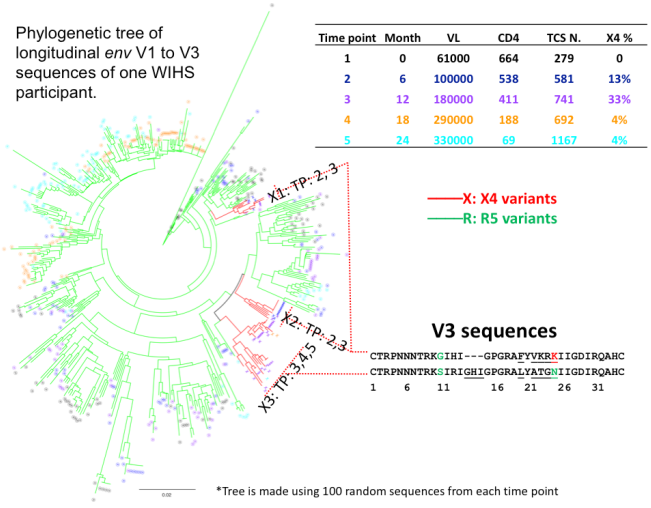
174 THE VIROME OF A NEW WORLD PRIMATE UNVEILS A RETROVIRUS THAT CAUSES IMMUNOSUPPRESSION

Cláudia Priscila Ramos Muniz[1], Dawn M. Dudley[2], Liliane T. Cavalcante[3], Gislaine Curty[1], Stefanie V. Santos[4], Alcides Pissinatti[5], David H. O'Connor[2], Marcelo Alves Soares[1], André Felipe Andrade dos Santos[3]
[1]Instituto Nacional de Cancer, Rio de Janeiro, Brazil, [2]University of Wisconsin, Madison, WI, USA, [3]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [4]Universidade Federal de São Paulo, São Paulo, Brazil, [5]Centro de Primatologia do Rio de Janeiro, Rio de Janeiro, Brazil
Background: The natural reservoirs for some viruses are still controversial, with several hypotheses raising the possibility of non-human primates (NHPs) cross-species transmission of viruses to human. For this purpose, it is extremely important to characterize viral infections in NHP. A colony of Brachyteles arachnoides, a New World primate (NWP) species hosted at Centro de Primatologia of Rio de Janeiro (CPRJ), Brazil, has been affected by a disease of unknown cause. In the last years, NHPs from this colony showed clinical signs similar to those observed in immunosuppression diseases. Immunohistochemistry analysis of deceseased animals revealed that the causa mortis was due to the consequences of a viral infection from the Retroviridae family. Transmission electron microscopy (TEM) images of liver and lung samples showed viral particles with siman foamy virus and simian retrovirus type D morphologies. In order to identify the viral agents that possibly led these NHPs to death, specimen 2506 was selected for this study
Methods: Saliva sample was collected and treated to digest unprotected nucleic acid. An RT-PCR reaction was performed to obtain cDNA from the RNA viruses while preserving DNA from DNA viruses. DNA libraries were constructed using the Nextera XT DNA Sample Preparation Kit (Illumina) and sequenced in a MiSeq Illumina platform. PCR and Sanger sequencing were performed to complete sequence gaps to acquire the complete genome. Phylogenetic analyzes were conducted using maximum likelihood in MEGA6.0.
Results: The complete genomes of a simian foamy virus (SFV) and a simian retrovirus (SRV) that infected the specimen were sequenced. Both findings corroborate with TEM images obtained from NHPs from this colony. Phylogenetic analyses showed that SFV from B. arachnoides grouped with NWP SFV, corroborating with the cospeciation hypothesis for this virus. No pathology has been associated with SFV infection so far, but it is known that it may be an opportunistic agent. Phylogenetic analysis showed the SRV found grouped with SRV from Asian monkeys. The clinical signs observed in the NWP specimen were similar to those found in sick Asian monkeys infected by SRV.
Conclusion: For the first time, the complete genomes from SFV and SRV infecting B. arachnoides were obtained. The SRV described in this study is the first exogenous retrovirus able to cause immunosuppression identified so far in a NWP, leading to its death.

175LB PRIMER ID SEQUENCING TO STUDY THE DEVELOPMENT OF CXCR4-USING HIV-1 VARIANTS

Shuntai Zhou[1], Ean Spielvogel[1], Sabrina Clark[1], Adaora Adimora[1], Catalina Ramirez[1], Andrew Edmonds[1], Igho Ofotokun[2], Seble Kassaye[3], Margaret Fischl[4], Stephen J. Gange[5], Alan Landay[6], Maria Villacres[7], Jack DeHovitz[8], Kathryn Anastos[9], Ronald Swanstrom[1]
[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]Emory University, Atlanta, GA, USA, [3]Georgetown University, Washington, DC, USA, [4]University of Miami, Miami, FL, USA, [5]Johns Hopkins University, Baltimore, MD, USA, [6]Rush University, Chicago, IL, USA, [7]University of Southern California, Los Angeles, CA, USA, [8]State University of New York at Albany, Rensselaer, NY, USA, [9]Montefiore Medical Center, Bronx, NY, USA
Background: HIV-1 uses CD4 as the main receptor and either CCR5 (R5 variants) or CXCR4 (X4 variants) as a coreceptor to enter the host cells. X4 variants are usually seen in the late stage of HIV-1 infection and are related to rapid disease progression. X4 and R5 variants have substantial sequence differences especially at the V3 region. However, the evolution pathways that drive development of X4 variants are unclear. We performed Primer ID deep

sequencing using longitudinal plasma samples from the Women's Interagency HIV Study (WIHS) cohort to study the development of X4 variants.
Methods: We identified 23 subtype B HIV-seropositive WIHS participants meeting the following criteria: 1) CD4 T+ cell counts declined from >500 cell//µl to <100 cells/µl; 2) therapy-naïve or on failed therapy with unsuppressed viral load; and 3) plasma samples available biannually during the period of CD4 decline. Multiplexed Primer ID MiSeq sequencing targeted HIV-1 PR, RT, IN and V1/V3 regions on longitudinal specimens. X4 variants were determined by both criteria: 1) Geno2pheno coreceptor algorithm with a false positive rate below 2%, and 2) variants form a distinct lineage.
Results: Seventeen participants (74%) had X4 variants at the last time point when CD4 was <100 cells/µl and 6 (23%) had R5 only viral populations. We sequenced all available longitudinal samples for eight X4 participants and two R5 participants with an average 6.6 biannual time points per participant. Seven of the eight X4 participants (87.5%) did not have X4 variants at baseline but developed X4 viruses as minority variants (mean abundance 21% in the viral population) at a median CD4 count of 538 cells/µL (IQR: 491-655). One participant had X4 variants at baseline with a CD4 count of 759 cells/µL. Three of the eight X4 participants (37.5%) had rapid CD4 decline (>300 cells/µL per year) after emerging of X4 variants and two of six R5 participants (33.3%) had rapid CD4 decline overall (p = 0.57). Phylogenetic analysis showed that X4 variants could emerge from multiple pre-existing lineages with distinct V3 sequence changes (Fig 1). Sequence changes at the V1/V2 region were associated with sequence changes in the V3 region during the development of X4 variants in most X4 participants.
Conclusion: X4 variants can emerge as minor variants early during the course of HIV infection. The co-evolution of the V1/V2 region and V3 region suggests that the compensatory mutations on the V1/V2 regions may be required to develop X4 tropism.



176 IDENTIFICATION OF FASNALL, A NOVEL FASN INHIBITOR THAT ATTENUATES HIV-1 REPLICATION

Manjusha Kulkarni[1], Annette Burkhouse[1], Menakshi Bhat[1], Yazan Alwarawrah[2], Phillip Hughes[2], Jesus Arcos[1], David Loiselle[2], Jordi Torrelles[1], Nicholas Funderburg[1], Timothy Haystead[2], **Jesse Kwiek**[1]
[1]The Ohio State University, Columbus, OH, USA, [2]Duke University, Durham, NC, USA
Background: HIV-1 engages host machinery to produce progeny, and thereby imposes a substantial burden to cellular metabolism. Thus, metabolic disorders, including body fat redistribution, often occur in people living with HIV-1. Many FA and lipid-biosynthesis enzymes use purine cofactors like ATP and NAPDH.
Methods: We performed a functional proteomics screen to define how HIV-1 infection regulates purine-binding proteins. We used fluorescence-linked enzyme chemoproteomic strategy (FLECS) to identify novel small molecule inhibitors.
Results: We observed that HIV upregulates fatty acid synthase (FASN) levels and increases de novo fatty acid synthesis. FASN is a 250kDa, multifunctional enzyme that in the presence of NADPH condenses acetyl-CoA and malonyl-CoA into palmitate. Reduction of FASN levels with siRNA inidcates that FASN is required during a late stage of HIV replication. To identify novel FASN inhibitors, we assembled a library of purine-like small molecules and screened for molecules that competed FASN from an affinity resin. Our lead molecule, Fasnall, is a thiophenopyrimidine-based molecule that potently inhibited FASN enzymatic activity in cell-based assays and in vitro. In both tissue culture and primary peripheral blood mononuclear cell models of HIV replication, Fasnall inhibited virion production (EC50 = 213 nM) with minimal effects on host cell viability.
Conclusion: Our primary result - that efficient HIV-1 replication requires FASN activity - complements previous work that demonstrates enveloped viruses such as hepatitis C virus (HCV), Dengue virus, and human cytomegalovirus (CMV) also require de novo fatty acid biosynthesis. In addition to its importance to viral replication, FASN and FASN-dependent increased de novo fatty acid biosynthesis is associated with breast cancer, melanoma, and hepatocellular carcinoma. In adults, most normal tissues obtain FA exogenously from diet, and as a result, most cells have limited de novo FA biosynthesis and express FASN at very low levels. Thus, de novo fatty acid biosynthesis is minimal in normal cells and required by both intrinsic (cancer) and extrinsic cellular perturbations (e.g. HIV). These features make FASN an attractive target for pharmacological intervention.

177 EXPRESSION OF MDM2 IN MACROPHAGES FAVORS HIV-1 INTEGRATION THROUGH INHIBITION OF P53

Yann Breton, Vincent Desrosiers, Michel Ouellet, Michel J. Tremblay
Laval University, Quebec City, QC, Canada
Background: Macrophages play an important role in the establishment and propagation of HIV-1 infection. Upon exposure to HIV-1, only a small proportion of macrophages are infected whereas most remain uninfected. To shed light on this issue, transcriptomic analyses were performed to compare infected and bystander populations and determine the molecular basis of HIV-1 permissiveness in macrophages. This study revealed MDM2 as a positive regulator of HIV-1 infection in macrophages. MDM2 is an E3 ubiquitin ligase involved in the DNA damage response and regulates the turn-over of various proteins, including p53.
Methods: Monocyte-derived macrophages (MDMs) were transfected with target-specific siRNAs and exposed to a competent R5 HIV-1 virus expressing all viral genes and a small GPI-anchored reporter (HSA). In some experiments, MDMs were treated with chemical inhibitors altering MDM2 functions before being infected. Infection was measured by flow cytometry for HSA expression and by qRT-PCR for the number of integrated HIV-1 genomic DNA copies (Alu-HIV-1 PCR).
Results: Knockdown of MDM2 induced a 2-fold decrease in the number of infected macrophages as measured by flow cytometry without affecting cell viability or the expression of viral genes. These results were reproduced with a VSV-G-pseudotyped virus. Integration assays showed a significant reduction in the number of integrated HIV genomes following knockdown of MDM2. These results were confirmed using chemical inhibitors of MDM2. As expected, knockdown of MDM2 by siRNA resulted in a significant increase in mRNA and/or proteins of p53-induced genes, including p21 (*CDKN1A*). The role of p53 and p21 in the susceptibility of MDMs to HIV-1 were further confirmed with specific siRNAs.
Conclusion: Altogether, our results indicate that the resistance to HIV-1 integration associated with MDM2 silencing is independent on the mode of entry and requires the activation of p53. Experiments using the chemical inhibitor Nutlin-3 are of particular interest as this inhibitor specifically blocks the interaction between MDM2 and p53 therefore suggesting that the observed resistance to HIV-1 results from the release/activation of p53 and not the absence of MDM2 *per se*. The expression level of MDM2 and the activation state of p53 are therefore important factors in the establishment of the infection in MDMs. Identification of viral cofactors regulated by MDM2 will bring a new understanding of signaling events controlling HIV-1 replication in macrophages.

178 INTERPLAY BETWEEN FOLATE CYCLE AND HIV-1 INFECTION IN MONOCYTE-DERIVED MACROPHAGES

Vincent Desrosiers, Yann Breton, Michel Ouellet, Michel J. Tremblay
Laval University, Quebec City, QC, Canada
Background: Macrophages play an important role in HIV-1 infection. These cells are suspected to act as viral reservoirs and thus preclude complete elimination of the virus in infected individuals. A transcriptomic analysis was performed to compare gene expression between non-infected, infected and

bystander populations. Following this analysis, 50 genes were selected based on their differential expression in HIV-1-infected macrophages. Within those genes, we found that the expression of the folate cycle enzyme Gamma-Glutamyl Hydrolase (GGH) was upregulated in infected cells early after infection. We suggest that, in primary human macrophages, folate derivatives like tetrahydrofolate (THF) may play a protective role against infection by HIV-1.
Methods: Monocyte-derived macrophages (MDMs) were transfected with small interfering RNAs (siRNAs) targeting folate cycle enzymes GGH, Folylpolyglutamate Synthase (FPGS) and Methylenetetrahydrofolate Reductase (MTHFR) using lipofectamine RNAiMAX™ 3 days prior to infection with HIV-1. In other experiments, MDMs were exposed to increasing concentrations of Raltitrexed (RTX), a specific inhibitor of Thymidylate Synthase (TS), to assess the effect of TS inhibition during HIV-1 infection. We developed an experimental model based on the identification of productively infected MDMs by a fully replicative molecular clone of R5-tropic HIV-1 expressing all viral genes and a small GPI-anchored reporter gene (murine Heat Stable Antigen; HSA). After infection (20 ng of p24 per 105 cells), percentages of productively infected cells were evaluated by flow cytometry and ELISA targeting the viral capsid (p24) at 3 to 12 days post-infection.
Results: Downregulation of GGH, FPGS, and MTHFR gene expression increases initial HIV1 infection in MDMs by 22%, 65% and 51% respectively. Viral production kinetics are similarly enhanced. Also, by targeting TS activity with RTX, we significantly reduce infection. This inhibitory effect can last several days without affecting cell viability.
Conclusion: Interplay between HIV-1 and the folate cycle may be a key factor in the susceptibility of MDMs to HIV-1 infection. Downregulation of enzymes that involved in intracellular folate retention increase the percentage of productively infected cells. Folate derivatives like THF may thus to be important cofactors in the restriction of HIV-1 infection in MDMs. Finally, TS could be explored as a target for intervention against HIV-1 infection in macrophages.

179 LOXL3 REGULATES HIV-1 INFECTION IN HUMAN PRIMARY MACROPHAGES

Laurent Hany, Michel Ouellet, Michel Tremblay
Laval University, Quebec City, QC, Canada

Background: One of the suspected reason for HIV persistence is the constitution of a long-lived reservoir inside target cells, such as CD4+ T cells and macrophages. Based on in vitro observations, only a small proportion of macrophages is initially susceptible and could contribute to the establishment of a reservoir early after infection. To better understand molecular mechanisms of macrophages permissiveness, we performed transcriptomic analysis of infected and uninfected bystander cells. Precise mapping of the interactions between HIV-1 and host signaling pathways identified potential novel regulators of HIV-1 replication in macrophages. One of these was a member of the lysyl oxidase family, Lysyl-Oxidase-like-3 (LOXL3), which is known to regulate collagen/elastin crosslinking.
Methods: Our team has developed a fully competent molecular clone of HIV-1 bearing a GPI-anchored reporter gene allowing the identification and separation of productively infected Monocyte-Derived Macrophages (MDMs). Sorting of infected and bystander cells allowed us to compare transcriptomic signatures within these two populations. In so doing, 50 modulated genes were screened for their effects on HIV-1 infection by siRNA-mediated knockdown. Among these, LOXL3 knockdown was found to significantly impact susceptibility to infection. Validation experiments were thus initiated to explore its effects on viral replication and infection of HIV-1 within macrophages and compare it to known susceptibility (CD4) and restriction (SAMHD1) factors.
Results: Gene silencing of LOXL3 results in a 2-fold increase in the percentage of MDMs infected by HIV-1 as early as 2-days post infection and in a significant enhancement of viral production. Interestingly, LOXL3 knockdown leads to an upregulation of CD4 expression at both mRNA and protein levels. However, downregulation of LOXL3 gene also increases infection by a single-round VSV-G-pseudotyped HIV-1, which mode of entry is CD4-independent.
Conclusion: Although increase in CD4 expression following LOXL3 gene silencing suggests a potential explanation for the observed enhanced susceptibility to infection, VSV-g pseudotyping experiments instead imply a post-entry mechanism of action. Nevertheless, our data suggest that LOXL3 could be a restriction factor for HIV-1 replication in primary human macrophages. Identification of the mechanisms underlying LOXL3-mediated restriction will bring a better understanding of signaling events controlling HIV-1 replication in macrophages.

180 SYNONYMOUS RECODED ENV GENE INDUCE LETHALITY AND LOSS OF PROTEIN EXPRESSION IN HIV-1

Ana Jordan-Paiz, Maria Nevot, Sandra Franco, Miguel Angel Martinez
IrsiCaixa Institute for AIDS Research, Badalona, Spain

Background: For the expression of HIV-1 late genes, the early expressed transinducer Rev is needed to transport viral mRNAs to the cytoplasm (e.g. Env mRNA). The genetic code is redundant and codon usage differs among different species. Protein expression is affected by the presence of "rare" codons. We aim here to explore the impact of synonymous codon usage on HIV-1 ENV expression and virus replication capacity.
Methods: Six codons, AGG, GAG, CCT, ACT, CTC and GGG of HIV-1 env gene were synonymously changed to CGT, GAA, CCG, ACG, TTA and GGA, respectively (as described by Shin et al, PNAS 2015); consequently 39 mutations were introduced. To obtain viral particles, the different parts of HIV-1 genome were PCR amplified and transfected in MT-4 cells. Viral replication was quantified by measuring HIV-1 capsid p24 antigen production. WT and recoded env genes were also introduced in an expression vector (pcDNA3.1) and, together with the rev gene, were transfected in 293T cells. Protein expression and Env mRNA production were determined by WB and qPCR, respectively.
Results: After transfection, we observed that the synonymously recoded Env gene (recoded-Env) was lethal for the virus; no syncitia and no p24 production were observed after five blind passages in MT-4 cells. WB analysis of Env expression in 293T cells revealed that, in contrast to WT, the recoded-Env mRNA protein was not being translated although there were not significant differences in Env mRNA production. Additional mutants were designed to see which mutations were responsible for this phenotype, without modifying env codon usage (CAI) or codon pair bias (CPB). New mutants included changes in total number substitutions and/or CpG content (see Table). All new mutant env genes generated replicative viruses, however, they displayed different replicative capacities. Remarkably, synonymous substitutions at the 3' end of the env gene were affecting, to a greater extent, the virus phenotype.
Conclusion: We show here that the HIV-1 replication capacity is affected by the codon usage. Our results also indicate that mutations in the 3' coding region of Env (gp41) can lead to lethality. Ex vivo expression experiments demonstrated that Env mRNA translation was affected. However, it remains to be elucidated whether the interaction of Env mRNA and Rev is affected. Overall, our results emphasize the relevance of synonymous substitutions in shaping virus phenotype.

Seq. name	Recovery (days after transfection)	N° mut	CPB [3]	CpG [4]	TpA [4]	CAI
WT-Env	4	-	0,046	26	194	0,13689505
Recoded-Env	-	39	0,048	42	192	0,13158661
Recoded-Env-mm	8	21	0,046	35	193	0,13408268
Recoded-Env-CpG	5	20	0,053	26	196	0,1295865
Recoded-Env-CpG2	10	36	0,055	26	194	0,1291150
Recoded-Env-5'WT	9	3	0,047	27	193	0,1360499
Recoded-Env-3'WT	11	36	0,046	41	193	0,1320015

181 ENHANCEMENT OF HIV-1 INFECTION BY BUPRENORPHINE

German G. Gornalusse[1], Lucia Vojtech[1], Claire Levy[1], Rogelio M. Valdez[2], Urvashi Pandey[2], Julie McElrath[2], Florian Hladik[1]
[1]University of Washington, Seattle, WA, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: Medication-assisted treatment (MAT) with buprenorphine is now widely prescribed to treat addiction to heroin and other illicit opioids. There is some evidence that illicit opioids enhance HIV-1 replication and accelerate AIDS pathogenesis, but the effect of buprenorphine is unknown.
Methods: We obtained peripheral blood mononuclear cells (PBMCs) from healthy volunteers and activated them with phytohemagglutinin and interleukin 2 for 72 hours in the presence of morphine or buprenorphine. We infected the cells with a panel of replication-competent CCR5-tropic HIV-1 reporter viruses encoding a secreted nanoluciferase gene, and measured infection by luciferase activity in the supernatants over time. We also surveyed opioid receptor expression in PBMC and vaginal leukocytes, as well as Langerhans cells derived from CD34+ hematopoietic stem cells, by qPCR.

Results: Buprenorphine increased HIV-1 infectivity at the three MOIs tested (0.1, 0.2 and 0.5) and over all tested periods (24, 48 and 72 hours; n=3 experiments). For example, at 72 hours, HIV infection was three to six times higher in the presence of 2 nM buprenorphine ($p<0.0001$). Morphine also enhanced HIV-1 infection, but to a much lesser extent and only at the higher dosage. At 100 µM, morphine caused a 1.4-fold increase of infection after 72 hours ($p<0.0001$), whereas at 1 µM, HIV-1 infectivity remained unchanged. In none of the leukocyte types tested, we found expression of the classical opioid receptors (mu, kappa or delta), but the nociception/orphanin FQ receptor (NOP also known as OPRL1) was present in blood and vaginal lymphocytes.
Conclusion: Our results suggest that buprenorphine, much more than morphine, increases the susceptibility of leukocytes to HIV-1 infection in vitro. Given that leukocytes do not express the classical opioid receptors, this increase in HIV susceptibility must occur through either OPRL1 or an unknown pathway. These findings are a first step toward understanding how opioids, including those used for MAT, affect HIV infection.

182LB EBV BORF2 INHIBITS AND SEQUESTERS HUMAN APOBEC3B TO PROTECT VIRAL GENOME INTEGRITY

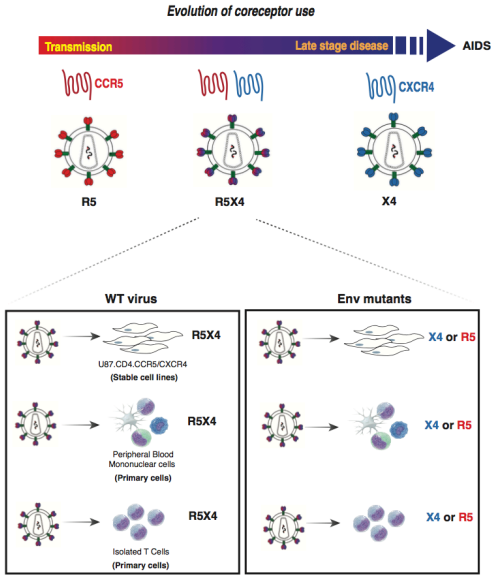
Adam Cheng[1], Jaime Yockteng Melgar[2], Lori Frappier[2], **Reuben S. Harris**[1]
[1]University of Minnesota, Minneapolis, MN, USA, [2]University of Toronto, Toronto, ON, Canada

Background: Human cells express up to seven different DNA cytosine deaminases, APOBEC3(A3)A-H, which have overlapping functions in innate antiviral immunity. Several A3s, most notably A3G, have been well characterized in inhibiting HIV-1 replication by converting C-to-U in retroviral single-stranded cDNA replication intermediates, thereby generating hypermutated viral genomes. To overcome A3-mediated restriction, viruses have evolved counteraction measures such as the lentiviral Vif protein, which nucleates the formation of a ubiquitin ligase complex that degrades A3 enzymes. We hypothesize that, like HIV-1 and related lentiviruses, herpesviruses including Epstein-Barr virus (EBV) possess mechanisms to counteract restriction by A3 enzymes.
Methods: The EBV ribonucleotide reductase subunit BORF2 was used in proteomic experiments to identify cellular binding partners. Interactions were confirmed using co-IP and mutagenesis experiments. Recombinant proteins were used in DNA C-to-U assays. Immunofluorescence and live cell imaging were used to address subcellular localization. CRISPR was used to generate BORF2-null EBV, and Sanger and next-generation sequencing were used to quantify viral genome integrity during lytic reactivation.
Results: The BORF2-APOBEC3B (A3B) interaction was discovered in a proteomic screen and validated by immunoprecipitation experiments and binding assays with recombinant proteins. Structure-guided mutagenesis experiments map the interaction to a conserved loop in the A3B catalytic domain, and biochemical studies demonstrate stoichiometric inhibition of A3B DNA cytosine deaminase activity by BORF2. Fluorescence and electron microscopy images, including movies of full cell division cycles, reveal a dramatic BORF2-dependent re-localization of nuclear A3B to perinuclear foci that may be residual bodies. CRISPR/Cas9-mediated deletion of BORF2 renders EBV susceptible to hypermutation by A3B.
Conclusion: The large double-stranded DNA herpesvirus EBV uses the large subunit of its ribonucleotide reductase, BORF2, to counteract A3B-mediated restriction/mutagenesis in a two-pronged approach through direct enzymatic inhibition and cellular relocalization. This mechanism is distinct from the proteasomal degradation mechanism used by lentiviruses and suggests new avenues for intervention.

183 R5X4 EVOLVE DISTINCT GP41 ACTIVATION PATHWAYS TO SENSE ALTERNATE CORECEPTOR BINDING

Annemarie Laumaea[1], Benjamin K. Dickerman[1], Jacqueline K. Flynn[1], Paul R. Gorry[2], Jason M. Mackenzie[3], Heidi E. Drummer[1], Pantelis Poumbourios[1]
[1]Burnet Institute, Melbourne, VIC, Australia, [2]RMIT University, Melbourne, VIC, Australia, [3]University of Melbourne, Melbourne, VIC, Australia

Background: Entry of HIV-1 is mediated by its envelope glycoproteins gp120 and gp41 (Env) that exist as a non-covalently associated trimer of heterodimers on the surface of virions. gp120 forms the outer layer and initial binding to its primary receptor CD4 creates a binding site for one of two obligatory chemokine co-receptors (CKR), CCR5 or CXCR4. CKR binding triggers refolding of gp41, enabling six-helix bundle formation that necessitates pore formation and transfer of viral core to the cell interior. gp120's interaction with CCR5 and/or CXCR4 classifies Env into R5 or X4 phenotypes, respectively. Transmitted/founder viruses that establish infection in a new host use CCR5 while X4 emerge and predominate in late stage disease in a subset of infected individuals. R5X4 isolates use both CKRs, emerge prior to the acceleration of T cell decline and the onset of symptomatic disease, and are believed to represent an evolutionary intermediate between R5 and X4 isolates. The molecular determinants that control CKR binding by R5 and X4 gp120 molecules is well defined however, downstream events that lead to the activation of the fusion function of gp41 is still unclear. We aimed to examine how receptor-induced signals by R5X4 Envs, are transmitted to activate gp41.
Methods: Near neighbour contacts within the gp120-gp41 association interface were identified by in silico structural screen and conservative substitutions were introduced to these sites in the primary R5X4 Env of the brain derived strain, dBR07. The ability of the mutant viruses to use alternative CKRs was assessed in a TZM-bl infectivity assay and subsequently in primary CD4+ T cells and PBMCs.
Results: Three gp41 mutants were identified with differential abilities to mediate infection via CCR5 versus CXCR4: F522Y in the FP and K574N and Q591A in heptad repeat 1. K574 and Q591 were critical for CCR5-mediated infection of PBMCs, primary CD4+ T cells and U87.CD4.CCR5 but dispensable for CXCR4-mediated infection. F522, however was essential for CXCR4-mediated infection of U87.CD4.CXCR4 cells, whereas infectivity for U87.CD4.CCR5 cells was retained. Interestingly, F522Y was not infectious for cells with low CCR5 expression in the presence of CCR5 antagonists. Importantly, K574N and Q591A retained their X4 phenotypes in the context of other R5X4 Envs.
Conclusion: The data suggest that R5X4 evolve distinct gp41-fusion activation pathways that sense alternative CKRs binding, and may represent a key step in the evolution of R5X4 and ultimately X4 HIV-1.



184 VARIABILITY OF HIV-1 V2 ENV DOMAIN FOR INTEGRIN BINDING: CLINICAL CORRELATES

Claudia Fabrizio, Davide F. Bavaro, Luciana Lepore, Antonella Lagioia, Gioacchino Angarano, Laura Monno, Annalisa Saracino
University of Bari, Bari, Italy

Background: The HIV $V2^{179-181}$ (HXB2 numbering) tripeptide mediates binding to α4β7 integrin, which is responsible for GALT homing. The exact role of V2 in viral transmission and replication and possible clinical correlates are still unclear. We aimed to assess V2 variability in naive HIV-1 infected patients and its association with clinical and viro-immunological features.
Methods: Gp120 sequences were obtained from 323 subjects newly diagnosed with HIV infection; V2 regions were evaluated for length, potential N-linked glycosylation sites (PNGs), net charge (NC) and tripeptide motif at residues 179-181. A possible association with HIV subtype, R5/X4 co-receptor tropism (CRT) (FPR 10%), duration of HIV infection (based on ambiguous nucleotides frequency in RT/PR, e.g. ≤0.2% ambiguity=recent infection) and patients'

variables (sex; age; risk factor; stage; baseline viro-immunological data) was explored.

Results: Patients were mainly males (85%), MSM (54%), median age 35 yrs (range 27-44), 41% with a recent HIV infection, AIDS in 15%, 67% infected with subtype B, and 82% with R5 variants. V2 data are shown in Table 1. No association was found between patients' features and V2 length, PNGs or NC. LDV was the most common $V2^{179-181}$ tripeptide (41.2%), followed by LDI (24.5%); Asp^{180} was highly conserved in both B and non-B strains (99%). 59.8% and 40.2% of B vs non-B sequences ($p \leq 0.001$) had a Leu^{179}. Val^{181} was detected in 62% and 38% of B/non-B ($p=0.04$) while Ile^{181} in 73% vs 27% of B/non-B subtypes ($p=0.034$), respectively. No correlation between CRT and $V2^{179-181}$ variants, or presence of LDV vs LDI motif was observed. Patients with L-strains had more frequently a recent infection (65% vs 37% in non-L, $p=0.01$); no other association between patient features and 179L/non-L variants was found. Conversely, patients with Val^{181} were younger (median age 32.3 vs 37.8, $p=0.004$), mainly MSM (63% vs 41%, $p \leq 0.001$), with higher CD4 ($p=0.04$), and an earlier stage at diagnosis (C3 1% vs 10%, $p \leq 0.001$) than patients with other variants. A multivariate analysis confirmed correlation with risk factor and stage.

Conclusion: Our results show a certain variability in V2 structure, including the α4β7 binding tripeptide, described as highly conserved. Due to potential therapeutic implications, further studies confirming our findings of a possible association of V2 features with viro-immunological characteristics are warranted.

V2 Features	Overall			B			Non-B			p value
V2 Length (median, range)	41 (39 - 45.5)			41.5 (36 - 55)			43.5 (37 - 48)			<0.001
PNGs (median, range)	2.12 (0 - 5)			2.12 (0 - 5)			3.5 (1 - 5)			<0.001
Net Charge (median, range)	1 (-4.1 - 6.9)			0 (-4.1 - 6.9)			1 (-2 - 4.9)			<0.001
Tripetide (179-181)	Type	nr	%	Type	nr	%	Type	nr	%	
	LDV	133	41.18%	LDV	75	34.88%	LDV	58	54.21%	<0.001
	LDI	79	24.46%	LDI	50	23.26%	LDI	28	27.10%	0.56
	SDI	17	5.26%	SDI	17	7.91%	SDI	0	0%	0.001
	SDV	10	3.1%	SDV	9	4.19%	SDV	1	0.93%	0.11
	DDV	7	2.17%	DDV	6	2.79%	DDV	1	0.93%	0.28
	IDV	6	1.86%	IDV	5	2.33%	IDV	1	0.93%	0.38
	LDL	6	1.86%	LDL	4	1.86%	LDL	2	1.87%	0.99
	QDV	5	1.55%	QDV	0	0%	QDV	5	4.67%	0.003
	HDV	4	1.24%	HDV	4	1.86%	HDV	0	0%	0.30
	PDI	4	1.24%	PDI	3	1.4%	PDI	1	0.93%	1
	QDI	4	1.24%	QDI	0	0.00%	QDI	4	3.74%	0.01
	VDV	4	1.24%	VDV	3	1.4%	VDV	1	0.93%	1
	FDV	3	0.93%	FDV	3	1.4%	FDV	0	0%	0.55
	DDI	3	0.93%	DDI	3	1.4%	DDI	0	0%	0.55
	MDI	3	0.93%	MDI	3	1.4%	MDI	0	0%	0.55
	NDL	3	0.93%	NDL	3	1.4%	NDL	0	0%	0.55
	TDI	3	0.93%	TDI	3	1.4%	TDI	0	0%	0.55
	Other	29	8.97%	Other	24	11.16%	Other	4	3.73%	0.03

185 HIV-1 CORE MORPHOLOGY ASSESSMENT USING SINGLE VIRION IMAGING BASED ON FRET

Anamaria D. Sarca[1], Hirofumi Fukuda[1], Luca Sardo[2], Jessica Smith[3], Kotaro Shirakawa[1], Kazuki Horikawa[4], Taisuke Izumi[1], Akifumi Takaori-Kondo[1]
[1]Kyoto University, Kyoto, Japan, [2]University of the Sciences, Philadelphia, PA, USA, [3]United States Army Medical Research Institute of Infectious Diseases, Frederick, MD, USA, [4]University of Tokushima, Tokushima, Japan

Background: There is an increasing importance to accurately characterize the morphology of HIV-1 virions, as it is closely related to their behavior as infectious particles. HIV-1 maturation, via Gag processing, leads to the formation of either closed (sealed) or open (unsealed) core virions. However, a microscopy method that allows the distinction of these HIV cores at single-virion level is not available. Thus, we developed the single virion visualization technology based on the principle of fluorescence resonance energy transfer (FRET).

Methods: Based on the infectious and replication-competent interdomain green fluorescence protein (iGFP) HIV-1 designed by Hubner et al (J Virol. 2007), we created the iFRET construct in which GFP is replaced with the cyan and yellow fluorescent protein pair (CFP and YFP) between the Gag MA-CA domains, with cleavage sequences between them and the adjacent domains. As control, we used iFRETΔPro, the protease deficient construct. FRET occurs between CFP and YFP in immature (uncleaved Gag) virions. Post Gag cleavage, these fluorescent proteins are dispersed inside and outside of the core. Stripping the viral membrane with detergent leads to complete loss of signal for some virions, indicating the presence of core sealing defects. To assess the quality of mature virion production by different cell types, we used the human T lymphocyte cell line (Jurkat cells) and the human embryonic kidney cell line, 293T cells. To check the infectivity of virions produced by these types of cells we used single round infection assays of TZM-bl cells.

Results: Using the iFRET construct, we discovered that up to 4% of virions remain immature and out of the ones that complete maturation, only 10% have a sealed core (in 293T cells). The infectivity of virions produced by Jurkat cells, which HIV-1 naturally targets, was up to ten-fold higher than that of virions produced by 293T cells, possibly also due to a higher number of mature, closed core, infectious virions released by Jurkat cells. We determined that Jurkat cells do indeed produce up to 2.2 times more sealed core virions than 293T cells ($p<0.05$).

Conclusion: Our single virion imaging system based on FRET can be used to distinguish and quantify immature and open/closed core mature HIV-1 populations in different cell type settings. Jurkat cells produce a significantly higher number of sealed core virions compared to 293T cells. Our results suggest that cell line dependent factors may alter the core formation during virus maturation.

186 NEF UPREGULATES FASL EARLY WHILE MHCs ARE DOWNREGULATED LATE IN HIV-INFECTED CELLS

Rodrigo Matus-Nicodemos, Daniel Douek, Richard A. Koup
NIAID, Bethesda, MD, USA

Background: HIV-1 Nef is a multifunctional early expressed protein. It selectively downregulates MHC molecules to prevent recognition by HIV-specific CD8 T cells. Nef also upregulates Fas ligand which leads to apoptosis of CD4 T cells and CD8 T cells. The temporal dynamics of these functions throughout the HIV replicative cycle is not known. To determine when these functions occur we developed a replicative cycle reporter system and measured these functions in HIV-infected cells.

Methods: A GFP IRES NEF reporter construct was inserted into the Nef ORF of the NL4-3 (X4-tropic) and ADA-AD8 (R5-tropic) replication-competent molecular clones. A separate GFP reporter virus without Nef was also generated. For infection, PHA/anti-CD28-activated primary CD4 T cells were incubated with reporter virus for 3 hours, washed, and further incubated for 15, 24 and 48 hours. At the indicated time point we performed surface staining for HLA-A02 or HLA-B07, then intracellular staining for FasL and Gag p24. We also stained for the downregulation of CD4, T cell activation by CD69 expression, and cell viability by co-staining for Annexin V and Vivid. Our experimental control was primary CD4 T cells that went through the experiment without virus infection.

Results: At 15, 24, and 48 hours after infection we detected two HIV-infected cell populations: GFP+p24-, expressing only Nef, and GFP+p24+, expressing Nef and Gag. CD4 was partially downregulated in the GFP+p24- population and completely downregulated in the GFP+p24+ population. FasL upregulation was detected at 15hr in both populations and remained high throughout the replicative cycle. Downregulation of MHC molecules was only observed in the GFP+p24+ population at the 48hr time point were HIV-induced cell death was observed. HIV-induced cell death was partially blocked by the caspase inhibitor, Z-VAD-FMK. We observed a significant increase in MHC expression in the both populations at 15 and 24hr. Finally, we also observed a significant increase in MHC expression in cells that up-regulated CD69.

Conclusion: Our results show that FasL is upregulated early in HIV-infected cells by Nef while downregulation of MHC molecules occurs late. These data suggest that MHC molecules presenting virus peptides in HIV-infected cells could be expressed for most of the virus replicative cycle and recognized by CD8 T cells. Therefore, strategies targeting early Nef functions, such as FasL upregulation, in HIV-infected cells could be more detrimental to the virus than late Nef functions.

187 VISUALISATION OF THE HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 CDNA BY CLICK CHEMISTRY

Flore De Wit, **Frauke Christ**, Sambasivarao Pillalamarri, Akkaledevi Venkatesham, Arthur Van Aerschot, Zeger Debyser
Katholieke University Leuven, Leuven, Belgium

Background: One of the key steps in HIV-1 replication is the reverse transcription of viral RNA into a double-stranded copy DNA (cDNA). This cDNA is subsequently transported in the form of a pre-integration complex (PIC) to the nucleus where it is finally integrated into the host chromosome by the viral integrase (IN). Although much is known about the biochemistry and inhibition of reverse transcription, many questions remain about its timing and location within the cellular environment.

Methods: A recently developed single virus imaging technique enables us to study IN (IN-eGFP) in individual viral complexes during early stages of the replication cycle. Different parameters including the number of fluorescent viral complexes, their distance to the nuclear envelope and intensity can be determined from these experiments. Although we can now identify single viral complexes in infected cells, we are unable to identify whether they contain reverse transcribed DNA. For this purpose, we combined our existing assay with the labelling of viral DNA using click chemistry. After addition of ethynyl-functionalised nucleosides during infection, these molecules are incorporated into the viral DNA by RT. The ethynyl-functional group on the nucleosides allows covalent linkage with azide reactive fluorophores via a copper-catalyzed azide-alkyne cycloaddition. It was shown earlier that HIV cDNA can be visualized by incorporation of EdU. However, this technique has some limitations. First, there is a high off-target labelling due to the incorporation of the nucleoside analogues by the host mitochondrial DNA polymerase. Secondly, viral DNA in the nucleus can not be dicriminated due to the incorporation of the functionalized nucleoside by the host DNA polymerase. Therefore, the use is limited to non-diving cells such as monocyte-derived macrophages (MDM). To overcome these limitations we develop RT specific ethynyl-functionalised nucleosides that are not incorporated by the cellular DNA polymerases.
Results: With our novel nucleoside analogues we lowered the off-target labelling of the cellular DNA and reached up to 2% co-localization of the total number of IN-eGFP with the viral DNA staining in HeLaP4 cells and even 10% in MDM.
Conclusion: This technology will allows us to simultaneous detect viral cDNA, IN-eGFP and capsid during the course of infection for a precise kinetic analysis of reverse transcription, trafficking, uncoating and nuclear import.

188 HIV RT STRAND TRANSFER AND NONTEMPLATED BASE ADDITION ARE MECHANISTICALLY INDEPENDENT

Joanna Luczkowiak, Tania Matamoros, Luis Menéndez-Arias
Centro de Biología Molecular Severo Ochoa, Madrid, Spain

Background: Strand transfer (ST) events occur twice during HIV reverse transcription, the first during minus-strand DNA synthesis and the second, when the plus-strand DNA is polymerized. Both events rely on RNase H cleavage and template homology. Previous studies have shown that template switching is favored by short unpaired 3´-end tails in the DNA, suggesting that RT's nontemplated nucleotide addition (NTA) activity could promote ST. We used in vitro ST and NTA assays and a panel of HIV-1 RTs to determine whether increased ST associates with high NTA activity.
Methods: Tested enzymes were the wild-type (WT) HIV-1 BH10 RT and mutant L92P; and the WT HIV-1 ESP49 (group O) RT and ten mutants containing the connection subdomain substitutions K358R/A359G/S360A (3M) alone, or in combination with F61A, K65R/E478Q, L92P, L92P/D443N, L92P/E478Q, V148I, T355A/Q357M, D443N or E478Q. RTs were expressed and purified by ionic exchange followed by affinity chromatography. ST activity was assessed in vitro with three synthetic oligonucleotides, including a radiolabeled DNA primer, a RNA donor, and a partially homologous DNA acceptor. NTA activity was measured with 32P-labeled blunt-ended DNA/DNA template-primers (T/Ps).
Results: RTs containing RNase H-inactivating mutations (all those having D443N or E478Q) were devoid of ST activity, while mutants containing F61A or L92P had very low ST activity (<7.5%). RTs with the highest ST efficiencies were 3M_T355A/Q357M (34.9%), 3M_V148I (29.3%), 3M (28.1%), WT HIV-1 ESP49 (13.9%) and WT HIV-1 BH10 (8.6%). All RTs except those having L92P showed NTA activity, and their best substrate was dATP, followed by dGTP, dCTP and dTTP. The 3M_V148I RT had high ST activity but low NTA activity (kobs = 0.013 min-1). In contrast, WT HIV-1 BH10 RT incorporated dATP efficiently on blunt-ended T/Ps (kobs = 0.227 min-1), but had relatively low ST activity. Overall, we found no correlation between the ST and NTA activities of tested RTs (as determined with a Pearson r test).
Conclusion: Our results demonstrate that ST and NTA are mechanistically independent, meaning that for a specific RT, high NTA activity is not necessarily associated with increased template switching. These data are expected to be helpful to understand HIV variability at putative recombination sites, while providing further insight towards the characterization of ST as a distinct target for antiretroviral intervention.

189 UBP43 (USP18) ABROGATES INTERFERON AND SAMHD1-MEDIATED RESTRICTION OF HIV-1

Edmund Osei-Kuffour[1], Kerstin Schott[2], Philipp A. Lang[1], Karl S. Lang[3], Renate König[2], Dieter Häussinger[1], Carsten Münk[1]
[1]Heinrich Heine University Hospital, Düsseldorf, Germany, [2]Paul Ehrlich Institut, Langen, Germany, [3]University Hospital of Duisburg-Essen, Essen, Germany

Background: Host intrinsic innate immune system directs antiviral defenses and viral restriction that includes, production of soluble factors such as type I and III interferon (IFN) and activation of restriction factors including SAMHD1. Ubiquitin-like protease 43 (USP18), negatively regulate IFN I and III by abrogating their signaling. SAMHD1 strongly inhibits HIV-1 replication in myeloid cells, however, it is efficiently antagonized by the HIV-2/SIV VPX. SAMHD1's antiviral function in non-cycling cells is negatively regulated by phosphorylation at residue T592 by cyclin A2/CDKs. Intrigued by the recent model of USP18 enforced viral replication in murine macrophages (Honke et al. 2011), we asked whether human USP18 would be a factor influencing HIV-1 replication.
Methods: THP-1 macrophage-like cells were generated that express USP18 or active site mutants. USP18 and SAMHD1 knockout THP-1 cells were generated by CRISPR-CAS system. Undifferentiated and PMA-differentiated THP-1 cells were infected by HIV-1 and -2 (+/- *vpx*) luciferase reporter viruses. The infection was monitored by their luciferase activity and by qRT-PCR. Immunoblots analyzed the cellular expression of USP18, SAMHD1 and phospho-SAMHD1. The interaction of SAMHD1 with USP18, cyclin A, CKD1/2 and SKP2 was analyzed by pull-down assays and also visualized by confocal microscopy. The effect of USP18 on the cell cycle and dNTP pool was analyzed by flow cytometry and by biochemical assays respectively. HIV-1 mediated IFN induction was analyzed by qRT-PCR.
Results: PMA-differentiated THP-1 cells are resistant to HIV-1 infection due to unphosphorylated SAMHD1 expression. This restriction is ablated when USP18 is expressed. USP18 expression in differentiated THP-1 cells enhanced HIV-1 infection by more than 40-fold and HIV-2Δ*vpx* by over 7-fold. HIV-1 infectivity rose by more than 100-fold in SAMHD1 knockout cells expressing USP18. Knockout of USP18 abrogated the infection of HIV-1 by more than 20 folds. SAMHD1 bound to USP18 in a complex with cylin A and CDK1/2. Also, USP18 interacted with SKP2, retained cylin A and down regulated p21, which induced phosphorylated SAMHD1 in differentiated THP-1.USP18 cells. USP18 abrogated IFN induction in the THP-1 cells, which correlated with higher HIV-1 infectivity. These activities of USP18 were independent of its ISG15 isopeptidase activity.
Conclusion: This data provides evidence of direct involvement of USP18 in IFN and SAMHD1-mediated restriction of HIV-1.

190 VPR ENHANCES VIRAL GENE EXPRESSION FROM UNINTEGRATED DNA IN A DCAF1-DEPENDENT MANNER

Sarah B. Nodder, Caitlin Miller, Hisashi Akiyama, Chelsea R. Ettinger, Rahm Gummuluru
Boston University, Boston, MA, USA

Background: While integration of HIV-1 DNA is essential for establishment of productive infection, unintegrated HIV DNA (uDNA) forms have been observed in several cell types, including resting CD4+ T cells, macrophages and dendritic cells (DCs), and are reported to be transcriptionally active. Expression of viral proteins from uDNA might contribute to virus-induced cytopathicity and immune activation, thus influencing virus reservoir in vivo. In this study, we demonstrate that virion-associated Vpr is required for optimal viral gene expression from uDNA.
Methods: HeLa cells, PMA-treated THP-1 cells (THP1/PMA), primary macrophages, or DCs were infected with luciferase (in place of nef) expressing, VSV-G pseudotyped single cycle HIV-1 (incorporating wild type Vpr or W54R, Q65R, H71R and R90K-Vpr mutants) in the presence or absence of raltegravir (Ral) or with viruses containing a mutation in the catalytic domain of integrase (D116N). Alternatively, cells were infected with GFP-expressing single cycle HIV-2, SIVmac, and SIVsmm (±Vpr) in the presence or absence of Ral. Total viral DNA, extrachromosomal 2-LTR circles and integrated proviruses was measured by quantitative PCR. Extent of virus gene expression from uDNA was determined by quantifying luciferase expression in cell lysates, GFP expression by FACS, or p24gag expression by ELISA at variable times post infection.
Results: Robust luciferase expression from uDNA (infections in the presence or Ral or infection with D116N integrase mutant) was only observed in the presence of Vpr. Furthermore, expression from uDNA in cells infected with Vpr-

deficient viruses was rescued by delivery of Vpr in trans. Importantly, expression from uDNA is stably maintained over time in macrophages in a Vpr-dependent manner. Mutations in Vpr that ablate its association with the CuI4A-DCAF-DDB1 ubiquitin ligase (Q65R and H71R) or prevent Vpr-induced DNA damage response (R90K) reduced viral gene expression from uDNA. Furthermore, the ability of Vpr to enhance transcription from uDNA was conserved amongst Vpr alleles from SIVsmm/SIVmac/HIV-2 lentiviral lineage.

Conclusion: Together, our data suggests an evolutionarily conserved role for Vpr in enhancing expression from uDNA which may contribute to persistence of virus reservoir in vivo, even in the continued presence of HIV integrase inhibitors.

191LB A NOVEL MODE OF RNA BINDING ASSISTS APOBEC3H IN THE MOLECULAR ARMS RACE AGAINST HIV

Jennifer Bohn[1], Keyur Thummar[2], Ashley York[2], Alice Raymond[2], William C. Brown[1], Paul Bieniasz[2], Theodora Hatziioannou[2], Janet L. Smith[1]
[1]University of Michigan, Ann Arbor, MI, USA, [2]The Rockefeller University, New York, NY, USA

Background: Several members of the APOBEC3 family of cytidine deaminases cause lethal hypermutation of retroviruses and retroelements via deamination of newly reverse-transcribed single stranded DNA (ssDNA). Their ability to bind RNA is essential for virion infiltration and antiviral activity, yet the mechanisms of viral RNA recognition are unknown.

Methods: By screening naturally occurring, polymorphic, non-human primate APOBEC3H (A3H) variants for biological and crystallization properties, we obtained a 2.24-Å crystal structure of pig-tailed macaque A3H bound to RNA.

Results: We found that A3H forms a dimer around a short, A-form RNA duplex both in vitro and in virions, a property that allows for A3H to identify and bind to sequences in the viral genome for efficient virion incorporation. Despite the bound RNA, A3H has both potent cytidine deaminase activity and high affinity for the ssDNA target, suggesting that both DNA and RNA may bind to A3H simultaneously.

Conclusion: In addition to facilitating virion incorporation, we propose a mechanism by which A3H may selectively bind to A-form duplexes, such as an RNA-DNA heteroduplex, to facilitate delivery of short-lived ssDNA to the deaminase active site immediately following reverse transcription.

192 INFANT T/F HIV-1 FROM PERIPARTUM TRANSMISSION ARE RESISTANT TO MATERNAL PLASMA

Amit Kumar[1], Claire E. Smith[2], Elena E. Giorgi[3], Joshua A. Eudailey[1], David R. Martinez[1], Karina Yusim[3], Ayooluwa O. Douglas[1], Lisa Stamper[1], Genevieve Fouda[1], Erin McGuire[1], Celia C. Lebranche[2], David C. Montefiori[2], Feng Gao[2], Sallie Permar[1]
[1]Duke Human Vaccine Institute, Durham, NC, USA, [2]Duke University, Durham, NC, USA, [3]Los Alamos National Laboratory, Los Alamos, NM, USA

Background: Mother to child transmission of HIV-1 involves selective transmission of 1 or a few viral variants. These infant transmitted/founder viruses are of particular interest, as a maternal or infant vaccine must block this group of viruses. Yet, the role of maternal autologous virus-neutralizing antibodies in selecting for infant T/F viruses is not well understood.

Methods: Sixteen peripartum transmitting HIV-1 mothers and paired infant plasma samples were selected from the Women and Infants Transmission Study, an ART naïve cohort. Single genome amplification method was used to obtain HIV Env genes from mother and infant samples. Maternal and infant SGAs were sequenced and analyzed using phylogenetic tree and highlighter plots. Infant T/F viruses were identified in all 16 peripartum infected infants and were cloned and generated as pseudoviruses. Pseudoviruses for non-transmitted maternal variants were also generated by overlap PCR method. The neutralization sensitivity of maternal and infant T/F viruses was assessed against maternal and infant plasma, and a panel of broadly neutralizing antibodies (bNAbs). Signature sequence analysis was performed to identify amino acid motifs predictive of autologous virus neutralization sensitivity.

Results: 62% of infants were infected with 1 T/F, virus while 38% were infected with 2 or more T/F viruses. 85% of infant T/F viruses tested were neutralization resistant to paired maternal plasma but were at least partially sensitive to HIV-1 bNAbs such as VRC-01, whereas 14-70% of circulating maternal non-transmitted viruses were neutralization sensitive to autologous plasma neutralizing antibodies. Infant T/F were more resistant to paired maternal samples than non-transmitted maternal variants ($p = 0.012$). In contrast, tiered heterologous neutralization sensitivity phenotyping of infant T/F viruses demonstrated a range from tier 1a to tier 3, indicating that heterologous plasma neutralization sensitivity does not predict paired maternal plasma neutralization sensitivity of infant T/F viruses.

Conclusion: Majority (86%) of infant T/F viruses were neutralization resistant to paired maternal plasma, while non-transmitted maternal viruses were variably resistant to autologous plasma, suggesting that infant T/F viruses are overall more neutralization sensitivity than non-transmitted maternal variants. Therefore, enhancing maternal autologous virus neutralizing antibodies during pregnancy could be a viable strategy to further reduce vertical HIV-1 transmission.

193 ZIKA VIRUS AND HIV-1 INTERPLAY IN HUMAN IMMUNE CELLS

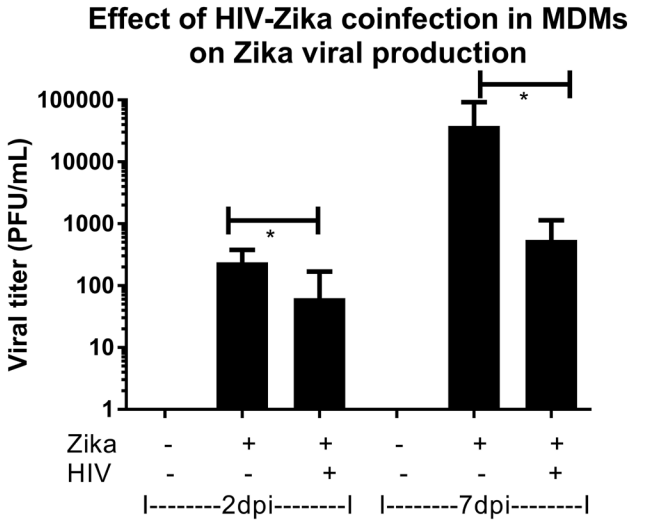
Joel Provost, Corinne Barat, Michel J. Tremblay
Laval University, Quebec City, QC, Canada

Background: Zika virus (ZKV) is an emerging pathogen that can lead to fetal abnormalities and death in utero. As cellular targets of ZKV in the blood are presently unknown, this project aims to gather information on this issue. Furthermore, as ZKV infections occur in regions endemic for HIV-1, the potential consequences of ZKV/HIV-1 coinfections must be explored.

Methods: Subpopulations of blood leukocytes were separated from blood of healthy donors using commercial kits and macrophages were differentiated from monocytes. ZKV was titrated using a standard plaque assay on VERO cells. HIV-1 infection was performed using a molecular clone expressing a GPI-anchored reporter (NL4-3 BALenv IRES HSA) allowing detection of infected cells by flow cytometry. Viral production was determined by a p24-specific ELISA. Percentage of ZKV-infected cells were determined by immunofluorescence. The role of autophagy on ZKV replication was evaluated by treating cells with a specific and potent inhibitor of autophagy (SPAUTIN-1). Target-specific siRNAs were used to identify potential cell surface receptors of ZKV attachment/entry.

Results: No replication of ZKV was observed in NK cells, CD4+ T lymphocytes, monocytes, and neutrophils. However, replication of ZKV could be observed following infection of MDMs with PL_Cal strain, which peaked at 7-9 days post-infection. Different strains of ZKV displayed different kinetics of replication. Coinfection between HIV-1 and ZKV in MDMs show that while HIV-1 replication is unaffected by coinfection with ZKV, ZKV replication is strongly inhibited by prior exposure of MDMs to HIV-1. Finally, results show that ZKV is highly sensitive to type I IFN released by MDMs exposed to HIV-1.

Conclusion: Among the primary human cells studied, only MDMs were susceptible to infection by ZKV. In our experimental model, production of ZKV by MDMs could be sustained over an extended period. This deserve more attention as infectious ZKV can be recovered from semen for as long as 6 months following infection. MDMs could thus harbor ZKV in peripheral tissues and allow its transmission long after acute infection is cleared. A better comprehension of the cellular targets of ZKV and its potential interactions with other pathogens will provide a stronger rational basis for the design of new drugs and therapies for ZKV-infected individuals and the relative importance of coinfections for the treatment of each condition.



194 STRUCTURAL AND RNA BINDING MODEL OF APOBEC3G N-TERMINAL DOMAIN FOR NEW DRUG DESIGNS

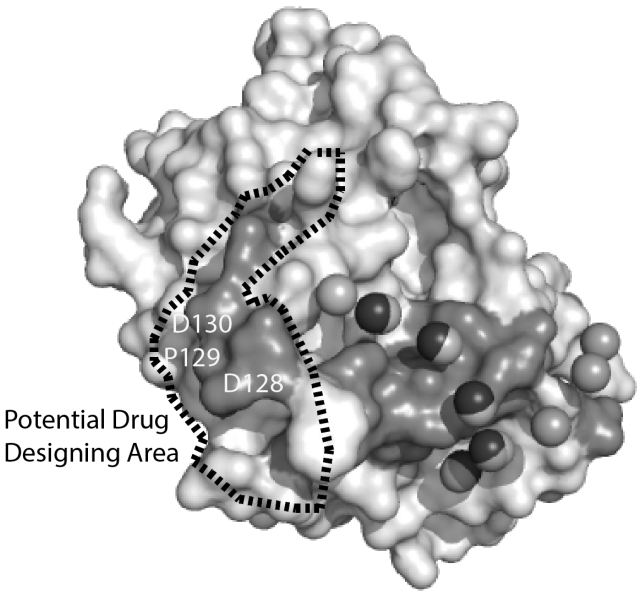
Hirofumi Fukuda[1], Anamaria D. Sarca[1], Kazuo Yamashita[2], Song Lin Li[2], Luca Sardo[3], Jessica Smith[4], Hirotaka Ebina[1], Kotaro Shirakawa[1], Kei Sato[1], Daron Standley[1], Yoshio Koyanagi[1], Taisuke Izumi[1], Akifumi Takaori-Kondo[1]
[1]Kyoto University, Kyoto, Japan, [2]Osaka University, Sukta, Osaka, Japan, [3]University of the Sciences, Philadelphia, PA, USA, [4]United States Army Medical Research Institute of Infectious Diseases, Frederick, MD, USA

Background: APOBEC3G (A3G) is a cellular protein that inhibits HIV infection. The interaction of the A3G N-terminal domain (NTD) with RNA is essential for its virion incorporation, but this interaction is not completely understood. A3G-NTD is also recognized by HIV-1 Viral infectivity factor (Vif) and A3G-Vif binding leads to A3G degradation. Designing inhibitors for A3G-Vif interactions is a novel drug development strategy; however, targeting A3G-Vif interaction could negatively affect A3G-RNA interaction that is required for A3G's antiviral activity. To develop a novel anti-HIV drug, it is necessary to understand A3G-RNA structural binding profile, we generated an in silico docking model to simulate the RNA-binding of A3G-NTD.

Methods: The solubilized A3G-NTD structure has been recently revealed, and its amino-acid homology is almost 80% of the wild-type A3G-NTD. RNA association ability may be diminished resulting in deficient virion incorporation. We constructed a model of wild-type A3G-NTD based on the solubilized A3G-NTD, then we simulated A3G-RNA docking patterns with single-stranded RNA. With this model, for each amino acid we calculated the RNA binding propensity (BP) by geometrical information and measured the contact frequency (CF) with RNA. We evaluated the accuracy of this structural model by introducing Alanine substitutions for amino acids, which were predicted to be directly involved in RNA binding based on their BP and CF.

Results: We confirmed the accuracy of our RNA docking model with several alanine-substituted mutants, which have been reported to associate with RNA or do not relate to RNA interaction. We have additionally determined three novel residues as RNA associated amino-acids by BP and CF calculated by the model, involved in RNA binding (N20, R55, and S95). Based on our model with residues, which have already been identified as binding sites for Vif (Three different RNA molecules with homology model in Figure), a wide area of the Vif interaction (colored dark grey on the model in Figure) is overlapped with the RNA binding surface.

Conclusion: Designing new drugs that can inhibit A3G-Vif interaction requires high specificity as not to affect RNA binding to the same N-terminal Domain. Our three-dimensional structural and dynamic RNA-binding model will provide new insights for this purpose. Based on this model, the area surrounding DPD motif enclosed with the dotted line in Figure might be a sole target for in silico drug designing to prohibit only A3G-Vif interaction.



195 SEMINAL CYTOKINE/CHEMOKINE NETWORK AND HIV TRANSMISSION IN MEN WHO HAVE SEX WITH MEN

Christophe Vanpouille[1], Andrea Lisco[2], Leonid Margolis[1], Laura Layman[3], Martin Hoenigl[3], **Sara Gianella**[3]
[1]National Institute of Child Health and Human Development, Bethesda, MD, USA, [2]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [3]University of California San Diego, La Jolla, CA, USA

Background: The cytokine/chemokine network in genital secretion reflects the functional status of immune cells in the genital tract, where the key events related to sexual transmission occur. Here, we describe differences in cytokine/chemokine levels in semen between HIV-infected men who did transmit and did not transmit HIV to their male sexual partner

Methods: Participants were men with primary HIV infection and their recent male sexual partners (HIV-positive or negative). HIV transmission among sero-concordant partnerships was defined as phylogenetic linkage (≤1.5% genetic distance in pol), and the HIV-positive partner with the earlier estimated date of infection (EDI) was considered the source. Among sero-discordant couples, the HIV-positive partner was considered the (potential) source. All analyses were restricted to source partners. Sources with sero-discordant partners were classified as non-transmitters (n=23), and those with sero-concordant phylogenetically-linked partners were considered transmitters (n=21). For each source partner (transmitter or non-transmitter), semen was collected and a panel of 34 cytokine/chemokines were measured by Luminex. Principal-components and clustering methods were used to select cytokine/chemokines with the strongest association with transmission, which were included in a multiple logistic regression model in the presence of the following covariates from the source partner: ART status, EDI, age, race/ethnicity, CD4+ and CD8+ cells, HIV RNA levels in blood and semen, presence of seminal HSV-2, EBV or CMV DNA.

Results: At the univariate level, participants classified as transmitters had significantly higher levels of IL-13, lower levels of M-CSF, INF-, IL-17, TGF- and Eotaxin compared to non-transmitters (Table 1). Individuals classified as transmitters were also more likely to be ART naïve, HIV-infected for >1 year, have lower CD4+ cells, detectable seminal HIV RNA and EBV DNA. In multivariable model, higher IL-13, lower Eotaxin and detectable HIV RNA in semen remained significantly associated with presence of HIV transmission within the observed partnership.

Conclusion: While detectable HIV RNA in semen was the strongest predictor of HIV transmission, altered cytokine/chemokine network might play a role in HIV transmission. For example, the observed association between higher IL-13 and HIV transmission is consistent with previous vaccine studies reporting stronger anti-HIV response when inhibitors of IL-13 were used and should be further investigated.

Table 1. Predictors of HIV transmission

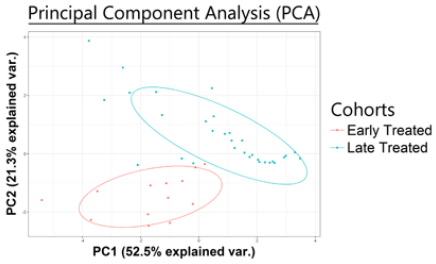
	Univariate Logistic Reg.		Multiple Logistic Reg.	
	OR	p-value	AOR	p-value
IL-13 (200 pg/ml)	7.68 (2.32-25.37)	**<0.01**	9.85 (2.36-41.14)	**<0.01**
M-CSF (log_{10} pg/ml)	0.11 (0.03-0.42)	**<0.01**		
INF-γ (100 pg/ml)	0.01 (0-0.28)	**<0.01**		
Presence of IL-17	0.10 (0.02-0.56)	**<0.01**		
TGF-β (log_{10} pg/ml)	0.53 (0.28-0.98)	**0.04**		
Eotaxin (log_{10} pg/ml)	0.35 (0.10-1.20)	0.10	0.21 (0.06-0.80)	**0.02**
ART naïve	7.31 (1.37-38.97)	**0.02**		
HIV-infected for >1 year	6.33 (1.59-25.22)	**<0.01**		
$CD4^+$ Cell Count (100 cells/μl)	0.72 (0.53-0.97)	**0.03**		
$CD8^+$ Cell Count (100 cells/ μl)	0.91 (0.77-1.06)	0.23		
Detectable HIV RNA in blood	7.05 (0.77-64.52)	0.08		
Detectable HIV RNA in semen	4.36 (1.11-17.13)	**0.03**	21.8 (1.2-403.3)	**0.04**
Presence of CMV DNA in semen	3.67 (0.93-14.39)	0.06		
Presence of EBV DNA in semen	4.75 (1.18-19.06)	**0.03**		
Presence of HSV 2 DNA in semen	1.90 (0.51-7.05)	0.33		
Age	0.98 (0.91-1.06)	0.63		
Race/Ethnicity				
White Non-Hispanic	*Reference*			
Hispanic	0.23 (0.04-1.32)	0.10		
Other (including multiracial)	1.15 (0.24-5.39)	0.86		

Legend: OR: Odds ratio, AOR: Adjusted Odds Ratio, IL-13: Interleukin-13, M-CSF: macrophage colony-stimulating factor, INF-γ: Interferon-γ, IL-17: Interleukin-17, ART: Antiretroviral therapy, CMV: Cytomegalovirus, EBV: Epstein Barr Virus, HSV 2: Herpes simplex virus type 2. Significant values are in bold.

196 BENEFICIAL IMPACT OF EARLY TREATMENT ON RESTRICTION FACTOR EXPRESSION PROFILE

Clarissa Van Hecke[1], Magdalena Sips[1], Eva Malatinkova[1], Ward De Spiegelaere[1], Karen Vervisch[1], Chris Verhofstede[1], Margaret Johnson[2], Sabine Kinloch-de Loes[2], Wim Trypsteen[1], Linos Vandekerckhove[1]
[1]Ghent University, Ghent, Belgium, [2]Royal Free Hospital, London, UK

Background: Host restriction factors become upregulated early on in HIV infection as part of the innate immune response to suppress viral infectivity and activity of some of them, e.g. SLFN11 has been linked to non-progressive phenotype of HIV infection. Early treated cohorts comprising of patients treated during acute seroconversion are considered a promising group to reach functional cure by acquisition of non-progressive phenotype. We evaluated HIV host restriction factors and cofactors in early and late treated cohorts and compared their profile with progressive and non-progressive HIV infection to further characterize their role in controlling infection.
Methods: The expression profile of seven HIV restriction factors and two cofactors (APOBEC3G, SAMHD1, BST2 (encoding TETHERIN), TRIM5, MX2, SLFN11, PAF1, PSIP1 (encoding LEDGF/p75) and NLRX1) was evaluated by qPCR in 104 HIV infected patients: patients treated during seroconversion (Early treated) or chronic infection (Late treated), long term non-progressors (LTNP), recent ART-naïve seroconverters, ART-naïve chronically infected patients and non-infected controls. Patients were recruited in Royal Free Hospital London and Ghent University Hospital. Principal Component Analysis (PCA) and Kruskal Wallis (KW) statistical analysis were performed.
Results: Both, univariate and PCA analysis demonstrated completely distinctive expression pattern of restriction factors in early- and late-treated cohorts. Restriction factor and cofactor levels of early treated HIV patients were significantly upregulated in comparison to late treated patients (APOBEC3G: $p<0.001$; NLRX1: $p<0.05$; SLFN11: $p<0.001$; BST2: $p<0.001$). Interestingly, further analysis demonstrated similarities between early treated patients and LTNP, such as upregulation of SLFN11 and BST2. Furthermore, a negative correlation found in LTNP between SLFN11 expression and integrated HIV DNA, total HIV DNA and viral load (Spearman r: -0.55; -0.42; -0.7) is indicative of the role of SLFN11 in restricting HIV reservoir.
Conclusion: Early treatment potentially prevents depletion of innate antiviral responses in comparison to late treated subjects. Elevated expression of SLFN11 and BST2 in LTNP and early treated subjects implies that these restriction factors actively contribute to the non-progressive phenotype in these cohorts.



197 HOST MICRORNA MIR-382-5P MAY EXERT A PROTECTIVE EFFECT ON HIV CONTROL

Marcial García[1], Ricardo Ramos[2], María Ángeles Navarrete[1], Carlos Cañada[1], Alfonso Cabello[3], Juan Carlos López-Bernaldo[4], Francisco Javier De La Hera[3], Vicente Estrada[5], Carlos Barros[6], Clara Restrepo[1], Manuel Fernández[3], Miguel Górgolas[3], José Miguel Benito[1], **Norma Rallón**[1]
[1]Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain, [2]Parque Científico de Madrid, Madrid, Spain, [3]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain, [4]University Hospital Gregorio Marañon, Madrid, Spain, [5]Hospital Universitario Clínico San Carlos, Madrid, Spain, [6]Hospital Universitario de Móstoles, Madrid, Spain

Background: It is known that host factors may regulate HIV replication. Host small regulatory RNAs (miRNAs) are among those potential host factors that can also regulate the expression of HIV RNA. However, evidence that specific miRNAs could be implicated in HIV pathogenesis is still elusive. In this study, we have evaluated the differential miRNA expression in different CD4 T-cell subsets in HIV infected individuals with different level of virological control.
Methods: We have compared expression of a panel of 20 validated and potential anti-HIV miRNAs from Elite controllers (EC), HIV+ patients with detectable HIV load and HIV negative controls in CD4 T-cells with particular phenotypes: resting memory (Trm) and peripheral follicular helper (pTfh) cells. Profiling of miRNAs was performed by Real Time PCR and analyzed with StatMiner software (Applied Biosystems) applying a false discovery rate (FDR) $\angle 0.05$. Ct values from endogenous controls (SNORD68, RNU6-2) were used to normalize all miRNA Ct values.
Results: We found higher expression of 16 miRNAs in pTfh cells compared to Trm cells but with no difference between studied groups. In contrast, only one miRNA (miR-382-5p) was upregulated in Trm cells compared to pTfh cells. Interestingly, the single miRNA (miR-382-5p) that was overexpressed in Trm cells was found only in uninfected subjects (adjusted p value=0.048) and in EC patients (adjusted p value=0.026) and not in chronically HIV infected patients with detectable HIV loads (adjusted p value=0.837).
Conclusion: Our data show that EC patients have significantly higher expression of miR-382-5p that is one of the miRNA suggested as implicated in the inhibiton of HIV-expression in primary resting CD4 T-cells through their interactions with the 3´end of HIV-RNA. This finding may reveal a new genetic host factor that confers protection from HIV replication and/or HIV latency.

198 NEF'S INFERIOR ABILITY TO DOWNREGULATE HLA-B CORRELATES WITH PLASMA VIRAL CONTROL

Francis Mwimanzi[1], Mako Toyoda[1], Macdonald Mahiti[1], Jaclyn Mann[2], Jeffrey N. Martin[3], David R. Bangsberg[4], Mark Brockman[5], Philip J. Goulder[6], Frank Kirchhoff[7], Zabrina Brumme[5], Thumbi Ndungú[2], Takamasa Ueno[1]
[1]Kumamoto University, Kumamoto, Japan, [2]KwaZulu-Natal Research Institute for TB and HIV, Durban, South Africa, [3]University of California San Francisco, San Francisco, CA, USA, [4]Oregon Health and Sciences University, Portland, OR, USA, [5]Simon Fraser University, Burnaby, BC, Canada, [6]University of Oxford, Oxford, UK, [7]Ulm University Medical Center, Ulm, Germany

Background: Patient-derived HIV-1 subtype B Nef clones downregulate HLA-A more efficiently than HLA-B. However, it remains unknown whether this property is common to Nef proteins across primate lentiviruses, and how antiviral immune responses may be affected.
Methods: We examined 263 Nef clones from diverse primate lentiviruses including different pandemic HIV-1 group M subtypes for their ability to downregulate MHC-A and MHC-B from the cell surface
Results: Though lentiviral Nef proteins differed markedly in their absolute MHC-A and MHC-B downregulation abilities, all lentiviral Nef lineages downregulated MHC-A on average 11-32% more efficiently than MHC-B. Nef genotype/phenotype analyses in a cohort of HIV-1 subtype C-infected patients (N=168), together with site-directed mutagenesis, revealed Nef position 9 as a subtype-specific determinant of differential HLA-A versus HLA-B downregulation activity. Nef clones harboring non-consensus variants at codon 9 downregulated HLA-B (though not HLA-A) significantly better than those harboring consensus at this site, resulting in reduced recognition of infected target cells by HIV-1-specific CD8+ effector cells in vitro. Among persons expressing protective HLA class I alleles, carriage of Nef codon 9 variants was also associated with reduced ex vivo HIV-specific T-cell responses and higher plasma viral loads.
Conclusion: Our results demonstrate that Nef's inferior ability to downregulate MHC-B compared to MHC-A is conserved across primate lentiviruses, and suggest that this property influences antiviral cellular immune responses and viral control in HIV-infected individuals.

199 MODULATION OF HIV RESTRICTION FACTORS BY BLOCKING CCL2/CCR2 IN VITRO AND IN VIVO

Daniela Angela Covino[1], Maria Clementina Galluzzo[1], Jing Lu[2], Cristina Purificato[1], Laura Catapano[1], Matteo Pellegrini[2], Maria Cristina Gauzzi[1], Stefano Vella[1], Eric Lefebvre[3], Mauro Andreotti[1], Laura Fantuzzi[1]
[1]Istituto Superiore di Sanità, Rome, Italy, [2]University of California Los Angeles, Los Angeles, CA, USA, [3]Allergan, Plc, South San Francisco, CA, USA

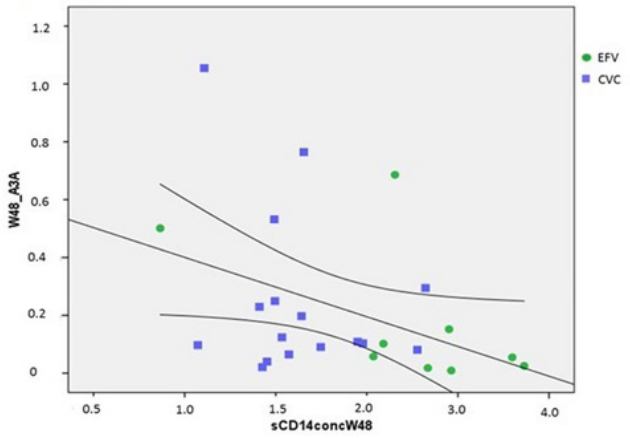
Background: Residual viremia and low-grade persistent inflammation in cART-treated subjects are nowadays considered the main challenges to achieve a cure. The CCL2/CCR2 axis plays key roles in chronic inflammation in these patients. We found that CCL2 blocking by specific antibodies (Ab) in monocyte-derived macrophages (MDMs) restricts HIV replication by inhibiting viral DNA accumulation independently of SAMHD1. The aim of this study was to identify cellular factors modulated by CCL2/CCR2 blocking in vitro and in vivo and potentially involved in the restriction of HIV replication.
Methods: Total RNA, extracted from uninfected and in vitro HIV-infected MDMs exposed to anti-CCL2 or control Ab, was subjected to poly (A) selection, reverse transcription, generation of cDNA libraries and sequencing on an Illumina Hiseq 2500 platform. Genes with logFC ≥ 1 (upregulated) or ≤ -1

(downregulated) and adjusted p-value <0.1 were classified as significantly differentially expressed. The differential expression profile of some genes was confirmed by qPCR and western blot. Whole cell extracts were obtained from PBMCs of 33 Study 202 (NCT01338883) HIV+ participants [n=17 from the CCR5/CCR2 antagonist cenicriviroc (CVC) arm; n=16 from the efavirenz (EFV) control arm] were used for western blot analysis of selected factors. Statistical analysis was done using the Mann–Whitney U or Wilcoxon signed-rank tests for unpaired or paired data.

Results: CCL2 blocking resulted in the differential expression of 1557 and 117 genes at 4 and 20 h, respectively, in uninfected MDMs, and of 79 and 251 genes at 1 and 4 days in HIV-infected MDMs. Among the up modulated genes annotated in categories related to innate immunity, we focused on the restriction factors Mx2 and APOBEC3A (A3A), whose mechanisms of action may account for the CCL2 blocking-mediated postentry inhibition of HIV replication. The upregulation of both genes by CCL2 blocking was confirmed by qPCR, while an increase of protein level was observed only for A3A in both uninfected and HIV-infected MDMs. In Study 202, A3A levels were increased in CVC (p=0.0004) but not EFV arm at week 48 of treatment, and inversely correlated with soluble CD14 levels (n=33; r=-0.4; p=0.048; Figure 1), which were increased in EFV arm (p=0.04) and slightly reduced in CVC arm.

Conclusion: Overall, these data suggest that the CCL2/CCR2 axis may represent a new therapeutic target to strengthen host innate immunity and reduce inflammation thus limiting HIV infection. RF-2011-02347224.

Figure.1 Correlation between A3A levels and soluble CD14 levels at Week 48 in Study 202 participants (n = 25; r = -0.4; p = 0.048)



200 TRIM21 –CRM-1 INTERACTION: A NOVAL MECHANISM FOR HIV RESTRICTION IN MURINE CELLS

Roqaya Sabbah-Abudaabes[1], Moshe Kotler[1], Richard Sutton[2], **Hila Elinav**[1]
[1]Hebrew University of Jerusalem, Jerusalem, Israel, [2]Yale University, New Haven, CT, USA

Background: Mice have been the favored animal model for researches, but unfortunately many obstacles humper HIV replication in mouse. One of these obstacles is over-splicing of viral RNA (vRNA) in murine cells, which leads to a reduction in RNA transportation that is mediated by Chromosome Region Maintenance-1 (CRM-1) protein. CRM-1 is responsible for transmitting the non-spliced, or partially spliced, vRNA molecules, which are essential for producing infectious virus, to the cytoplasm. Our previous study showed that mouse CRM-1(mCRM-1) is distinct from the human protein (hCRM-1) in 21 amino acids. Three of these amino acids (411, 412, 414) are critical for the export of viral mRNA to the cytoplasm. Interestingly, these amino acids are not the binding site for the viral Rev protein that is the adaptor of the viral RNA to CRM-1. Thus, we hypothesized that another protein binds to this site (411-414), resulting in mCRM-1 inhibition, or hCRM-1 activation.Our goal was to identify proteins that bind differently to CRM1-vRNA complex in mouse and human cells, and to reveal the functional distinctions between the two CRM-1 variants

Methods: Gene encoding hCRM-1, mCRM-1 and mutant (mutCRM-1)-which is identical to hCRM-1 except for amino acids in 411, 412 and 414 positions-were cloned into HA-Tag plasmid. We transfected these plasmids to human and mouse cell lines (HEK 293T and B78CyT1 respectively) and co-transfected the plasmids with HIV lentivector, in both cell lines as well. We used Co-Immunoprecipitation to elucidate the proteins binding to CRM-1, and identified then by Mass Spectrometry

Results: We obtained 1680 and 993 proteins interacting with different CRM-1 variants in human cells and murine cells, respectively. Among them, Trim21 exhibited higher affinity for both mCRM-1 and mutCRM-1 (5 and 4 times higher, respectively), in comparison to huCRM-1. This result suggests that Trim21 inhibits the mCRM-1. Sept7, demonstrated similar properties, with lower affinity (2.5 times to mCRM-1 and 1.6 times to mutCRM-1). Additionally, we identified 20 proteins with enhanced association to CRM-1 only in murine cells and only in the presence of HIV.

Conclusion: We identified 2 proteins that are potential inhibitors for mCRM-1, but their role in HIV replication should be further investigated. Fully understanding of their functions will significantly promote the use of mice models in studying HIV reproduction and pathogenesis, and development of new effective treatments.

201 NEF ANTAGONIZES TIM-MEDIATED INHIBITION OF HIV-1 RELEASE: ROLE OF SERINCs

Minghua Li[1], Abdul A. Waheed[2], Eric O. Freed[2], **Shan-Lu Liu**[1]
[1]The Ohio State University, Columbus, OH, USA, [2]National Cancer Institute, Frederick, MD, USA

Background: The T cell immunoglobulin and mucin domain (TIM) proteins inhibit release of HIV-1 and other enveloped viruses by interacting with cell- and virion-associated phosphatidylserine (PS).

Methods: We examined HIV-1 release that is inhibited by TIM proteins in the presence or absence of Nef and/or SERINCs.

Results: We show that the Nef proteins of HIV-1 and other lentiviruses antagonize TIM-mediated restriction. TIM-1 more potently inhibits the release of Nef-deficient relative to Nef-expressing HIV-1, and ectopic expression of Nef, or knockdown of TIM proteins, relieves restriction. HIV-1 Nef does not downregulate TIM-1 expression, but promotes its internalization from the plasma membrane. Intriguingly, depletion of SERINC proteins attenuates TIM-mediated restriction of HIV-1 release, especially that of Nef-deficient viruses, indicating that Nef counteracts TIM-1, at leas in part, through SERINCs. Consistent with this model, MLV glycoGag and EIAV S2 proteins also counteract TIM-mediated inhibition of HIV-1 release.

Conclusion: Our work reveals a new role for Nef in antagonizing TIM-1, and highlights a complex interplay between Nef and and HIV-1 restriction by TIMs and SERINCs.

202 IMPACT OF NATURAL HIV-1 NEF POLYMORPHISMS ON SERINC5 ANTAGONISM

Steven W. Jin[1], Nirmin Alsahafi[2], Xiao Mei T. Kuang[1], Philip Mwimanzi[1], Heinrich Gottlinger[3], Zabrina Brumme[1], Andrés Finzi[2], Mark Brockman[1]
[1]Simon Fraser University, Burnaby, BC, Canada, [2]Centre de Research du Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada, [3]University of Massachusetts, Worcester, MA, USA

Background: Nef enhances HIV-1 infectivity by downregulating host restriction factor SERINC5 from the cell surface. Mutations at several highly-conserved Nef residues impair SERINC5 antagonism, but few studies have evaluated the impact of natural sequence variation on this function. Furthermore, no reports have examined this function for Nef alleles isolated from HIV-1 elite controllers (EC) who display low plasma viral load in the absence of therapy.

Methods: Nef alleles from 45 EC and 46 chronic progressors (CP) were isolated from plasma viral RNA. SERINC5 expression on the cell surface was assessed by flow cytometry following co-transfection of CEM T cells with Nef clones and SERINC5-iHA; and results were normalized to wild type Nef (SF2 strain). Natural polymorphisms associated with function were identified by statistical analyses of linked Nef genotype-phenotype datasets and confirmed by site-directed mutagenesis. Infectivity was measured by exposing TZM-bl reporter cells to HIV-1 particles (5ng p24); replication capacity was assessed using Jurkat reporter T cells.

Results: EC Nef clones displayed lower ability to downregulate SERINC5 (median 80 [IQR 38-95]% activity vs WT) compared to CP clones (96 [IQR 75-100]%) (p=0.0005). 18 Nef polymorphisms were associated with differential SERINC5 antagonism, of which eight were confirmed by mutagenesis. Among the eight validated Nef polymorphisms, two that displayed the greatest selective impairment of SERINC5 activity were both HLA class I escape

mutations: K94E (51% activity), driven by HLA-B*08; and H116N (80% activity), driven by HLA-B*57. Furthermore, NL4-3 viruses encoding Nef K94E and/or H116N displayed reduced infectivity and lower replication capacity, compared to WT virus (both p<0.0001).
Conclusion: Our results demonstrate that Nef's ability to counteract SERINC5 is modulated by natural sequence variation. Polymorphisms in two highly immunogenic CTL epitopes (restricted by B*08 and B*57) selectively impaired this Nef function, illustrating constraints on HIV-1 adaption and identifying potential targets for therapeutics that disrupt Nef/SERINC5 interactions.

203 HSV-1/HSV-2 INFECTION IN MACAQUES AND REACTIVATION AFTER EXPOSURE TO HETEROLOGOUS HSV

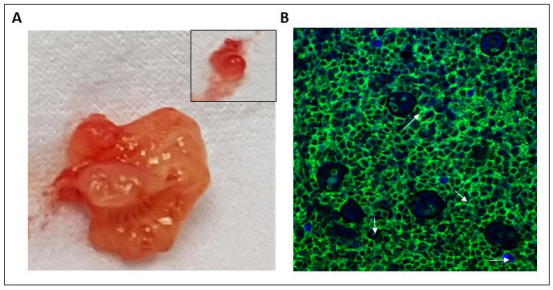
Priya Srinivasan[1], Jining Zhang[1], Clare Burn[2], Tyana Singletary[3], Dawn Little[4], Lara Pereira[1], Pedro Mesquita[2], Betsy Herold[2], James M. Smith[1]
[1]CDC, Atlanta, GA, USA, [2]Albert Einstein College of Medicine, Bronx, NY, USA, [3]Anyar, Inc, Fort Walton Beach, CA, USA, [4]LifeSource Biomedical, LLC, Mountain View, CA, USA

Background: HIV and herpes simplex virus 1 and 2 (HSV-1, HSV-2) are common coinfections and infection with one can increase the risk of infection with the other. The risk of HIV acquisition has been reported to be increased up to five times in HSV- infected individuals. It is important to develop a relevant animal model to evaluate the efficacy of preexposure prophylaxis (PrEP) modalities in the context of HSV/HIV coinfection. We have developed a macaque model for vaginal HSV infection using HSV-1 Bx 1.1, a primary isolate from Bronx, New York, and HSV-2 SD90, a low-passage clinical isolate from South Africa.
Methods: Four SHIV162p3-positive female rhesus macaques received 30 mg of depot medroxyprogesterone acetate every six weeks, starting three weeks prior to the first HSV exposure. A crossover study was conducted in two phases. In phase 1 two animals received HSV-1 and two received HSV-2 (10^8-10^9 PFU) once weekly intravaginally for four weeks followed by an eleven-week rest period. In phase 2 the groups were switched and the same schedule was followed with the addition of cytobrush sampling of the vaginal wall just prior to each inoculation. We monitored for vaginal HSV shedding (strain specific RT-PCR, gB region) throughout the study. Flow cytometry was used to analyze changes in mucosal T cells.
Results: HSV shedding was detected in all phase 1 macaques one week post challenge, with one HSV-1 animal positive at two weeks and one HSV-2 animal positive at three weeks post challenge. After the crossover, the HSV-2 infected animals from phase 1 showed a stronger and more consistent reactivation of HSV-2 after infection with HSV-1 than the reactivation of HSV-1 in the other group, with HSV-2 shedding detectable starting two days after the first HSV-1 inoculation and continuing for ten days after the last HSV-1 exposure. Mucosal CD4+ and CD8+ T cells following HSV infection expressed high levels of CD69 consistent with what is observed in humans.
Conclusion: Successful infection of macaques with primary clinical isolates of HSV-1 and HSV-2 results in an infection that can be reactivated upon exposure to heterologous HSV strains. This model can help us better understand the mechanisms behind the increased risk and will be used to assess the effect of HSV infection on HIV PrEP efficacy and to also identify antiviral drugs that can prevent both HIV/HSV acquisition.

204 ASSESSING BIOLOGIC RISK FOR HIV TRANSMISSION IN TRANSGENDER WOMEN

Alexandra Schuetz[1], Carlo Sacdalan[2], Nisakorn Ratnaratorn[2], Yuwadee Phuang-Ngern[3], Eugène Kroon[2], Rungsun Rerknimitr[4], Suthat Chottanapund[2], Denise C. Hsu[1], Tanyaporn Wansom[1], Nelson L. Michael[5], Merlin L. Robb[6], Robert J. O'Connell[1], Jintanat Ananworanich[6], **Sandhya Vasan**[1]
[1]US Military HIV Research Program in Thailand, Bangkok, Thailand, [2]Thai Red Cross AIDS Research Center, Bangkok, Thailand, [3]Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, [4]Chulalongkorn University, Bangkok, Thailand, [5]US Military HIV Research Program, Silver Spring, MD, USA, [6]US Military HIV Research Program, Bethesda, MD, USA

Background: High HIV infection rates in transgender women (TGW) are largely attributed to increased behavioral risk factors. However, effects of exogenous hormones on the immune system and injectable fillers or sex reassignment surgery (SRS) on immune activation may alter HIV risk.
Methods: A cross-sectional study of HIV negative volunteers including 10 MSM, 10 natal or cis-women (CW) and 8 TGW post SRS was conducted. Peripheral blood mononuclear cells (PBMC) and mucosal mononuclear cells (MMC) isolated from sigmoid biopsies (TGW, MSM, CW), and cervical (CW) and neovaginal (TGW) swabs were analyzed. Lymph node (LN) biopsies underwent immunohistochemical staining.
Results: Median lifetime sexual partners was higher in TGW (53) vs. CW (3, p=0.006) and MSM (25, p=NS). Among TGW, mean age of initial gender dysphoria was 7yrs, cross dressing 13yrs, hormone initiation 14yrs, and SRS 24yrs. Median duration of hormone use in TGW was 7.6yrs, with 5/8 using estrogen/progesterone, and 3/8 estrogen only. Median time post SRS was 1.3yrs, all by penile inversion, with 7/8 still using dilators post SRS. All TGW reported anal sex; 7/8 reported neovaginal sex. No difference in frequency of CD4+ or CD8+ T cells in PBMC and sigmoid MMC among groups was found. Frequency of neovaginal CD4+ T cells was decreased (1.8%) and CD8+ T cells increased (77.7%) vs. sigmoid and cervical CD4+ (54.4% and 48.3%), and CD8+ (33.6% and 30.2%) T cells (p<0.001, all). Neovaginal CD4+CCR5+ T cell frequency was lower in than cervical MMC (1.2% vs 35%, p=0.02), but comparable to sigmoid MMC (31.1%, p=NS). MFI of CD4+CCR5+ T cells was higher in neovaginal MMC (1491) vs. sigmoid MMC (761, p=0.04), but similar to cervical MMC (578, p=NS). Increased activated CD4+ T cells (HLA-DR+/CD38+), were seen in cervical MMC (2.3%) vs. sigmoid (1.1%) and neovaginal MMC (1.0%, p=0.02 and p=0.05, respectively). Filler use was higher in TGW (63%) than MSM (10%) or CW (0%). One TGW using hip fillers had multiple inguinal siliconomas, corresponding with high frequency of peripheral Ki67+CD4+ expression (0.4% vs median 0.1% in TGW) and Ki67+CD4+ cells in her inguinal LN.
Conclusion: CD4/CD8 T cell composition of neovaginal MMC differs from sigmoid and cervical MMC. There was no increase in frequency of neovaginal activated CD4+ or CD4+CCR5+ T cells. Higher use of fillers in TGW may contribute to systemic immune activation, although studies are ongoing. Characterization of biologic HIV risk factors specific to TGW may inform additional prevention strategies.



A. Inguinal siliconomas in TGW with silicone hip fillers (gross pathology)
B. Activated Ki-67+ (blue) CD4+ (green) cells (indicated by white arrows) in adjacent inguinal lymph node in the same TGW (60x)

205 RACIAL DIFFERENCES IN A4B7 EXPRESSION OF THE CCR6+ SUBSET OF CD4+ T CELLS

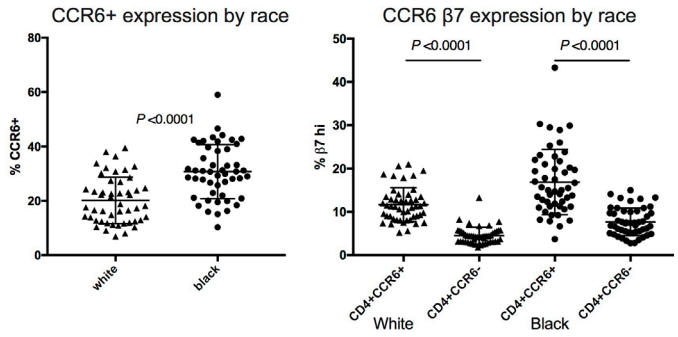
Alyssa R. Martin[1], Aida Sivro[2], Zoe Packman[3], Livia R. Goes[1], Lyle McKinnon[2], Jacquie Astemborski[3], Gregory D. Kirk[3], Shruti H. Mehta[3], Claudia Cicala[1], James Arthos[1], Andrew D. Redd[1], Anthony S. Fauci[1], Thomas C. Quinn[1]
[1]NIH, Bethesda, MD, USA, [2]CAPRISA, Durban, South Africa, [3]Johns Hopkins University, Baltimore, MD, USA

Background: The α4β7 heterodimer is important for CD4+ T cell trafficking to the gut. Cells that express high levels of α4β7, including the CCR6 expressing Th17 subset of CD4+ T cells, are highly susceptible to HIV infection. Previous research found that black men who have sex with men (MSM) have higher levels of CD4+ β7hi expressing cells than white MSM, suggesting that racial differences in α4β7 expression may be related to increased risk of HIV acquisition. This difference in α4β7 expression has not been studied in people who inject drugs (PWID), in men and women of multiple racial groups, or in terms of differences in CD4+ T cell subset expression of α4β7.
Methods: PBMC samples from HIV seronegative PWID were stained and analyzed by flow cytometry for expression of β7 integrin (as a proxy of α4β7 heterodimer expression), CCR6 (to identify Th17 cells), and activation markers. 100 subjects (25 white males, 25 black males, 25 white females, 25 black females) were included, with 10 replicates from different visits to assess stability of β7 expression over time. Matched data were compared using the Wilcoxon matched-pairs signed-ranks test. The Mann-Whitney U test was used to compare racial differences in β7 expressing cells. Covariate associations were

assessed with multivariable linear regression on log-transformed CD4+β7hi expression.

Results: All patients had a history of injecting drugs with 39% actively using injection drugs at the time of sample collection. CD4+ T cell expression of β7 integrin was within range of previously described values (median = 7.8%, IQR = 6.1-11.9%). CD4+β7hi cell levels were stable over a one year period in 10 individuals (p = 1.00). No sex difference in β7 expression was observed in multivariate analysis. Black PWID had a higher frequency of CD4+β7hi cells than white PWID (median = 10.9% vs. 6.7%, respectively; p < 0.0001). Black PWID also had higher proportions of CD4+CCR6+ cells than white PWID (median = 29.6% vs. 18.5% of total CD4+; p < 0.0001). CD4+CCR6+ cells were more likely to be β7hi than CD4+CCR6- cells (median= 12.6% vs. 5.4%; p < 0.0001) and CD4+CCR6+β7hi cells were highest in black PWID.

Conclusion: Black PWID have significantly higher levels of α4β7 expression compared to white PWID similar to previous findings in MSM. Our results further indicate that this difference is associated with higher proportions of β7hi expressing CCR6+ Th17 cells among black PWID, which may contribute to increased risk of HIV acquisition in black compared to white populations.



206 5′ UTR SNP RS111686073 MODIFIES EXPRESSION OF TAPASIN IN BLACKS

Victoria E. Walker-Sperling[1], Veron Ramsuran[2], Vivek Naranbhai[3], Maureen Martin[1], Hongchuan Li[1], Stephen K. Anderson[1], Louis-Marie Yindom[4], Sarah Rowland-Jones[4], Krista Dong[3], Thumbi Ndungú[5], Bruce D. Walker[3], Mary Carrington[1]

[1]National Cancer Institute, Frederick, MD, USA, [2]CAPRISA, Durban, South Africa, [3]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [4]University of Oxford, Oxford, UK, [5]University of KwaZulu-Natal, Durban, South Africa

Background: Tapasin (hereafter TAPBP) is a transmembrane glycoprotein mediating the binding of TAP and MHC-I within the peptide loading complex in the endoplasmic reticulum, the interaction of which is important for optimal peptide loading. Absence of TAPBP in mice is known to affect MHC-I expression and CD8+ T cell development, and viruses such as cytomegalovirus are known to inhibit TAPBP gene transcription to impair antigen presentation in infected cells. Due to the importance of TAPBP in antigen presentation and T cell development, we hypothesized that expression of TAPBP would also affect HIV pathogenesis, and the genetic markers of expression could potentially serve as indicators for risk in the context of HIV outcome. Thus, we decided to examine the TAPBP gene to identify any single nucleotide polymorphisms (SNPs) that affected expression and ascertain the underlying mechanisms.

Methods: After scanning TAPBP for common SNPs, rs111686073 (G/C) was identified as a variant found only in blacks that significantly correlated with expression via qPCR in two South African cohorts. To verify the effect on expression, constructs of different lengths were generated from the 5′ UTR of TAPBP and examined with luciferase assays in HeLa cells. Electrophoretic mobility shift assays were performed to determine if the transcription factors AP-2a or Sp1, predicted to bind by Alibaba2, mediated the change in expression.

Results: The SNP rs111686073, located in the 5′ UTR, was found to cause significant changes in mRNA levels in two separate black cohorts (p = 0.002, 0.004; Figure 1A). Luciferase assays confirmed that the SNP altered expression with the G variant conferring higher expression than the C variant (p = 0.0004; Figure 1B). The SNP was found to be a binding site for the transcription factor AP-2a, which appears to increase expression (Figure 1C).

Conclusion: The SNP rs111686073 is significantly associated with TAPBP expression, and the G variant results in increased expression over the C variant in luciferase assays, although AP-2a binds both. EMSA analysis indicates that the binding affinity of AP-2a likely mediates the observed effect on TAPBP expression. We hypothesize that the lowered expression of TAPBP may alter TAPBP-dependent HLA-B expression and antigen presentation and thus affects CD8+ T cell development. These effects may be important to keep in mind for vaccine studies and further understanding of HIV pathogenesis.

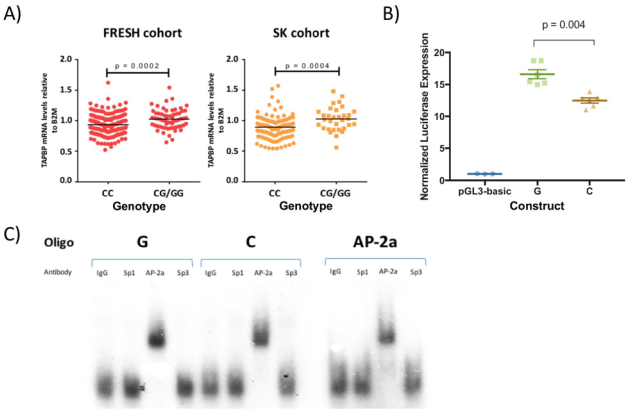


Figure 1. rs111686073 variants affect TAPBP expression. A) Two black cohorts show evidence of the G variant causing higher TAPBP expression via qPCR. B) Luciferase data normalized to the pGL3-basic vector with two constructs with the 5′ UTR varying only at the SNP. C) EMSA with HeLa nuclear extract binding to oligomer probes with the SNP and predicted binding sites included and control AP-2a binding site oligomer.

207 CELL RECRUITMENT EVENTS DURING THE MENSTRUAL CYCLE ASSOCIATE WITH SHIV SUSCEPTIBILITY

Alison S. Kohlmeier, Ivana Massud, Susan Ruone, Mian-er Cong, James Mitchell, Frank Deyounks, Gerardo Garcia-Lerma

CDC, Atlanta, GA, USA

Background: The luteal phase of the menstrual cycle represent a time point of increased susceptibility to sexually transmitted infections (STIs) including HIV. During the luteal phase, proinflammatory cytokines produced from the female reproductive tract (FRT) promote leukocyte trafficking from the circulation to drive local tissue remodeling and menstruation. We performed a longitudinal immune characterization from PBMC of pigtail macaques to identify FRT recruitment events and understand when SHIV infection is more likely to occur.

Methods: Blood PBMC was collected from pigtail macaques (n=6) undergoing weekly vaginal challenges with 50 TCID50 doses of SHIV162p3 (SHIV) during the course of 9 weeks (2 menstrual cycles). NK, B and T cells, monocytes, and professional antigen presenting cells were measured for population frequency of the viable leukocyte pool using flow cytometry. Total CD4 and CD8 T cells were similarly evaluated for CCR5 expression. Plasma samples collected weekly were analyzed for progesterone levels using an enzyme immunoassay (EIA). SHIV infection status was monitored by serology and RT-PCR.

Results: Consistent with the known increase of NK cells in the FRT during the luteal phase of the menstrual cycle, elevated progesterone levels from typical uninfected cycling animals significantly associated with a reduced frequency of NK cell populations (p=0.005); likely reflecting FRT recruitment. Unexpectedly, the reduced NK population was associated with decreased T cell population frequency (p=0.03) and increased CCR5 expression frequency on CD4 T cells (p=0.09). As CCR5 is a chemokine receptor important for T cell trafficking into sites of inflammation and a coreceptor of HIV, we notably found that in seroconverted animals, increased CCR5 CD4 T cells and decreased CD3 populations were detected at the estimated time of infection. At the estimated time of infection, 4 out of 4 animals exhibited below average CD3 frequency and above average CCR5 expression on CD4 T cells, and 3 out of 4 animals exhibited below average NK frequency.

Conclusion: We found that changes in the frequency of circulating NK and T cell populations, likely correlating with FRT recruitment during the luteal phase of the menstrual cycle, also associated SHIV susceptibility. These data suggest that evaluating circulating leukocyte measurements may refine our understanding of luteal phase susceptibility and provide a useful biomarker to study HIV infection from vaginal exposure.

208 DETERMINANTS OF SUBOPTIMAL IMMUNOLOGICAL RESPONSE AFTER ART INITIATION IN ACUTE HIV

Ryan C. Handoko[1], Donn Colby[2], Eugène Kroon[2], Mark de Souza[2], Suteeraporn Pinyakorn[3], Peeriya Prueksakaew[2], Jennifer Chiarella[1], Shelly J. Krebs[3], Irini Sereti[4], Victor Valcour[5], Nelson L. Michael[3], Nittaya Phanuphak[2], Jintanat Ananworanich[3], Serena S. Spudich[1]

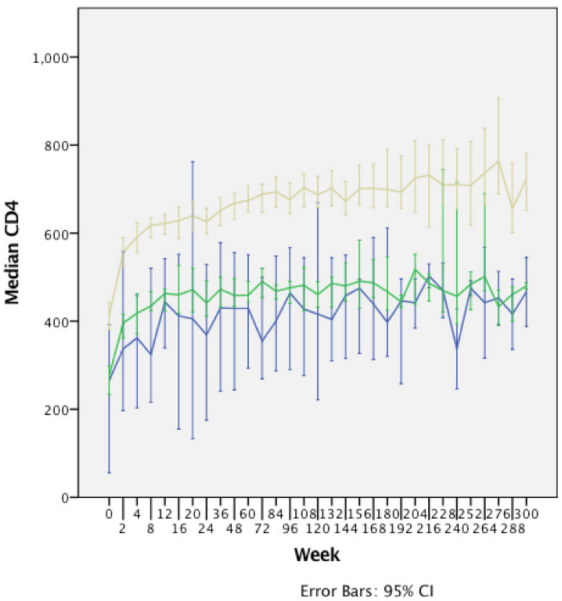
[1]Yale University, New Haven, CT, USA, [2]SEARCH, Bangkok, Thailand, [3]US Military HIV Research Program, Silver Spring, MD, USA, [4]NIAID, Bethesda, MD, USA, [5]University of California San Francisco, San Francisco, CA, USA

Background: Up to 30% of antiretroviral therapy (ART) treated individuals with suppressed chronic HIV infection fail to recover CD4+ T cell counts to a normal level (>500 cells/μL). We investigated if suboptimal immunological response (SR) also occurs when ART is started during acute HIV infection (AHI), and identified factors associated with SR.

Methods: Thai AHI participants (n=289) underwent blood and optional cerebrospinal fluid (CSF; n=79) sampling followed by immediate ART. Those with ≥48 weeks of documented HIV-RNA <50 copies/mL were stratified by latest CD4+ T cell count to suboptimal response (SR; CD4<350 cells/μL), intermediate response (IR; 350≤CD4<500), and complete response (CR; CD4≥500). Clinical and laboratory parameters were assessed at baseline and latest study visit (median 144 weeks, range 60-420). CSF markers of immune activation, neuropsychological (NP) testing, and mood assessments were examined at 96 weeks. Mann-Whitney test was used for cross-sectional analyses between groups.

Results: ART was started at a median 19 days post-infection and 3.8% (11/289) and 15.2% (44/289) had SR or IR, respectively. The degree of immunological response occurred early after ART in AHI and appeared to persist over time (Figure 1). At baseline, CD4+ T cell count was lower in the SR group compared to the CR group (median, 265 vs. 410 cells/μL, p=0.002), while blood HIV RNA, CD8+ T cell count, and CD4/CD8 ratio did not differ. After ART, CD8+ T cell count (median, 318 vs. 618 cells/μL, p=0.001) and CD4/CD8 ratio (median, 1.05 vs. 1.18, p=0.047) were lower in the SR group compared to the CR group. Blood sCD14 was elevated in SR and IR groups combined (n=3), compared to CR (n=26), at week 96 (median, 1.68 vs. 1.13 μg/L, p=0.008). Blood IL-6 was lower in SR and IR groups combined (n=8), compared to CR (n=69), at week 96 (median, 0.13 vs. 0.61 pg/mL, p=0.032). SR and CR did not differ in performance on NP testing or psychiatric indices at baseline or 96 weeks. However, baseline CSF neopterin was elevated in SR and IR groups combined (n=10), compared to the CR group (n=69, median, 2938 vs. 1623 pg/mL, p=0.050).

Conclusion: Suboptimal immunological response, associated with low CD4 count at baseline and persistent low CD8 count during treatment, occurs in a small subset of individuals despite treatment in the earliest stages of infection. Furthermore, poor response is associated with neuroinflammation at baseline and systemic inflammation during treatment, as measured by sCD14 and CD4/CD8 ratio.



209 CD4 INCREASE <100 CELLS/MM³ DURING 2 YEARS OF ART IS ASSOCIATED WITH WORSE OUTCOMES

Sol Aldrete[1], Kirk A. Easley[2], Jeong H. Jang[2], Tian Dai[2], Yi No Chen[3], Jason Okulicz[4], Brian K. Agan[5], Mirko Paiardini[6], Vincent C. Marconi[2]

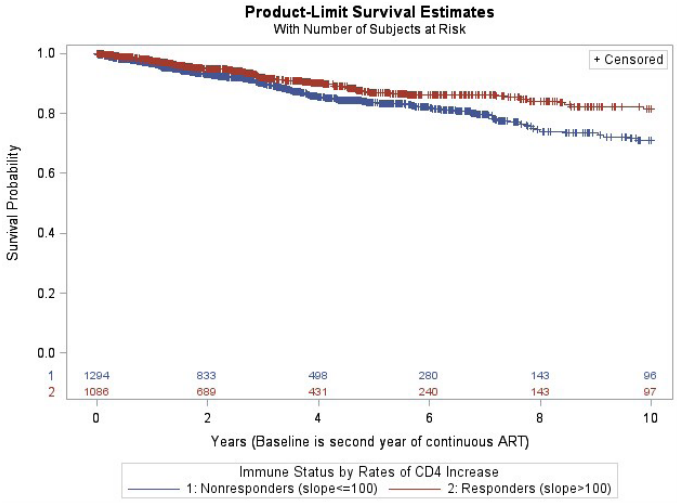
[1]Medical College of Wisconsin, Wauwatosa, WI, USA, [2]Emory University, Atlanta, GA, USA, [3]Atlanta VA Medical Center, Decatur, GA, USA, [4]Brooke Army Medical Center, San Antonio, TX, USA, [5]Uniformed Services University of the Health Sciences, Bethesda, MD, USA, [6]Emory Vaccine Center, Atlanta, GA, USA

Background: Immune non-responders (INR) have increased morbidity and mortality despite antiretroviral therapy (ART). There is no consensus in the literature on how best to define INR and most definitions have not been associated with clinical endpoints. We aimed to identify the CD4 T-cell recovery pattern most highly predictive of a composite clinical outcome.

Methods: We included treatment naïve patients who remained virologically suppressed for at least 2 years after starting ART from three large cohorts with distinct patient characteristics [HIV Atlanta VA Cohort Study (n=262), The US Military HIV Natural History Study (n=1014), and The Infectious Disease Program Cohort of the Grady Health System in Atlanta, Georgia (n=1146)]. A composite clinical outcome was created to indicate mortality, AIDS and non-AIDS events. The CD4 T cell recovery pattern most highly predictive of the composite outcome was modeled. Rates of CD4 increase were obtained using a mixed-effects model specifying that CD4 counts follow a linear model regression over time, with a random intercept and slope for each patient. Additionally, a two-stage modeling and joint modeling was used to enable both longitudinal repeated CD4 cell count and clinical endpoint data to be modeled together.

Results: The total cohort included 2,422 patients, 86.9% were male, 61.6% were black, with a median age of 37 years at ART start. The average yearly linear CD4 cell count rate of increase was 102 cells/mm³/year during two years of continuous ART (joint modeling). The composite endpoint rate decreased 20% per 100 cells/mm³/year increase in CD4 count (adjusted hazard ratio [aHR] = 0.80, 95%CI: 0.65-0.99, p =0.04). The rate of CD4 increase was highly associated with the composite endpoint for any given fixed intercept value, CD4 nadir or CD4 baseline. Immune responders (CD4 cell count ≥ 100 cells/mm³/year) had lower clinical endpoint rates (aHR = 0.73, 95%CI: 0.56-0.94, p =0.01) compared to INR (two-stage modeling).

Conclusion: CD4 T cell counts are prone to measurement error and high patient variability, which makes the modeling approaches attractive. We proposed defining INR as failure to increase ≥ 100 cells/mm³/year during the first two years on ART.



210 EFFECTS OF LONG-TERM ART ON SIVAGMSAB-INFECTED PIGTAILED MACAQUES

Benjamin Policicchio[1], **Paola Sette**[1], Ranjit Sivanandham[1], Cui Ling Xu[1], Tianyu He[1], Egidio Brocca-Cofano[1], Kevin D. Raehtz[1], Ellen P. Penn[1], Tammy Dunsmore[1], George S. Haret-Richter[1], Russell Tracy[2], Cara Wilson[3], Alan Landay[4], Cristian Apetrei[1], Ivona Pandrea[1]

[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]University of Vermont, Colchester, VT, USA, [3]University of Colorado, Aurora, CO, USA, [4]Rush University Medical Center, Chicago, IL, USA

Background: By infecting pigtailed macaques (PTMs) with SIVagmsab, we developed a new model of highly pathogenic SIV infection. This model is useful for HIV pathogenesis studies, as it faithfully reproduces classical features of HIV including a high degree of gut dysfunction, persistent immune activation and inflammation (IA/INFL) and high incidence of comorbidities. For model validation, it is critical to determine if available antiretroviral (ARV) therapies control virus replication at levels comparable to those in HIV-infected patients. While SIV is notoriously difficult to control with ARVs, a coformulated combination of three ARVs (reverse transcriptase inhibitors Emtricitabine [FTC] and tenofovir disoproxil fumarate [PMPA] and integrase inhibitor Dolutegravir [DTG]) induces robust virus control in SIVmac239-infected rhesus macaques.
Methods: To assess the coformulated therapy efficacy, six SIVagmsab-infected PTMs received the coformulated regimen starting from 48 days post-infection (dpi) and lasting for 11 months. Plasma viral loads were determined by qRT-PCR assay (detection limit: 30 copy/ml). CD4+ T cells in blood, intestine and lymph node, immune activation and inflammation markers were frequently monitored.
Results: SIVagmsab infection peaked at 108-109 copies/ml by 10 dpi and reached a set point of 105-107 copies/ml by 42 dpi. ARV administration resulted in a rapid decline (approx. 2 log) of plasma viremia within 48 hours, with a slower decline occurring over the next 30 days. VLs eventually became undetectable by conventional QRT-PCR between 16 and 164 days post-treatment (dpt), being then relatively well controlled, with only rare blips occurring during the follow-up. ART resulted in a robust restoration of the CD4+ T cells in both intestine and lymph node. Residual immune activation and inflammation were detected in ARV-treated PTMs.
Conclusion: Our results demonstrate that the coformulated ARV regimen administered long-term to an SIV model with extremely high viral loads and severe gut damage is effective in controlling virus replication and results in robust CD4+ T cell restoration. Similar to ARV-treated HIV-infected patients, the PTMs experience residual immune activation and inflammation. Our results thus validate the SIVagmsab model and open large avenues for its use for pathogenesis and treatment studies involving ART.

211 EFFECTS OF SUBCLINICAL CMV REPLICATION ON T-CELL ACTIVATION DURING EARLY ART

Aaron Christensen-Quick[1], Marta Massanella[2], Andrew Frick[1], Celsa A. Spina[1], Milenka Vargas[1], Masato Nakazawa[1], Christy M. Anderson[1], Sara Gianella[1]
[1]University of California San Diego, San Diego, CA, USA, [2]Centre de Research du Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada

Background: We previously showed that subclinical Cytomegalovirus (CMV) replication was associated with increased activation of CD4+ T cells during chronic HIV-infection and with a slower decay of HIV DNA in people starting antiretroviral therapy (ART) during early HIV infection. Here, we investigate changes in T cell activation that associate with CMV replication in the setting of early ART.
Methods: We investigated 246 peripheral blood mononuclear cell (PBMC) samples from 64 individuals starting ART during early HIV infection with subsequent virologic suppression up to 90 months (<50cp/ml, no viral blips, median 4 time-points/participant). In each PBMC sample, levels of CMV DNA were measured by ddPCR. Expression of immunological markers of activation (HLA-DR+CD38+) on five T-cell memory subsets [Naïve (Tn, CD27+CD45RA+), Stem Cell Memory (Tscm, CD27+CD45RA+CD95+), Central Memory (Tcm, CD27+CD45RA-), Effector Memory (Tem, CD27-, CD45RA-), and Terminally Differentiated (Ttd, CD27-, CD45RA+)] were measured in CD4+ and CD8+ T cells by flow cytometry. Significant differences in % of activated lymphocyte markers by CMV shedding status were identified using Generalized Linear Mixed Effects models. Models were checked for the effects of relevant covariates (Nadir CD4+, Time to ART, Race, Age, and Peak HIV RNA).
Results: Participants started ART within a median of 3 months of estimated date of HIV infection (IQR: 1.5-8.5), and were followed for a median of 33 months (IQR: 19-50) while on suppressive ART. During follow-up, CMV was detected in 60/246 time points. Individuals with detectable CMV had significantly higher % of activated CD8+ Tem and Ttd subsets at the time of ART initiation, but no differences in CD8+ Tn or Tcm (Table 1). We did not detect differences in CD4+ T cell activation at ART start. Over time, detectable CMV was associated with faster decay of activated CD8+ T cells (Tem and Ttd). Interestingly, during CMV replication, activated CD4+ Tscm presented a significantly slower decay rate, compared with samples with no detectable CMV. These results persisted when relevant covariates were included in the models.
Conclusion: Unlike chronic ART, no effect of subclinical CMV replication was observed on CD4+ T cell activation in the setting of early ART start. While CD8+ T cell activation was initially elevated in the setting of CMV replication, it normalized rapidly during early ART. The effect of CMV on Tscm activation merits further evaluation, as it might be relevant to HIV persistence.

Table 1: Effect of CMV on the decline in T-cell activation during suppressive ART

Model Outcomes		Model Predictors: Presence of CMV — Difference in Activated T-Cells by CMV at initiation of ART: Est.	CI	p-val		Model Predictors: CMV * Time on ART — Difference in decline of % Activated T-Cells by CMV status: Est.	CI	p-val	
CD4+	Total	0.05	(-0.39,0.49)	0.82		0.00	(-0.11,0.11)	0.97	
	T_N	0.00	(-0.44,0.42)	0.99		0.01	(-0.09,0.11)	0.86	
	T_{SCM}	-0.30	(-0.67,0.16)	0.21		0.11	(0.01,0.20)	**0.03**	*
	T_{CM}	0.09	(-0.25,0.43)	0.61		-0.01	(-0.09,0.08)	0.89	
	T_{EM}	0.33	(-0.09,0.73)	0.11		-0.07	(-0.17,0.04)	0.21	
	T_{TD}	0.22	(-0.29,0.72)	0.40		-0.04	(-0.16,0.09)	0.58	
CD8+	Total	0.54	(0.08,0.99)	**0.02**	*	-0.13	(-0.25,-0.01)	**0.04**	*
	T_N	0.28	(-0.08,0.64)	0.12		-0.09	(-0.18,0)	**0.04**	*
	T_{CM}	0.09	(-0.35,0.51)	0.70		-0.02	(-0.14,0.09)	0.69	
	T_{EM}	0.63	(0.18,1.09)	**<0.01**	*	-0.15	(-0.28,-0.03)	**0.02**	*
	T_{TD}	0.70	(0.31,1.08)	**<0.01**	*	-0.18	(-0.28,-0.09)	**<0.01**	*

Legend: *CMV Cytomegalovirus; ART Antiretroviral therapy; Est. Coefficient from GLM Beta Model; CI 95% Confidence interval for coefficient; T_N Naïve; T_{SCM} Stem Cell Memory; T_{CM} Central Memory; T_{EM} Effector Memory; T_{TD} Terminally Differentiated;* **** = p<0.05.*** *All models included the fixed effects of CMV (detectable versus undetectable), time since ART initiation (log2 months), and CMV by time; however, the model estimates for the lower order time term are not displayed.*

212 SPECT/CT IMAGING OF CD4-POOL SUGGESTS A NOVEL CORRELATE OF BENIGN DISEASE PROGRESSION

Sharat Srinivasula[1], Jorge Carrasquillo[2], Insook Kim[1], Chang Paik[3], H. Clifford Lane[3], **Michele Di Mascio**[4]
[1]Leidos Biomedical Research, Inc, Frederick, MD, USA, [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA, [3]NIH, Bethesda, MD, USA, [4]NIH, Rockville, MD, USA

Background: Global changes in the amount of lymphoid tissue have not been studied in the settings of acute, chronic progressive (CP) or long-term non-progressive (LTNP) SIV infection. A better understanding of changes in the total body immune system, especially in those organs capable of expanding or contracting in size, e.g. lymph nodes, may advance our knowledge of SIV pathogenesis.
Methods: Uninfected (U, n=10) or SIV (mac251 or mac239)-infected (n=10) rhesus macaques were studied with in vivo CD4 pool SPECT imaging using 99mTc- F(ab')2-CD4R1, and volumetric imaging with Computed-Tomography (CT). Only animals with no evidence of immunogenicity to the radiotracer were included. In the cross-sectional analyses, the first scan after 5 months of untreated infection was used. 3 animals were also imaged longitudinally in acute and chronic phase. CD4 pool in the clusters of axillary lymph-nodes (AxLns) was quantified as maximum Standardized-Uptake-Value (SUVmax) of the anti-CD4 probe. The volume of these AxLn (LN-size-Max) were determined from the co-registered CT images.
Results: Five of the SIV infected animals showed features of LTNPs with CD4 T cell count >600 during the entire period of untreated infection (median nadir:743 cells/µl; median SIV RNA set-point:3,760 copies/ml. 4/5 had a protective haplotype). The remaining five showed features of CP with CD4 T counts <500 (median nadir:177 cells/µl; median SIV-RNA of 140,000 copies/ml, 1/5 had a protective haplotype). The SUVmax of the AxLns and the spleen was positively correlated with the peripheral blood CD4 T cell count (r, AxLn = 0.51 (P=0.01); Spleen = 0.74 (P<0.001)). In addition, a positive correlation was observed between the SUVmax and the LN-size-Max (r=0.42, P=0.03). AxLns were larger in the LTNP group compared to the U (P<0.001) or CP groups (P<0.05). No statistically significant differences were noted between the U and CP groups. In the longitudinal study, splenic CD4-pools decreased in all 3 animals in acute phase concomitant with paradoxical increases in the AxLn CD4 pool as well as increases in the volume of AxLns. During the chronic phase of infection, the size of AxLns was reduced in 2 animals (with CP features) but not in the third animal (with LTNP features, B017+).
Conclusion: SPECT/CT imaging during acute and chronic SIV infection highlighted an unexpected association between the size of lymph nodes and the CD4 pool, that may suggest a novel correlate of non-progressive SIV infection.

213 INFLAMMATORY MONOCYTES CONTRIBUTE TO IMPAIRED INFLUENZA VACCINE RESPONSES IN AGING

Varghese George, Suresh Pallikkuth, Rajendra Pahwa, Lesley R. de Armas, Stefano Rinaldi, Margaret Roach, Li Pan, Maria F. Pallin, Celeste Sanchez, Margaret Fischl, Gordon Dickinson, Allan Rodriguez, Maria L. Alcaide, Savita Pahwa

University of Miami, Miami, FL, USA

Background: Influenza vaccine responses are often impaired in old age and in HIV infection despite virologic control with ART but innate immunologic determinants are not well understood

Methods: Virologically suppressed HIV+ (n=139) and healthy control (HIV-, n=137) participants classified by age as young (Y,19-39yr), middle-aged (M,40-59yr) and old (O,≥60) were evaluated for monocyte- and NK cell subsets by flow cytometry pre- and post-influenza vaccination. Group comparisons and correlations with age, HIV infection and influenza Ab titers were determined by the Mann-Whitney and Spearman test respectively

Results: At pre-vaccination, mean frequencies of inflammatory monocytes (IM, CD14+CD16+) calculated as a percent of total monocytes (LiveCD45+CD3-CD56-HLADR+CD14+) were significantly higher in O and M compared to Y in both HIV+ (O,1.5%,M 1.1%,Y 0.4%) and HIV- (O 1.8%,M 0.9%,Y 0.5%). Among HIV+ integrin α (CD11b) expression on IM was also highest in O (MFI, O 1884, M 1250, Y 1150). Overall, CD11b MFI on IM correlated with age (r=0.17, p=0.03), CC chemokine receptor-2 MFI (CCR2,r=0.30,p=0.002) on IM and plasma levels of soluble Tumor Necrosis Factor Receptor-1 (sTNFR1,r=0.6,p=<0.0001), and exhibited inverse correlation with post-vaccination influenza H1N1 antibody titers (r=-0.24,p=0.0003). When HIV+ participants were divided based on IM CD11b MFI into CD11bhi (MFI>1961) and CD11blow (MFI<533), those with CD11bhi IM showed higher plasma sTNFR1 (1381 vs 1042pg/ml,p=0.003) higher monocyte CCR2 MFI (3650 vs 2719,p=0.001) and lower post-vaccination serum Ab titers at d7 (HAI titer 366 vs 695, p=0.03) as well as d28 (440 vs 896, p=0.02). FACS sorted purified IM from CD11bhi versus IM from CD11blow expressers also showed higher CXCL-10 (log¬2 expression,37 vs 33,p=0.03) and LPS stimulated secretion of TNFα (1098 vs817pg/ml,p=0.05) and IL-6 (1586 vs 957 pg/ml, p=0.05) in culture supernatants. In HIV+ CD11bhi IM expressers, antigen-specific CD4 T cell proliferation by Cell Trace dye dilution assay was greater in PBMC depleted of IM compared to total PBMC (6.1%vs 3.1%,p=0.05). Among NK cells (LiveCD45+CD3-CD14-CD56+) terminally differentiated subset (CD56loCD16hi) was higher in HIV+ compared to HIV- in all age groups at pre-vaccination but did not correlate with vaccine responses. This NK cell subset or CD11b+ IM did not change post-vaccination

Conclusion: CD11bhi inflammatory monocytes are exacerbated with aging in HIV+ and negatively impact immune function involved in Ab response to influenza vaccination

214 TRANSCRIPTOME PROFILING AND DATA MINING: PREDICTIVE GENES OF HIV DISEASE PROGRESSION

Francisco Diez Fuertes[1], Esther Calonge[2], Maria Pernas[2], Humberto Erick De La Torre Tarazona[2], Isabelle Casademont[3], Anavaj Sakuntabhai[3], José Alcamí Pertejo[2]

[1]Institute de Salud Carlos III, Majadahonda, Spain, [2]Institute of Health Carlos III, Madrid, Spain, [3]Institute Pasteur, Paris, France

Background: The elite controller (EC)-long term non-progressors (LTNP) represent a spontaneous model of activation of the immune system against HIV-1, maintaining high levels of CD4+ T cell counts and undetectable viral replication in the absence of antiretroviral therapy (ART). The use of transcriptome studies combined with data mining reveals potential markers of HIV disease progression.

Methods: Peripheral blood mononuclear cells transcriptome of 30 HIV-infected individuals were sequenced in a HiSeq2000 System (Illumina), including 8 EC-LTNPs, 8 viremic LTNPs (vLTNP) and the same 7 typical progressors before (preTP) and after (postTP) receiving ART. The predictive model of disease progression was created combining the transcript abundance estimation obtained from Cufflinks with a bias-corrected feature selection procedure based in leave one out cross-validation and a hierarchical Bayesian classification. Error rate (ER) and the average of minus log predictive probabilities (AMLP) at the true value were used to evaluate the optimal selection of predictive genes. A final classification model was build, obtaining the probability for each individual to be classified as EC-LTNP, vLTNP, preTP and postTP.

Results: A mean of 33,670,437 100 bp-reads was obtained for each library (91.7% reads mapped to the human transcriptome). The best predictive model was achieved using the abundance estimation of only 20 mRNAs among the whole transcriptome as predictive variables (ER = 0.287 and AMLP= 1.058). Ten out of these 20 genes are interferon regulated genes (IRGs), including genes related with host antiviral immune responses (HERC5, IFI44, MX1, XRCC6), target genes of P-TEFb (EPSTI1, PARP12, PARP14), ribosomal protein pseudogenes (RPL5P4, RPL4P5, RPL4P4) and eukaryotic translation elongation factor genes (EEF1G, EEF1B2, EEF1B2P3). The functional annotation of these 20 genes revealed two enriched pathways, antiviral mechanism by IFN-stimulated genes (q=0.044) and ISG15 antiviral mechanism (q=0.044). Using the estimated expression of these genes, the majority of the individuals were correctly classified (n=22, 73.3%).

Conclusion: Potential markers of HIV disease progression were described combining a solid transcript abundance estimation with data mining approaches, pointing to the importance of interferon regulation in preserving high CD4+ T cell counts and HIV-1 control capacity, as well as the modification of transcription/translation machineries of cells by mechanisms that need to be investigated.

215 CD4 T CELL DEPLETION IN PRIMATES IS ASSOCIATED WITH LOSS OF INNATE LYMPHOID CELLS

Joseph Mudd[1], Kathleen Busman-Sahay[2], Sarah DiNapoli[1], Stephen Lai[1], Virginia Sheikh[1], Andrea Lisco[1], Claire Deleage[1], Brian Richardson[3], David J. Palesch[1], Mirko Paiardini[4], Mark Cameron[3], Irini Sereti[1], R. Keith Reeves[5], Jacob D. Estes[2], Jason Brenchley[1]

[1]NIAID, Bethesda, MD, USA, [2]AIDS and Cancer Virus Program, Frederick, MD, USA, [3]Case Western Reserve University, Cleveland, OH, USA, [4]Yerkes National Primate Research Center, Atlanta, GA, USA, [5]Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: Innate lymphoid cells (ILCs) maintain mucosal barrier integrity and are depleted in HIV-1 infection. Interestingly, ILCs are not permissive to HIV-1 or SIV infection, and depletion of ILCs is not a generalized feature of all viral infections. There is thus considerable interest in understanding the exact mechanisms of ILC loss in HIV/SIV infections.

Methods: IL-33R+ ILC2s and cKit+ ILC3s in gut-draining mesenteric LNs (MLNs) of SIV-, viremic SIV+ untreated, ART-treated SIV+, and SIV+ Elite Controller (EC) rhesus macaques (RMs) were assessed proportionally by flow cytometry and numerically by immunohistochemistry. To recapitulate HIV/SIV pathology in settings devoid of viral replication, MLN ILCs were assessed in SIV- RMs treated with a CD4-depleting antibody. Some of these animals received DSS, inducing low-grade endotoxemia. In addition we studied a cohort of HIV- persons with idiopathic CD4 lymphophenia (ICL), defined by CD4 counts < 300 cell/ul in the absence of any known immunodeficiency.

Results: cKit+ ILC3s (capable of producing IL-17) were proportionally depleted in the acute (p=0.006, N=10) and chronic SIV+ MLN (p=0.0007, N=11). cKit+ ILC3s were depleted numerically in the acute (p=0.007) and chronic (p=0.007) SIV+ MLN as well . When compared to MLN ILC3 proportions in healthy animals (N=10), control of viremia was associated with reconstitution, or preservation of MLN ILC3s in ART-treated (N=6) or EC RMs (N=5), respectively. Importantly, proportions of MLN ILC3s in all animals correlated inversely with sCD14 in plasma (p= 0.008, r= -0.5). Experimental CD4 depletion in healthy RMs was sufficient to reduce MLN ILC3 percentages (p=0.03, N=2). This was observed more significantly in healthy RMs receiving anti-CD4 and DSS (p=0.0009, N=5), yet not in DSS-treated only RMs (N=2). In striking concordance to CD4-depleted healthy RMs, HIV- subjects with ICL (N=11) displayed lower numbers of blood ILC3 (p=0.0008) and ILC2 (p=0.0001). In MLNs of RMs, cKit+ ILC3s were localized to the CD4 T cell-rich paracortex, and ILC3 proportions in all SIV+ RMs correlated directly with proportions of CD4 T cells in the MLN (p=0.003, r=0.25).

Conclusion: CD4 T cell loss appears to be the main driver of ILC depletion that occurs in HIV/SIV infection as it is also observed in experimental CD4 depletion in primates without SIV infection and also in patients with idiopathic CD4 lymphopenia. These data suggest that mechanisms other than direct viral replication affect ILC homeostasis in SIV/HIV infection.

216 HIV UNSPLICED RNA EXPRESSION INDUCES INNATE IMMUNE ACTIVATION AND T CELL DYSFUNCTION

Hisashi Akiyama, Caitlin Miller, Chelsea R. Ettinger, Anna C. Belkina, Jennifer Snyder-Cappione, Rahm Gummuluru
Boston University, Boston, MA, USA

Background: A hallmark of HIV-1 infection in vivo is systemic chronic immune activation, which has been postulated to lead to HIV-associated non-AIDS complications (HANA) and dysfunction of T cells. While many factors have been hypothesized to cause aberrant immune activation, recent studies suggest chronic low-level production of type I interferons (IFN-I) as the driving force for chronic inflammation and T cell exhaustion in vivo. In this study, we demonstrate that persistent expression of HIV-1 unspliced viral RNAs in myeloid cells is the trigger that induces IFN-I responses and contributes to T cell dysfunction.

Methods: Monocyte-derived macrophages (MDMs) were derived from CD14+ cells purified from PBMCs. MDMs were infected with HIV-1, and expression of CD169, a myeloid cell specific interferon stimulated gene (ISG), and IP-10 was measured as markers of immune activation. Autologous PBMCs were co-cultured with HIV-1-infected MDMs and expression of a panel of inhibitory receptors (IRs) on T cells was analyzed. Finally, production of IFNγ from IR+ T cells upon stimulation was measured by intracellular cytokine staining.

Results: Establishment of productive HIV-1 infection in MDMs resulted in robust upregulation of CD169 and IP-10, which was abrogated upon treatment of MDMs with HIV-1 entry, reverse transcription, integration or viral transcription inhibitors or upon treatment with an IFN-I neutralizing reagent (B18R), suggesting that activation of MDMs was dependent on de novo viral gene expression and is mediated by soluble IFN-I. Infection of MDMs with a panel of HIV-1 mutants revealed that Rev-dependent nuclear export of unspliced RNA (usRNA), but not viral protein expression was necessary for ISG induction and MDM activation. Interestingly, PBMCs co-cultured with HIV-1-infected MDMs up-regulated IRs on both CD4+ and CD8+ T cells, and IFNγ production from IR+ T cells upon stimulation was significantly reduced. Importantly, this T cell exhaustion phenotype was not observed when nuclear export of viral usRNA was inhibited in HIV-infected MDMs or upon initiation of co-cultures in the presence of B18R.

Conclusion: Our findings suggest that persistent expression of HIV-1 usRNA in macrophages contributes to chronic immune activation and impairment of effector T cell functions and that use of HIV RNA expression inhibitors as adjunct therapy might abrogate aberrant inflammation and restore immune function in HIV-infected individuals on HAART.

217 INSULIN-LIKE GROWTH FACTOR 1 INVERSELY RELATES TO MONOCYTE ACTIVATION MARKERS IN HIV

Lindsay T. Fourman, Natalia Czerwonka, Sofia D. Shaikh, Takara L. Stanley, Kathleen V. Fitch, Janet Lo, Steven K. Grinspoon
Massachusetts General Hospital, Boston, MA, USA

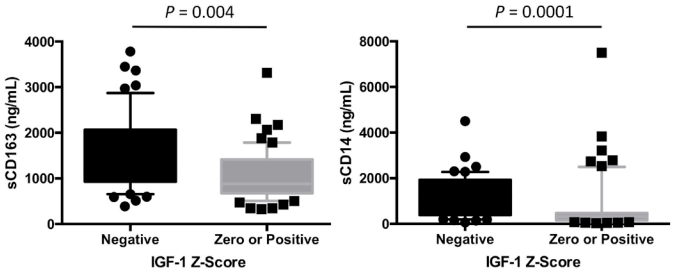
Background: Monocyte activation is increased among people living with HIV (PLWH), and may contribute to the development of HIV complications including atherosclerosis and neurocognitive dysfunction. Thus, strategies that dampen monocyte activity in HIV are critically needed. Insulin-like growth factor 1 (IGF-1) is an endogenous peptide that exerts endocrine and autocrine/paracrine effects. IGF-1 is low in chronic inflammatory states, whereas augmentation of IGF-1 reduces monocyte-specific inflammation in animal models of atherosclerosis and inflammatory bowel disease. Here, we investigate for the first time the association of IGF-1 with monocyte activation markers in PLWH and uninfected controls.

Methods: 131 PLWH (46.7±8.2 years, 67% men, CD4 count 556 [392,816] cells/mm^3, undetectable VL 75%, ART use 81%) and 65 well-matched controls (45.4±7.1 years, 62% men) without known cardiac disease or viral hepatitis were recruited previously. IGF-1 and inflammatory markers were measured. Variables were compared between HIV and non-HIV groups using Student's two-tailed t-test if normally distributed, Wilcoxon rank-sum test if not normally distributed, and chi-square test if categorical. IGF-1 z-score was related to log-transformed inflammatory markers in HIV and non-HIV groups using Pearson correlation. Markers associated with IGF-1 z-score were tested in multivariable models controlling for factors that may affect inflammation.

Results: PLWH had higher sCD163 (1081 [711,1564] vs. 820 [591,1054] ng/mL, P = 0.0002) and MCP-1 (261 [179,359] vs. 223 [166,271] pg/mL, P = 0.01) than uninfected controls. sCD14 also tended to be greater among PLWH (431 [223,1692] vs. 327 [162,1222] ng/mL, P = 0.08). CRP, IL-6, LPS, and IGF-1 were similar between HIV and non-HIV groups. Among PLWH, IGF-1 inversely related to sCD163 (r = -0.28, P = 0.002) and sCD14 (r = -0.29, P = 0.002). There was no association of IGF-1 with MCP-1, CRP, IL-6, or LPS in PLWH, or between IGF-1 and any inflammatory marker in controls. The relationship of IGF-1 with sCD163 and sCD14 remained significant among PLWH in multivariable models accounting for age, sex, smoking, BMI, visceral fat, statin use, VL, and ART. For every 1-unit decline in IGF-1 z-score, sCD163 increased by 14% (95%CI 0.23%, 29%), and sCD14 increased by 29% (95%CI 1.4%, 63%).

Conclusion: In PLWH, there was a robust inverse association of IGF-1 with monocyte activation markers. Interventional studies are needed to examine IGF-1 as a novel therapy to reduce monocyte activation in HIV.

Low IGF-1 Z-score is Associated with Increased sCD163 and sCD14 Among People Living with HIV



IGF-1 is expressed as a z-score in which 0 denotes the mean for an individual's age and sex. Boxes span 25th to 75th percentiles, whereas whiskers span 10th to 90th percentiles. *P*-values were determined using Wilcoxon rank-sum test.

218 EXOSOMES ARE ASSOCIATED WITH IMMUNE ACTIVATION AND OXIDATIVE STRESS IN HIV PATIENTS

Sukrutha Chettimada, David Lorenz, Vikas Misra, Dana H. Gabuzda
Dana–Farber Cancer Institute, Boston, MA, USA

Background: Exosomes are nanovesicles released from most cell types including immune cells. Prior studies suggest exosomes play a role in HIV pathogenesis, but little is known about exosome cargo in relation to immune responses and oxidative stress. Here, we characterize protein and RNA cargo of circulating exosomes in HIV patients and examine their relationship to immunological and oxidative stress markers.

Methods: Plasma exosomes were isolated from 92 subjects (n=51 HIV+, age 37-60 years, 70% male, on ART with suppressed or low viral load [undetectable or <2500 HIV RNA copies/ml, respectively] and n=41 HIV- controls matched for age, gender, race). Exosomes were characterized by electron microscopy, nanoparticle tracking analysis (NTA), and immunoblotting for exosome markers. The plasma metabolome was characterized by LC-MS/MS to examine inter-relationships between plasma exosomes and metabolite changes related to immune activation and oxidative stress. Exosomal protein cargo was assessed by LC-MS/MS proteomics and RNA cargo by small RNA sequencing.

Results: Plasma exosomes were more abundant in HIV-positive subjects compared to controls based on immunoblotting for exosome markers and NTA (median 6.76 vs. 3.41 X 10^11 particles/ml, respectively, p=.038). Plasma exosome markers correlated positively with oxidative stress markers (cystine, oxidized cys-gly, p<0.05) and inversely with PUFA (DHA, EPA, DPA, p<0.05). Untargeted proteomics detected markers of exosomes (CD9, CD63, CD81), immune activation and inflammation (CD14, CRP, HLA-A, HLA-B, CSF1R, LILRB1), and oxidative stress (CAT, PRDX1, PRDX2, TXN, SEPP1) in plasma exosomes. Small RNA-seq analysis of exosomal RNA cargo identified several classes of small RNAs, including microRNA (10%), snoRNA (8%), tRNA (20%), and piRNA (60%). MiRNA target enrichment analysis suggested these exosome-associated miRNAs could have potential functional roles in pathways involved in HIV infection, Wnt and Notch signaling, inflammation, and stress responses.

Conclusion: HIV-positive individuals on ART have higher abundance of plasma exosomes compared to HIV-negative controls, and this increase correlates with markers of oxidative stress. Exosome cargo includes proteins related to immune activation, inflammation, and oxidative stress, and may have pro-inflammatory and redox effects during pathogenesis. Exosomal small RNA cargo may also influence pathogenesis and stress responses.

219 CONTROLLED STUDY TO EVALUATE IMMUNOLOGIC EFFECT OF ISOTRETINOIN ON HIV-1 INFECTION

Nina Lin[1], Bernard J. Macatangay[2], Ellen S. Chan[3], Heather Ribaudo[3], Karin L. Klingman[4], Linda Boone[5], Jonathan Z. Li[6], Maureen A. Kane[7], Francesca Aweeka[8], Charles Rinaldo[2], Ian McGowan[9], Daniel R. Kuritzkes[6], Douglas Kwon[10]
[1]Boston University, Boston, MA, USA, [2]University of Pittsburgh, Pittsburgh, PA, USA, [3]Harvard University, Cambridge, MA, USA, [4]DAIDS, NIAID, Bethesda, MD, USA, [5]Social &Scientific Systems, Silver Spring, MD, USA, [6]Brigham and Women's Hospital, Boston, MA, USA, [7]University of Maryland, Baltimore, MD, USA, [8]University of California San Francisco, San Francisco, CA, USA, [9]Magee–Womens Research Institute, Pittsburgh, PA, USA, [10]Massachusetts General Hospital, Boston, MA, USA

Background: HIV-associated immunologic defects in the gut are thought to contribute to chronic inflammation, which is central to HIV disease progression. Since retinoic acid (RA) is known to play an important role in gut homeostasis, we conducted a multicenter clinical trial to investigate the effects of RA on systemic and gut T cell activation, inflammation, and CD4+ T cell reconstitution.
Methods: HIV-infected adults on suppressive ART were randomized 2:1 to receive 16-wks of isotretinoin or no treatment (control). A subset underwent baseline and wk 16 colonoscopies for terminal ileum and transverse colon mucosal biopsies. All participants were followed to wk 28 to assess durability of effects. Per-protocol analyses included only participants who completed treatment (for isotretinoin arm) without virologic failure. Treatment group differences were assessed via Wilcoxon rank-sum tests.
Results: 76 participants were enrolled, with 39 isotretinoin vs 26 control included in the per-protocol analyses. 12 isotretinoin vs 6 control participants underwent the colonoscopy substudy. Participants were 7% female, with median age 49 yrs, and median CD4+ T cell count 552 cells/mm^3. No deaths or grade 4 adverse events were reported. Greater increases in T cell activation (%HLA-DR+/CD38+) among CD4+ (median +1.01% vs +0.17%) and CD8+ (+3.24% vs +0.52%) cells were observed in the isotretinoin than control arm at wk 16, but reverted post-treatment. Similarly, soluble markers of inflammation (IL-6, sCD163, CRP, sCD14) had greater increases with isotretinoin that reverted post-treatment. In contrast to blood, the median decrease in gut CD8+ T cell activation was greater with isotretinoin vs control (-6.3% vs 1.6%). Notably, blood CD4+ T cell numbers increased over the study in the isotretinoin arm (+27 cells/mm^3 to wk 28). CD4+T cell cycling (%Ki67+) did not change in the blood but increased in the terminal ileum with isotretinoin (+2.6%).
Conclusion: Isotretinoin treatment resulted in increases in cellular and soluble markers of immune activation and inflammation that were not sustained after removal of therapy. There was an overall increase in systemic CD4+ T cell count with isotretinoin treatment over 28 wks. This was accompanied by an increase in gut CD4+ T cell proliferation and decreased intestinal CD8+ T cell activation during treatment. Together, these data suggest that RA has differential effects on systemic and gut compartments, with immunological benefits in HIV-infected adults on suppressive ART.

Table 1. Summary for changes in immunology markers by study arm

			Change from Baseline to week 14/16 (Treatment phase)		Change from baseline to week 28 (Overall)	
Immunology Marker	Study Arm	N	Median [95% CI]	P-value*	Median [95% CI]	P-value*
% HLA-DR+/CD38+(CD8+)	Isotretinoin	39	3.24 [1.44, 6.29]	0.030	-0.69 [-1.97, 2.66]	0.791
	Control	26	0.52 [-0.36, 2.41]		0.03 [-1.65, 2.74]	
% HLA-DR+/CD38+(CD4+)	Isotretinoin	39	1.01 [0.37, 2.26]	0.050	0.12 [-0.76, 0.93]	0.613
	Control	26	0.17 [-0.79, 0.91]		0.34 [-0.92, 1.22]	
% Ki67+(CD8+)	Isotretinoin	39	0.02 [-0.02, 0.07]	0.185	-0.05 [-0.13, 0.03]	0.873
	Control	26	-0.01 [-0.08, 0.05]		-0.01 [-0.12, 0.07]	
% Ki67+(CD4+)	Isotretinoin	39	0.01 [-0.09, 0.14]	0.491	-0.07 [-0.14, 0.03]	0.350
	Control	26	-0.01 [-0.13, 0.07]		0.00 [-0.15, 0.18]	
CD4 T-cell Count [cells/mm^3]	Isotretinoin	38	17 [-21, 37]	0.064	27 [7, 52]	0.039
	Control	26	-39 [-97, 8]		-14 [-59, 19]	
I-FABP [percent change]	Isotretinoin	39	-7.5 [-18.1, 15.7] %	0.090	16.5 [-1.3, 40.0] %	0.067
	Control	26	9.4 [-8.5, 30.8] %		-14.6 [-34.5, 23.2] %	
Zonulin [percent change]	Isotretinoin	39	1.7 [-8.9, 27.5] %	0.685	-7.4 [-23.6, 32.7] %	0.143
	Control	26	12.8 [-9.6, 34.3] %		23.5 [-3.9, 54.0] %	
sCD14 [percent change]	Isotretinoin	39	5.7 [-0.4, 20.8] %	0.051	-3.9 [-7.6, 5.2] %	0.502
	Control	26	-5.3 [-13.4, 5.1] %		-0.5 [-8.0, 10.1] %	
IL-6 [percent change]	Isotretinoin	39	27.2 [3.0, 44.3] %	0.003	5.0 [-15.9, 33.7] %	0.879
	Control	26	-7.8 [-17.6, 4.5] %		-1.4 [-23.2, 34.3] %	
hsCRP [percent change]	Isotretinoin	39	58.4 [18.7, 86.6] %	0.020	-18.4 [-47.9, 40.7] %	0.119
	Control	26	-17.0 [-33.1, 40.6] %		-10.5 [-26.8, 86.0] %	
sCD163 [percent change]	Isotretinoin	39	39.7 [16.5, 50.5] %	0.001	-3.8 [-11.8, 30.2] %	0.984
	Control	26	-2.3 [-9.0, 28.9] %		9.3 [-13.5, 33.6] %	
Terminal Ileum:	Isotretinoin	11	2.6 [0.1, 4.5]	NA		
% Ki67+(CD4+)	Control	6	2.1 [-5.0, 5.4]			
Transverse colon:	Isotretinoin	12	-6.3 [-7.9, -2.6]	NA		
% HLA-DR+/CD38+(CD8+)	Control	6	1.6 [-7.9, 6.5]			

*Wilcoxon rank-sum p-value evaluating the difference in changes between the two study arms.

220 HIV-1 UNMASKS THE PLASTICITY OF INNATE LYMPHOID CELLS

Yetao Wang, Kyle Gellatly, Alan Derr, Smita Jaiswal, Alper Kucukural, Patrick McDonel, Thomas Greenough, Jean Marie Houghton, Manuel Garber, **Jeremy Luban**
University of Massachusetts, Worcester, MA, USA

Background: Pharmacologic suppression of HIV-1 viremia preserves CD4+ T cells and prevents AIDS but does not eliminate systemic inflammation. As possible explanation for ongoing inflammation we examined the effect of HIV-1 infection on innate lymphoid cells (ILCs). ILCs are innate counterparts of T cells that lack clonotypic antigen receptors or other lineage-defining cell surface markers, and carry out a large range of biological functions, including roles in host defense against pathogens and maintenance of homeostasis in inflamed tissues.
Methods: We characterized the ILC subpopulations present in the blood and colon lamina propria of HIV-1-negative people and HIV-1+ people.
Results: Homeostatic cytokine-producing CD127+ innate lymphoid cells (ILCs) were depleted from the blood and colon of HIV-1+ people, irrespective of antiretroviral therapy. Common γ-chain cytokines that are elevated during HIV-1 infection converted CD127+ILCs into inflammatory CD127-ILCs, and shifted CD127-ILC1s into cytotoxic NK cells. Pseudotemporal clustering of transcriptomes from thousands of cells identified a developmental trajectory from CD127-ILC1s to memory NK cells that was defined by WNT-transcription factor TCF7. WNT inhibition prevented the cytokine-induced transition of CD127-ILC1 cells into NK cells. Consistent with reported HIV-1-specific killing activity, TCF7+ memory NK cells were increased in the blood of HIV-1+ people, concomitant with the reduction in CD127-ILC1s.
Conclusion: These studies demonstrate that ILC plasticity contributes to ongoing inflammation and expanded NK cell memory in HIV-1 infection, and indicate that targeted WNT inhibition may augment antiviral therapy.

221 SYSTEMIC ACTIVATION OF NOVEL IGA+ NATURAL KILLER-LIKE B CELLS IN HIV/SIV INFECTIONS

Chiadika Nwanze, **Cordelia Manickam**, R. Keith Reeves
Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: Recently, a novel innate immune cell subset termed natural killer-like B (NKB) cells was identified in mice that rapidly responded to microbial infection and primed the innate antiviral response. Despite a critical role for innate immunity in blocking or limiting viral transmission and disease, the presence and role of NKB in primate HIV/SIV infections is completely unknown.
Methods: To identify NKB in primates, up to 18-color polychromatic flow cytometry was used for phenotypic and functional assays. NKB were identified in both rhesus macaques and human samples by flow cytometry excluding lineage markers (CD3–CD14–CD127–) and then positive boolean gating of CD20, NKG2A/C and/or NKp46.
Results: NKB were found at similar frequencies in the circulation of humans (n = 20) and rhesus macaques (n = 12) (range, 0.01 to 0.2% of total lymphocytes) and were systemically distributed at similar frequencies in tonsil, mesenteric and peripheral lymph nodes, colon, and jejunum. NKB were notably enriched in spleen (median, 0.4% of lymphocytes) but frequencies were not altered in any tissue following HIV/SIV infections, and not influenced by ART status. Interestingly, NKB uniquely and uniformly expressed high levels of IgA regardless of tissue, but demonstrated increased IgM and IgG in HIV-infected patients and SIV-infected macaques, which could suggest class-switching or mobilization of de novo cells. NKB also upregulated CD40, HLA-DR, CD16 and NKp46 during infection - highly suggestive of virus-induced activation. Work from our lab and others have shown NKB production of IFN-γ, IL-12, and IL-18, but we found only low-to-moderate expression of granzyme B, and NKB were negative for perforin and had low evidence of cytolytic potential.
Conclusion: These results demonstrate the first conclusive evidence of for systemic NKB in rhesus macaques and humans, and demonstrate their significant perturbation during HIV/SIV infections. Although the full functional niche of this subset is unknown, our preliminary evidence suggests they may be most closely related to other innate B cell lineages (B1). Regardless, their systemic distribution, particularly accumulation in mucosal tissues and secondary lymphoid organs, as well as strikingly high expression of IgA could make these novel cells unique targets for future HIV immunotherapeutics or vaccine strategies.

222 IL-15 DRIVES THE GENERATION AND SURVIVAL OF SENESCENT CD8 T CELLS IN HIV INFECTION

Stephen R. Morris[1], Bonnie Chen[2], Soumya Panigrahi[2], Scott F Sieg[2], Souheil A Younes[2], Sara Gianella[3], Michael M. Lederman[2], **Michael L. Freeman**[2]
[1]Louis Stokes Cleveland VA Medical Center, Cleveland, OH, USA, [2]Case Western Reserve University, Cleveland, OH, USA, [3]University of California San Diego, La Jolla, CA, USA

Background: There is a significant expansion of activated CD8 T cells in HIV infected people, even when virus is controlled with antiretroviral therapy (ART). This expansion leads to an inversion of the CD4/CD8 ratio, and a low ratio is linked to increased co-morbidities, including increased cardiovascular disease (CVD) risk. Many of the expanded CD8 T cells express the fractalkine receptor (CX3CR1) and contain cytolytic granules, suggesting these cells can traffic to sites of endothelial cell dysfunction and contribute to CVD. CX3CR1+ CD8 T cells are highly enriched for senescent cells calling into question how these poorly replicative cells are maintained long-term. Here we tested the role of the inflammatory cytokine IL-15 in promoting the formation and survival of senescent CD8 T cells.

Methods: Peripheral blood CD8 T cells were isolated from ART-treated HIV-infected individuals (n=14) or HIV-uninfected controls (n=9) and analyzed by surface and intracellular flow cytometry. In some experiments, cells were treated in culture with recombinant IL-2 (100U/mL), recombinant IL-15 (20ng/mL), or anti-CD3 (5ng/mL) and anti-CD28 (5µg/mL) for 1, 2, 4, or 7 days.

Results: Principal component and t-stochastic neighbor embedding analyses reveal that CX3CR1+ CD8 T cells are a fundamentally distinct population of memory CD8 T cells characterized by elevated expression of CD57, a marker of immune senescence. To determine what factors contribute to the persistence and expansion of a poorly replicative T cell population, we sorted subpopulations of CX3CR1+ CD8 T cells and stimulated with IL-2, IL-15, or via T cell receptor (TCR) ligation. IL-2 and IL-15, but not TCR signals, supported CD57+ CD8 T cell viability, and IL-15 and TCR signals, but not IL-2, promoted proliferation of CD57+ CD8 T cells. Although both IL-15 and TCR signals upregulated c-myc expression and oxidative phosphorylation, only IL-15 also induced expression of the pro-survival factor Bcl-2. Additionally, IL-15 upregulated CD57 expression on sorted CX3CR1+CD57- CD8 T cells.

Conclusion: IL-15 induced the generation, proliferation, and survival of CX3CR1+CD57+ CD8 T cells. This effect was consistent with an upregulation of c-myc, mitochondrial activity, and Bcl-2 expression. As elevated IL-15 has been demonstrated in chronic untreated HIV infection, and in HIV-uninfected individuals with CVD, our data suggest that the proinflammatory environment in HIV disease contributes to the generation of and maintenance of senescent cytotoxic CD8 T cells.

223 REGULATION OF B CELLS BY IGG3 IN HIV-INFECTED INDIVIDUALS

Christine Youn[1], Lela Kardava[1], Haewon Sohn[2], James W. Austin[1], Wei Wang[1], Clarisa M. Buckner[1], Marissa Hand[1], Kathleen Gittens[3], Richard Kwan[3], Michael Sneller[1], Tae-Wook Chun[1], Susan K. Pierce[2], Susan Moir[1]
[1]NIAID, Bethesda, MD, USA, [2]NIAID, Rockville, MD, USA, [3]NIH, Bethesda, MD, USA

Background: The role of B cells in HIV immunopathology has been actively studied over the past few decades. Early antibody responses to vaccination or natural infection, including HIV, often involve IgG3. In chronic HIV viremia, we recently observed abnormalities involving the binding of soluble IgG3 to IgM-expressing B cells. Here, we describe a regulatory role for soluble IgG3 B-cell binding in chronic HIV-infection.

Methods: Flow cytometry was performed to identify and sort B-cell populations. Biochemical and molecular analyses were performed to identify soluble and surface-expressed immunoglobulins (Ig). IgG3 complexes (IgG3-C) were isolated from serum by PEG precipitation. Imaging cytometry and total internal reflection fluorescence (TIRF) microscopy were used for colocalization analyses. Calcium influx and phosphorylation assays were performed for functional analyses.

Results: Peripheral blood B cells were isolated from 108 HIV-infected individuals. Frequencies of IgG3+IgM+ B cells were found to vary by disease status, being highest in infected individuals with chronic HIV viremia while completely absent in HIV-negative individuals. IgG3+IgM+ B cells were also restricted to certain B-cell subsets, namely tissue-like memory (TLM) cells and to a lesser extent, naïve cells. Trypsin treatment and mixed light chain pattern suggested that soluble IgG3 was bound to the surface of IgM B-cell receptor (BCR) expressing cells. Transcriptional analyses confirmed that IgG3+IgM+ B cells exclusively expressed IGHM mRNA. Imaging cytometry and TIRF microscopy revealed a significant colocalization between IgM and IgG3 on TLM B cells. TIRF analyses demonstrated that in the absence of IgG3, IgM was evenly distributed on the cell surface. In contrast, when IgG3 bound to the cells, IgM-BCR was highly clustered, consistent with antigen-induced polarization, and highly colocalized with IgG3. PEG precipitation of Ig complexes from serum of individuals with high- but not low-intensity IgG3+IgM+ B cells led to binding of IgG3-C to B cells of HIV-negative individuals. TIRF microscopy, as well as anti-CD32 treatment, demonstrated involvement of CD32b in the binding of soluble IgG3. Lastly, IgG3+IgM+ TLM B cells responded poorly to BCR stimulation, as observed by calcium signaling and phosphorylation of downstream substrates.

Conclusion: Our study provides a new functional role of IgG3 in dampening the B-cell response in HIV-infected individuals through its strong association with IgM-expressing TLM B cells.

224LB RESISTANCE OF HIV-INFECTED MACROPHAGES TO CTL KILLING DRIVES IMMUNE ACTIVATION

Kiera L. Clayton[1], David R. Collins[2], Joshua Lengieza[1], Farokh Dotiwala[3], Judy Lieberman[3], Bruce D. Walker[1]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]Boston Children's Hospital, Boston, MA, USA

Background: CD4 T lymphocytes are the principal target of HIV infection, but macrophages can also become infected and contribute to viral pathogenesis. CD8 cytotoxic T lymphocytes (CTLs) control virus levels during acute and chronic stages of HIV infection and reduce HIV disease progression. Most studies have focused on CTL control of infected CD4 T cells with less focus on infected macrophages. Recent work suggests that SIV-infected macrophages are relatively resistant to CTL-mediated killing, but the mechanism behind their differential susceptibility is unknown. Thus, the objective of this work was to characterize the interactions between CTLs and HIV-infected targets, both CD4 T cells and macrophages, to delineate immunoevasion mechanisms of macrophage resistance to CTL-mediated elimination.

Methods: Monocytes were matured into macrophages while CD4 T cells were activated to permit infection with HIV. Flow cytometry-based elimination assays and HIV Gag p24 ELISA-based suppression assays were used to asses the susceptibility of autologous HIV-infected targets to CTL-mediated killing. Flow cytometry and ELISA-based recognition assays were used to characterize the CTL degranulation and cytokine response to the targets. Imaging flow cytometry was used to assess effector-target conjugates while cytokine-bead arrays characterized pro-inflammatory chemokines released by macrophages.

Results: We demonstrate that macrophages exhibit delayed CTL-mediated killing as compared to CD4 T cells ($p<0.0001$), resulting in inefficient HIV suppression ($p = 0.0005$). Mechanistic studies reveal that delayed killing of macrophages is caspase-3- and granzyme B-dependent, whereas rapid killing of CD4 T cells is caspase-independent and does not require granzyme B. Moreover, impaired killing of macrophages is associated with prolonged effector-target contact time ($p=0.0022$) and greater CTL IFN-γ expression ($p = 0.0047$), inducing macrophage production of pro-inflammatory chemokines that trigger recruitment of monocytes and T cells.

Conclusion: These results suggest that inefficient CTL-mediated killing of macrophages may contribute to reservoir persistence and chronic inflammation in HIV infection. An improved understanding of the precise mechanisms underlying the observed resistance to target cell killing and resulting hypersecretion of pro-inflammatory cytokines and chemokines will be necessary to develop approaches capable of efficiently eliminating infected macrophages and hampering chronic inflammation.

225 SPECIFIC CTFH FREQUENCY CORRELATES WITH MEMORY B CELL RESPONSES IN HIV CONTROLLERS

Lisa Chakrabarti[1], Mathieu Claireaux[1], Moran Galperin[1], Daniela Benati[1], Alexandre Nouel[1], Madhura Mukhopadhyay[1], Pierre de Truchis[2], David Zucman[3], Samia Hendou[4], Faroudy Boufassa[4], Olivier Lambotte[2]
[1]Institute Pasteur, Paris, France, [2]AP–HP, Paris, France, [3]Hopital Foch, Suresnes, France, [4]INSERM, Le Kremlin-Bicetre, France

Background: Follicular helper T cells (Tfh) play an essential role in the affinity maturation of the antibody response by providing help to B cells. To determine whether this CD4+ T cell subset may contribute to the spontaneous control of HIV infection, we analyzed the phenotype and function of circulating Tfh (cTfh) in patients from the ANRS CO21 CODEX cohort who naturally controlled HIV-1

replication to undetectable levels (HIC group), and compared them to treated patients with similarly low viral loads (ART group).
Methods: HIV-specific cTfh (Tet+) were detected by Gag MHC-II tetramer labeling in the CD45RA- CXCR5+ CD4+ T cell population. The function of cTfh was analyzed by the capacity to promote IgG secretion in cocultures with autologous memory B cells.
Results: HIV-specific cTfh (Tet+) proved more frequent in the controller group than in the treated patient group (P=0.002). The frequency of PD-1 expression in Tet+ cTfh was increased in both groups (median >75%) compared to total cTfh (<30%), but the intensity of PD-1 expression per cell remained higher in the ART group (P=0.02), pointing to the persistence of abnormal immune activation in treated patients. The function of cTfh, analyzed in coculture with memory B cells, did not show major differences between groups in terms of total IgG production, but proved significantly more efficient in the controller group when measuring HIV-specific IgG production. The frequency of Tet+ cTfh correlated with HIV-specific IgG production (R=0.71 for Gag-specific and R=0.79 for Env-specific IgG, respectively).
Conclusion: Taken together, these findings indicate that key cTfh/B cell interactions are preserved in controlled HIV infection, resulting in potent memory B cell responses that may play an underappreciated role in HIV control.

226 INTERACTION OF HOST AND VIRAL GENOMICS ON HIV DISEASE PROGRESSION IN RAKAI UGANDA

Genevieve L. Wojcik[1], Michael A. Eller[2], David Serwadda[3], Kate Grabowski[4], Fred Wabwire-Mangen[3], Anthony Ndyanabo[5], Merlin L. Robb[2], Nelson L. Michael[2], Leigh Anne Eller[2], Ronald H. Gray[4], Thomas C. Quinn[6], Oliver Laeyendecker[6]
[1]Stanford University, Stanford, CA, USA, [2]Walter Reed Army Institute of Research, Silver Spring, MD, USA, [3]Makerere University, Kampala, Uganda, [4]The Johns Hopkins University, Baltimore, MD, USA, [5]Rakai Health Sciences Program, Kalisizo, Uganda, [6]NIAID, Baltimore, MD, USA

Background: Viral and host genetic factors have been associated with beneficial and detrimental impacts on HIV disease progression. We assessed the impact of host genetics, after controlling for viral factors on disease progression in a Ugandan population where subtypes A and D circulate. Previous studies in this population have demonstrated that subtype D is much more pathogenic than subtype A.
Methods: A total of 393 HIV seroconverters infected between 1997 and 2001 in Rakai Uganda were genotyped on Illumina's Multi-Ethnic Global Array (MEGA). HIV subtype data was generated using the multi region hybridization assay using probes specific for subtypes A, C and D. Viral load was assessed with Roche Amplicor version 1.5. Set point viral load was defined as the median viral load for all time points tested after the initial HIV positive visit and prior to AIDS. AIDS was defined as a CD4 count <250 cells/ul or WHO stage 4. Rapid HIV progressors were defined as AIDS or death within 4 years of infection. SNP associations with set point viral load and CD4 slope were evaluated with linear regression. Logistic regression was used to identify SNPs associated with rapid progression, controlling for HIV subtype and set point viral load. Proportional hazards regression was used to estimate hazard ratios of years to death or AIDS, adjusted for subtype. Analyses were restricted to variation in the Major Histocompatability Complex (MHC) class I and II regions and adjusted for age at infection and sex.
Results: The minor allele of rs2524119 was associated with decreased CD4 slope ($P=3.04x10^{-5}$; Beta=-9.3) and is located upstream of HLA-B and HLA-C. Set point viral load was associated with class I SNP variants rs60993483 ($P=6.68x10^{-5}$; Beta=-0.53) within HLA-H/HLA-G and rs1051488 ($P=5.88x10^{-5}$; Beta=-0.26). Rapid progression was associated with a HLA-B within rs551116093 (OR=2.49; $P=3.15x10^{-5}$). HLA-B (rs2524084; HR= 0.57; $P=3.75x10^{-4}$) was associated with years to death or AIDS among individuals with subtype D.
Conclusion: CD4 slope, set point viral load, rapid progression, and years to death or AIDS were found to be associated with MHC class I variants, highlighting the importance of human genetic variation in HIV pathogenesis, independent of other known viral and host factors.

227 FC DEPENDENT ANTI-HIV-SPECIFIC ANTIBODY FUNCTIONALITY DISTINGUISHES HIV CONTROLLERS

Sanket Kant[1], Franck P. Dupuy[1], Chris Leeks[1], Alexandre Barbe[1], Ningyu Zhang[1], Cindy X. Zhang[1], Jean-Pierre Routy[1], Petronela Ancuta[2], Cécile Tremblay[2], Nicole Bernard[1]
[1]Research Institute of McGill University Health Centre, Montreal, QC, Canada, [2]Centre de Research du Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada

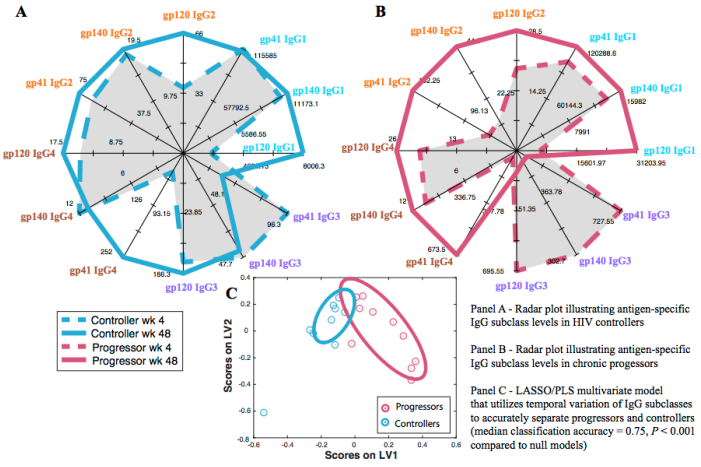
Background: Antibodies (Ab) bridge antigen expressing cells with Fc receptor (FcR)+ innate effector cells mediating multiple functions. Engagement of FcRs on monocytes triggers phagocytosis. Ab-antigen complexes can also initiate the complement (C') cascade. Elite Controllers (EC) are HIV infected individuals with viral loads (VL) <50 copies/ml plasma (c/mlp) without treatment. We hypothesized that if Fc-mediated functions play a role in HIV control, EC would differ from HIV+ untreated progressors (UTP, VL > 2000c/mlp), antiretroviral therapy (ART) treated individuals (TP, VL < 50c/mlp), and viremic controllers (VC, VL < 2000c/mlp) in terms of anti-HIV envelope (gp120)-specific IgG functionality. Here, we compared Ab-dependent (AD) complement deposition (ADCD) and AD cellular phagocytosis (ADCP) assays in these groups.
Methods: Plasma samples from 18 UTP, 24 TP, 36 EC and 16 VC were quantified for total IgG and anti-gp120-specific IgG concentrations by ELISA. The ADCD assay assessed the frequency of gp120-coated and HIV-infected CEM.NKr. CCR5 target cells (T) positive for the complement component C3b on their cell surface. The ADCP assay measured the phagocytosis of gp120-functionalized fluorescent beads by THP-1 (E) monocyte-like cells. Activity was measured as the area under the curve (AUC) of the ADCD and ADCP score (% fluorescent T/E x the mean fluorescence intensity (MFI) of T/E), respectively for 2 plasma IgG concentrations. Positive and negative controls for these assays were pooled plasma from HIV+ and HIV- individuals
Results: UTP and EC had significantly higher concentrations of anti-gp120 specific Ab than TP ($p<0.0001$, Kruskal-Wallis test with Dunn's post tests). ADCD and ADCP activity levels in plasma from UTP, EC and VC did not differ from each other significantly but was higher than in plasma from TP ($p<0.0001$ for all, Dunn's). When ADCD and ADCP results were normalized to the concentration of each sample's anti-gp120 Ab, between group differences disappeared.
Conclusion: The higher levels of ADCD and ADCP activity in plasma from EC, VC and UTP than in TP were due to differences in anti-gp120 specific Ab concentrations present in these samples and could not be attributed to between-group differences in the ability of the anti-gp120 specific Abs to support these functions. Future research should address how EC and VC maintain high concentrations of anti- gp120 specific Abs in a setting of HIV VL suppression.

228 TEMPORAL VARIATION OF IgG SUBCLASSES DIFFERENTIATES HIV CONTROLLERS AND PROGRESSORS

Jishnu Das[1], Saheli Sadanand[1], Amy Chung[2], Todd J. Suscovich[1], Hendrik Streeck[3], Davey M. Smith[4], Susan J. Little[4], Douglas Lauffenburger[5], Douglas D. Richman[4], Galit Alter[1]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]University of Melbourne, Melbourne, VIC, Australia, [3]Institute for HIV Research, Essen, Germany, [4]University of California San Diego, San Diego, CA, USA, [5]MIT, Cambridge, MA, USA

Background: Given the emerging appreciation for the role of antibody(Ab)-dependent effector functions and IgG subclass distributions among spontaneous controllers of HIV, we sought to examine whether Ab-associated features diverged in early HIV infection between subjects who ultimately became controllers versus those who became progressors.
Methods: IgG was purified from plasma from nine acutely infected subjects who subsequently controlled HIV spontaneously (controllers) and ten acutely infected individuals who did not control viremia (progressors). Ab profiles were compared at weeks 4, 12, 24 and 48 post-infection. Levels of clade B gp120-, gp140-and gp41-specific IgG Ab subclasses were measured. Additionally, gp120-specific Ab-dependent cellular phagocytosis (ADCP), cellular cytotoxicity (ADCC), cellular viral inhibition (ADCVI) and NK activation (ADNKA) were assessed.
Results: We found that no individual Ab-dependent effector function or subclass level at any timepoint was significantly associated with long-term HIV control. However, a multivariate LASSO/PLS model that used the overall temporal variation of Ab-associated variables, was able to accurately differentiate controllers and progressors (median classification accuracy measured in a 5-fold cross-validation framework = 0.75, $P < 0.001$ compared to null models). In contrast to controllers, progressors showed greater dynamic changes in gp120-specific subclass selection profiles, with increasing levels of Env-specific IgG2 Abs and losses in Env-specific IgG3 Abs. Moreover, progressors, but not controllers, lost ADCVI function over time. These results demonstrate that maintaining functional Abs such as IgG3, and not gaining less functional Abs, such as IgG2, together play a role in controlling viremia.

Conclusion: Our results suggest that comprehensive Ab profiling coupled with systems analyses, can accurately define humoral immune profiles that track with distinct clinical outcomes following acute HIV infection. Specifically, the maintenance of gp120-specific and gp140-specific IgG3 may contribute to control of disease in spontaneous controllers. Thus, strategies to induce stable IgG3 responses may preserve control of the viral reservoir. Further analyses of fine epitope specificities on the viral envelope of IgG3 and IgG2 Abs during acute infection, along with additional effector functional measurements, may shed light on specific targets and mechanisms of antiviral control.



229 ART REDUCES T CELL ACTIVATION AND IMMUNE EXHAUSTION MARKERS IN HIV CONTROLLERS

Jonathan Z. Li[1], Florencia P. Segal[1], Ronald Bosch[2], Christina Lalama[2], Randall Tressler[3], Cornelius N. Van Dam[4], Michael Keefer[5], Mary Carrington[6], Mathias Lichterfeld[1], Daniel R. Kuritzkes[1], Xu G. Yu[7], Alan Landay[8], Paul E. Sax[1]
[1]Brigham and Women's Hospital, Boston, MA, USA, [2]Harvard University, Boston, MA, USA, [3]NIAID, Bethesda, MD, USA, [4]University of North Carolina Greensboro, Greensboro, NC, USA, [5]University of Rochester, Rochester, NY, USA, [6]NIH, Frederick, MD, USA, [7]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [8]Rush University Medical Center, Chicago, IL, USA

Background: Despite low or undetectable plasma HIV RNA, many HIV controllers (HCs) have detectable viral replication and elevated systemic inflammation. We assessed the effect of ART on HIV suppression, viral reservoir, immune activation, markers of inflammation, and quality of life in HCs.
Methods: A5308 is a prospective, open-label study of RPV/FTC/TDF in ART-naive HCs with viral loads (VLs) <500 cp/mL for ≥12 months. After 48 weeks of ART, HCs had the option to be followed for an additional 48 weeks with optional ART. The primary outcome was the change in %CD38+HLA-DR+ CD8+ T cells after 24-48 weeks of ART. Outcomes were evaluated by repeated measures GEE models. Immune phenotyping was performed by flow cytometry. Soluble inflammatory markers were measured by ELISA. Residual viremia (RV) was measured by the integrase single-copy assay (iSCA); reservoir size by levels of total HIV DNA in CD4+ cells. Quality of life (QoL) was measured by the EQ-5D questionnaire.
Results: Thirty-five HCs completed ≥24 weeks of ART and were analyzed. Before ART, HCs with undetectable VL by the iSCA had higher CD4+ counts than those with detectable VL (median 1128 vs. 659 cells/mm^3, P=0.03) and lower levels of both CD8+ (median 19.4% vs. 26.5%, P=0.04) and CD4+ cell activation (2.3% vs. 2.9%, P=0.04). RPV/FTC/TDF was well tolerated, resulting in a modest, but significant improvement in self-reported QoL; two-thirds of HCs elected to continue ART through 96 weeks. ART was effective in further reducing RV: 81% of HCs had detectable RV pre-ART vs. 6% after 24-48 weeks of ART (P<0.001). ART use resulted in a significant decline in the %CD38+HLA-DR+CD8+ cells at 24-48 (-4.0%, P=0.001) and 72-96 (-7.2%, P<0.001) weeks after ART initiation. After ART initiation, several markers of immune exhaustion (%PD1+, %TIGIT+, %CD160+ on CD8+ cells and %CD160 on CD4+ cells) declined. ART use decreased IP-10 levels, but increased levels of sCD163. There were no significant changes in the CD4+ counts or levels of total HIV DNA. Four HCs discontinued ART with ≥10 weeks of subsequent follow-up. All 4 HCs maintained VL<40 copies/mL at the last study time point, a median of 26 weeks after stopping ART.
Conclusion: One year of ART reduced T cell activation and markers of immune exhaustion in HIV controllers, in some cases with further decreases after two years of ART. ART was well tolerated and did not adversely affect controller status when discontinued. These results provide additional support for ART in HIV controllers.

230 EFFICIENT ANTIBODY PROFILE IN HLA-B*57+ HIV CONTROLLERS

Jéromine Klingler[1], Angeline Rouers[2], Géraldine Laumond[1], Sylvie Schmidt[1], Camille Ducloy[1], Luzia Mayr[1], Thomas Decoville[1], Nathalie Salomé[1], Assia Samri[2], Veronique Avettand-Fenoel[3], Faroudy Boufassa[4], Christine Rouzioux[3], Olivier Lambotte[4], Arnaud Moris[2], Christiane Moog[1]
[1]INSERM, Strasbourg, France, [2]INSERM, Paris, France, [3]AP–HP, Paris, France, [4]INSERM, Le Kremlin-Bicetre, France

Background: Current HIV vaccination strategies strive to induce anti-HIV antibodies (Abs), several types of which are of interest. Among them, neutralizing Abs (NAbs) are able to protect macaques against experimental infection but are difficult to induce by vaccination. HIV Controllers (HIC; undetectable viral load without treatment) constitute an interesting cohort for the analysis of their Ab profile. Indeed, IgG1s and IgG3s polyfunctional activities and anti-gp41 IgG2s induction were associated with HIV control and slower disease progression. Recently, the frequency of HIV-Env-specific memory B cells has been correlated with the neutralization breadth in HIC patients positive for the HLA-B*57 protective allele. These data suggest that a specific Ab profile might have been induced in HIC patients, participating in the control of HIV.
Methods: Our study aims to characterize the isotypes and functional responses of Abs induced in sera of 37 HIC (separated in 2 groups: HLA-B*57+ or HLA-B*57-), comparing to 21 chronic progressors (evolving to disease). We analyzed the distribution of isotypes in the different cohorts by ELISA and the neutralization activities by TZM-bl neutralization assays. The correlation between the detection of anti-HIV Abs and functional activities was analyzed by a Spearman rank correlation.
Results: We found no differences in the induction of anti-HIV IgAs between HIC and chronic progressors, whilst chronic progressors induce more anti-HIV IgGs and anti-HIV-IgG2s than HIC. On the contrary, HIC patients induce higher proportions of anti-HIV IgG3s. Noteworthy, HIC patients display neutralizing activities against several HIV strains including transmitted/founder viruses, despite the presence of low antigen detection. Remarkably, these neutralizing activities positively correlate with IgG subtypes detection in the subgroup of HLA-B*57+ HIC, but not in HLA-B*57- HIC or chronic progressors.
Conclusion: These results demonstrate that HIC patients display an unexpected Ab isotype profile. The detection of anti-HIV Abs is associated with neutralizing activity in HLA B*57+ HIC, suggesting that neutralization may contribute to HIV control in this subgroup of patients. Conversely, the absence of correlation between Ab profile and neutralization in HLA B*57- HIC further suggest that additional Ab functions may be involved. An in-depth characterization of the Ab profile will guide the design of new immunogens for a future vaccine.

231 THE CHAMP COHORT: POST-TREATMENT CONTROLLERS IDENTIFIED FROM 9 CLINICAL STUDIES

Golnaz Namazi[1], Jesse Fajnzylber[1], Evgenia Aga[2], Ronald Bosch[2], Edward P. Acosta[3], Jeffrey Jacobson[4], Paul Volberding[5], Daniel Skiest[6], Ronald T. Mitsuyasu[7], Robert T. Schooley[8], Ann Collier[9], Jean-Pierre Routy[10], Bruce D. Walker[11], Jonathan Z. Li[1]
[1]Brigham and Women's Hospital, Boston, MA, USA, [2]Harvard University, Cambridge, MA, USA, [3]University of Alabama at Birmingham, Birmingham, AL, USA, [4]Temple University, Philadelphia, PA, USA, [5]University of California San Francisco, San Francisco, CA, USA, [6]Tufts University, Boston, MA, USA, [7]University of California Los Angeles, Los Angeles, CA, USA, [8]University of California San Diego, La Jolla, CA, USA, [9]University of Washington, Seattle, WA, USA, [10]McGill University, Montreal, QC, Canada, [11]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

Background: HIV post-treatment controllers (PTCs) are rare individuals who exhibit sustained HIV remission after treatment interruption (TI). A concerted international effort is needed to identify PTCs given their scarcity at any given research center or clinical trial. We describe PTCs identified from 9 clinical trials and cohorts as part of the Control of HIV after Antiretroviral Medication Pause (CHAMP) cohort. Understanding the incidence of PTC and their post-TI viral dynamics may provide mechanistic insights and has implications for the design of trials aimed at achieving HIV remission.

Methods: PTCs were identified from the AIDS Clinical Trials Group (ACTG) studies, the Montreal Primary HIV Infection cohort, the Seattle Primary Infection Program, and the Ragon HIV Controllers cohort. PTCs were defined as individuals who underwent TI and maintained VLs ≤400 copies/mL at ≥2/3 of the time points for at least 24 weeks. Viral load and CD4+ dynamics were compared between PTCs and post-treatment non-controllers (NCs) from ACTG TI trials who received no immunologic intervention and exhibited loss of viral control post-TI.
Results: A total of 58 PTCs were identified. PTCs were more commonly identified in those treated during early infection compared to those treated during chronic infection (11.6% vs. 4.4%, Fishers exact P=0.006). The median duration of documented viral control for the PTCs was 96 weeks. For participants treated during early infection, there was no significant difference between the highest reported pre-ART VL for the PTCs vs. NCs (median 4.6 vs. 4.7 $\log_{10}$ copies/mL). Over 24 weeks of TI, CD4+ counts were generally preserved in PTCs, but declined significantly in NCs (median +4 vs. -200 CD4+ cells/mm^3, P<0.001). A VL ≥1000 copies/mL within the first 24 weeks was commonly seen in the PTCs: 24% of PTCs had a peak post-TI VL of 1000-9,999 copies/mL and 10% of PTCs had a peak VL ≥10,000 copies/mL. In those with post-TI VL peak ≥1000 copies, the median VL decline was 1.0 $\log_{10}$ over the subsequent 2 weeks (range 7-15 days).
Conclusion: PTCs were more frequently identified in those treated during early HIV infection and post-treatment control was associated with preserved CD4+ counts over the first 24 weeks. TI trials that restart ART at the 1,000 copy/mL VL threshold will miss 1/3 of PTCs, while trials that use a 10,000 copy/mL threshold will miss 10% of PTCs. Even in PTCs with peak post-TI VLs ≥1000 copies/mL, viral control was achieved relatively rapidly.

232LB TARGETING HIGHLY NETWORKED CTL EPITOPES AS A MECHANISM OF ELITE HIV-1 CONTROL

Gaurav D. Gaiha[1], Elizabeth Rossin[2], Christian Landeros[1], Itai Muzhingi[1], Chioma A. Nwonu[1], Bruce D. Walker[1]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Broad Institute of MIT and Harvard, Cambridge, MA, USA

Background: Evaluation of cytotoxic T lymphocyte (CTL) epitopes by sequence-based methods such as amino acid (AA) conservation has not yielded a specific set of targets that confer elite HIV-1 control, in large part due to the lack of evidence linking sequence conservation to viral fitness cost. As a result, it has been challenging to leverage insights from elite controllers to generate a rationally designed T cell-based vaccine for the population at-large. In this study, we utilized a new approach - known as structure-based network analysis (SNA) - that systematically evaluates protein structure to define residues of structural and functional importance. Our hypothesis is that highly networked AAs identified by SNA would incur a viral fitness cost if mutated, and also be enriched in CTL epitopes targeted by elite controllers.
Methods: Relying on structural data rather than sequence data, SNA builds networks of non-covalent interactions between AA side chains, and quantifies the sum contribution of each residue to the protein's global structure assigned as an AA network score. Applying this approach to all available crystal structures for HIV-1 allowed us to quantitate network scores for 71% of the entire HIV proteome and 86% of reported optimal CTL epitopes.
Results: Correlation of network scores with viral sequence entropy values revealed a strong negative association (P<0.001), but also identified multiple sequence conserved residues that were poorly networked. In vitro mutagenesis of conserved residues with high and low network scores revealed a differential mutational sensitivity (P<0.0001), with only disruption of highly networked residues leading to impaired HIV infectivity. Assessment of proliferative CTL responses in 134 HIV+ individuals also revealed a strong enrichment of highly networked residues in epitopes targeted by persons who spontaneously control HIV (P<0.001). Moreover, plasma viral sequencing revealed markedly reduced mutation rates specifically in highly networked epitopes, despite robust CTL targeting. Importantly, networked epitopes identified by SNA were found in both controller (e.g. B*5701) and non-controller HLA alleles.
Conclusion: These findings demonstrate the superior ability of SNA to define fitness-constrained residues and implicate targeting highly networked epitopes by CTLs as a putative mechanism of immune control across diverse HLA. Application of this approach provides a rational framework for the design of a broadly applicable T cell-based vaccine for HIV-1.

233LB WOUND HEALING MECHANISMS REQUIRED IN PATHOGENESIS CONTROL OF SIV IN NATURAL HOST

Fredrik Barrenas[1], Kevin D. Raehtz[2], Lynn Law[3], Richard Green[3], Guido Silvestri[4], Steven E. Bosinger[4], Qingsheng Li[5], Matthew Thomas[3], Jean Chang[3], Elise Smith[3], Reem A. Dawoud[4], Cristian Apetrei[2], Ivona Pandrea[2], Michael Gale[3]
[1]Uppsala University, Uppsala, Sweden, [2]University of Pittsburgh, Pittsburgh, PA, USA, [3]University of Washington, Seattle, WA, USA, [4]Emory University, Atlanta, GA, USA, [5]University of Nebraska–Lincoln, Lincoln, NE, USA

Background: Protracted inflammation is a primary driver of HIV pathogenesis. Several African non-human primates (NHPs) remarkably avoid AIDS despite lifelong infection with SIV, and mucosal CD4+ cell depletion. Comparative pathogenesis studies between natural SIV hosts and AIDS-susceptible NHP species can reveal disease mechanisms and treatment targets. Also, NHP studies enable close examination of the first virus-host interactions, showing how the natural and pathogenic host responses diverge.
Methods: We devised a systems biology approach to investigate the early host response to high-dose rectal SIV transmission, by transcriptomic comparative analysis of a natural reservoir host SIV model species, African green monkeys (AGMs – Chlorocebus sabaeus, N=28) and a pathogenic model, rhesus macaques (RMs - Macaca mulatta, N=24). Serial necropsies were performed at time points as early as one-day post-infection, and RNA-Seq was performed on rectal tissues for both AGMs and RMs.
Results: To explore diverse aspects of acute SIV infection, we created a functionally annotated co-expression network. Innate immune response, representing an early response to SIV infection, were activated earlier in the AGMs, and closely associated with induction and response to type I and III interferons. By contrast, the RM response included general immune activation, including anti-bacterial, LPS-driven responses. The AGM response was concomitant with rapid activation of wound healing processes and epithelial remodeling. RMs, by contrast, activate the inflammatory stage response to wounding, but lack tissue remodeling gene activation. This response included a significant TGF-β signature. IHC confirmed preserved expression of epithelial wound healing protein FN in AGMs, but not RMs. Using RNA-Seq, we found overexpression of several key regulators of wound healing in sorted monocytes from AGMs, compared to RMs. This overexpression was present before SIV challenge, suggesting that natural hosts are constitutively poised to resist SIV pathogenesis.
Conclusion: These results show that the response to SIV infection in natural and pathogenic host organisms diverge during the early acute stage. Natural hosts activate antiviral immune responses that favor wound healing, and avoid tissue damage from excessive inflammation.

234 PERSISTENT DYSREGULATION OF HIV-SPECIFIC T FOLLICULAR HELPER CELLS DURING ART

Julia Niessl[1], Amy E. Baxter[1], Antigoni Morou[1], Elsa Brunet-Ratnasingham[1], Madelene Lindqvist[2], Parsia A. Vagefi[3], Eileen P. Scully[2], Jean-Pierre Routy[4], Daniel E. Kaufmann[1]
[1]Université de Montréal, Montreal, QC, Canada, [2]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [3]Massachusetts General Hospital, Boston, MA, USA, [4]McGill University, Montreal, QC, Canada

Background: Germinal center follicular T helper cells (GC Tfh) provide B cell help to support high affinity antibody responses. HIV infection leads to impairment of GC Tfh and their circulating counterpart (circulating Tfh, cTfh) contributing to inefficient humoral response to HIV. Tfh impairment persists in HIV-infected subjects on antiretroviral therapy (ART) despite viral control. Due to technical limitations in assessing antigen (Ag)-specific Tfh, previous studies on mechanisms of Tfh impairment have been restricted to bulk Tfh. Therefore, it remains unclear if this Tfh dysfunction is HIV-specific or reflects a global dysregulation of the Tfh compartment.
Methods: Here, we used co-expression of the surface activation-induced markers CD40L and CD69 after Ag stimulation to identify HIV-specific CD4 independently of their functional profile. We studied blood of HIV+ subjects on ART and compared phenotype and function of the CD4 responses specific to HIV Ags (Gag, Env, Nef) to those specific for another chronic but controlled virus (CMV) and to responses to a resolved infection or vaccine (HBV) within the same donors.
Results: We observed a preferential expansion of cTfh within HIV-specific CD4 responses when compared to CMV and HBV. In contrast to non-cTfh cells and to all other Ags tested, Gag-specific cTfh exhibited an increased CXCR3+ Th1-like

polarization. Gag-specific CD4, but particularly cTfh, were characterized by high expression of multiple co-inhibitory receptors. Longitudinal samples collected before and after ART initiation revealed that this dysregulated phenotype was established during the untreated phase of infection and persisted despite subsequent viral control. More Gag-specific cTfh produced Tfh- (CXCL13, IL-21) and, surprisingly, Th1-cytokines (IL-2, IFNγ, TNFα) after Ag stimulation compared to CMV, suggesting a functionally dysregulated profile. Importantly, this increased production of cytokines by cTfh was mirrored by the functional profile of GC Tfh, as observed in surgical lymph node (LN) biopsies.
Conclusion: Our results thus reveal that in contrast to cTfh responses to other viruses in the same subjects, HIV-specific cTfh show a persistently expanded and activated phenotype in HIV+ subjects on ART. This might reflect a functional hyperactivity of GC Tfh in the LN that has been associated with aberrant B cell responses. These permanent alterations may contribute to lack of restoration of effective HIV-specific immunity despite prolonged ART, and complicate HIV cure efforts.

235 NEUTROPHIL DYNAMICS IN SIV-INFECTED PIGTAILED MACAQUES BEFORE AND AFTER ART

Egidio Brocca-Cofano[1], Tianyu He[1], Ranjit Sivanandham[1], Benjamin Policicchio[1], Paola Sette[1], Tammy Dunsmore[1], George S. Haret-Richter[1], Alan Landay[2], Cristian Apetrei[1], Ivona Pandrea[1]
[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]Rush University Medical Center, Chicago, IL, USA

Background: Neutrophils are important effectors of innate immunity. They are rapidly mobilized at the site of infection and fight pathogens through phagocytosis, killing of the infected cells or activation of adaptive immune cells. The interaction between platelet and neutrophils is critical for the neutrophil chemotaxis and function at the inflammation sites. During HIV infection, neutrophil counts and function are impaired, which may lead to the increased rates of opportunistic infection. We investigated the dynamics, proliferation, apoptosis and function of neutrophils in a highly pathogenic SIV infection and the impact of antiretroviral treatment (ART) on these parameters.
Methods: Seventeen pigtail macaques were included. All animal were infected intravenously with 300TCID50 of SIV. After 42 days, all animals received a triple coformulated antiretroviral therapy (ART) containing tenofovir, emtricitabine and dolutegravir (PMPA+FTC+DTG). Neutrophil absolute counts, apoptosis and proliferation were assessed by flow cytometry. T assess phagocytosis and respiratory burst activity, functional assays were performed, measuring PARs and TF expression on neutrophils after LPS and thrombin stimulation. Cytokines secreted by neutrophils post-PMA stimulation were measured by Luminex.
Results: SIV infection induced a significant loss of circulating neutrophils. After ART, neutrophil numbers were partially recovered, but did not reach the baseline levels. High postinfection levels of apoptosis of neutrophils, which persisted post–ART, may be the factor behind neutrophil loss. Significant increases of neutrophil proliferation (Ki-67) occurred early in SIV infection. During late infection, proliferation decreased below the baseline, suggesting a loss of neutrophil replicative capacity. SIV infection significantly decreased phagocytosis and respiratory bust of neutrophils and ART does not provide any short- or long-term benefit. PAR-1 and TF expression on neutrophils increased after LPS stimulation. A clear decrease of neutrophil capacity to secrete cytokines was observed. ART only partially improved neutrophil function.
Conclusion: Significant decrease of neutrophil counts and function occur in SIV infection, and are not restored by ART. Phagocytosis and respiratory burst alterations, together with LPS-dependent increases of PARs and TF may contribute to the tissue damage and coagulation abnormalities observed during SIV infection.

236 CHARACTERIZATION OF FDC-BOUND VIRAL PRODUCTS DURING HIV/SIV INFECTION

Matthew Bronnimann[1], **Joy M. Folkvord**[1], Pamela Skinner[2], Eva Rakasz[3], Elizabeth Connick[1]
[1]University of Arizona, Tucson, AZ, USA, [2]University of Minnesota, Minneapolis, MN, USA, [3]University of Wisconsin, Madison, WI, USA

Background: During chronic HIV/SIV infection, the B-cell follicle is a major site of virus replication, and large numbers of infectious viral particles accumulate on follicular dendritic cells (FDCs) in the form of immune complexes (ICs). Despite the importance of the B-cell follicle in HIV/SIV persistence, the establishment and composition of FDC-bound HIV/SIV ICs remains poorly characterized. In this study we analyzed FDC-bound viral products during HIV/SIV infection.
Methods: Formalin fixed paraffin embedded (FFPE) lymph nodes (LNs) from acutely infected (7 dpi) and chronically infected (Non SAIDS, 69-118dpi) rhesus macaques or chronically HIV-infected humans were evaluated. Rhesus macaque tissue sections were stained with antibodies to CD20 (B-cells) and smooth muscle myosin heavy chain (FDC networks) and combined with in situ hybridization for SIV RNA (RNAScope ACD). For Human/HIV studies, 1-2 sections of FFPE or snap frozen LNs and tonsils from chronically infected untreated and healthy participants were evaluated. FFPE sections were analyzed for HIV RNA (RNAscope) and snap frozen sections were stained with antibodies to IgD (rings FDCs) and Nef. Imagescope (Leica) was used for quantification. FDC-bound SIV RNA was quantified by positive pixel counts on FDC networks with RNA+ cells excluded. Data were analyzed using Mann-Whitney tests and Spearmen coefficients (r).
Results: The percent LN comprised of FDC networks tended to be larger in chronic (n=8) compared to acute (n=6) SIV infection (p=0.08; medians, acute=5.24% chronic=18.73%). FDC-bound SIV RNA was not observed during acute infection, but was detected in all chronic infections. The size of the FDC-bound RNA reservoir strongly correlated with plasma SIV load in chronic infection (r=0.857, p=0.01). In chronic HIV infection, FDC-bound HIV RNA was detected in all LNs tested. Additionally, HIV-Nef+ staining was evident on FDC networks in most LNs (6/8) and tonsils (1/1), but was absent in healthy controls.
Conclusion: No FDC-bound SIV RNA is established during the first 7 days of acute SIV infection despite high viral loads, consistent with the notion that antibodies are necessary for the establishment of this reservoir. The strong relationship between FDC-bound RNA and plasma viral load suggests that they are in equilibrium with each other. Because Nef is a known immune-modulator, the accumulation of Nef on FDC networks may contribute to dysfunction of Tfh and other follicular cell subsets.

237 HIV-2 IMPACT ON LYMPHOID ORGANS: EVIDENCE OF VIRAL REPLICATION AND TISSUE DISRUPTION

Ana Antão, Ana Pires, Cristina Ferreira, Helena Nunes-Cabaço, Sandra Mauricio, Cheila Rocha, Paula Matoso, Rui M. Victorino, Susana M. Fernandes, **Ana E. Sousa**
Universidade de Lisboa, Lisbon, Portugal

Background: The ability of HIV to replicate in secondary lymphoid organs (SLO) and disrupt lymph node (LN) architecture are considered main determinants of disease progression. HIV-2+ individuals feature slow rate of CD4 T cell decline and AIDS progression, maintain low to undetectable viremia in the presence of disseminated viral reservoirs, and high titers of broadly neutralizing antibodies throughout the disease course. Thus, this naturally-occurring attenuated infection provides a unique setting to investigate HIV-host interplay in SLO that has been poorly explored.
Methods: We conducted a parallel study of 1) archived LN from HIV-2+, HIV-1+ and seronegative individuals using immunochemistry, and 2) in vitro infection of tonsil organ cultures (TOCs) with HIV-2 and HIV-1 primary isolates with different co-receptor usage.
Results: HIV-2+ individuals featured very different CD4 T cell counts at the time of lymph node collection (744, 444, 255 and 73 cells/μl), but in all of them we could find viral replication, as assessed by p27 staining. Using the in vitro model we further confirmed comparable levels of HIV-2 and HIV-1 replication in terms of proviral DNA and gag mRNA levels, although the amount of cells producing virus (KC57+) were significantly lower in HIV-2 X4 than in HIV-1 X4 isolates. Moreover, the pattern of viral impact on the cellular populations was remarkably reproducible between TOCs, with a preferential depletion of follicular CD4 T cells (TFH), particularly upon infection with HIV-2 X4. Interestingly follicular regulatory CD4 T cells (TFR) were less depleted and CXCR5+CD8+ T cells were maintained. Importantly, LN from HIV-2+ patients featured a progressive CD4 T cell depletion in agreement with blood CD4 T cell decline, which was more marked than in the 12 HIV-1+ LN evaluated. Of note, FOXP3+ and CD8 T cells were preserved in non-germinal center areas. Regarding LN architecture, we found significant collagen deposition with reticulin network disruption, even in early stage HIV-2+ individuals, as compared to both seronegatives (n=8) and HIV-1+. Additionally, HIV-2+ LN featured less hyperplasic germinal centres than HIV-1+ LN, but their morphology were more disrupted.

Conclusion: Altogether, our data support continuous viral replication in SLO and an altered germinal center organization in HIV-2 infection. Their contribution to the benign HIV-2 course deserves further investigation that may reveal new strategies to control HIV reservoirs.

238 CD163+ LYMPH NODE MACROPHAGES ARE CORRELATED WITH LYMPH NODE FIBROSIS IN CHRONIC HIV

Brooks I. Mitchell[1], Fredrick Yost[1], Glen M. Chew[1], Michelle L. D'Antoni[1], Ashley Marumoto[1], Jodi Anderson[2], Caitlin David[2], Nancy Hanks[1], Dominic Chow[1], Timothy Schacker[2], Lishomwa C. Ndhlovu[1], Cecilia Shikuma[1]
[1]University of Hawaii at Manoa, Honolulu, HI, USA, [2]University of Minnesota, Minneapolis, MN, USA

Background: Despite being on effective antiretroviral therapy (ART), many HIV-infected individuals have impaired reconstitution of CD4 T cells. This is partly due to the fibrosis of lymphoid tissues (LT), which impedes signals important for T cell homeostasis. Macrophages (Mφ) are key regulators of tissue remodeling and fibrosis, though their involvement in LT fibrosis during chronic HIV has yet to be defined.

Methods: Inguinal lymph node (LN) excisions were performed by a board-certified surgeon on 6 virally-suppressed HIV-infected participants on ART and 4 HIV-uninfected participants recruited at the University Clinics at Kaka'ako at the John A. Burns School of Medicine. Immediately after excision, LN was divided into portions used for quantification of CD206+, CD163+, and CD169+ LN Mφ populations by multi-parametric flow cytometry and quantification of collagen fibers and CD4 T cells by IHC. Soluble markers of Mφ activation, fibrosis, and immune checkpoints were measured in cryopreserved plasma using ELISAs and Luminex. Statistical analyses performed were T-tests and Pearson correlations.

Results: HIV-infected participants were older than those uninfected (median age: 59 years vs. 51; p=0.036). All participants were male and Caucasian, with no significant differences between groups. All HIV-infected participants were virally suppressed with a median current CD4 count of 538 cells/µl, nadir CD4 count of 65 cells/µl, and CD4 CD8 T cell ratio of 0.66. HIV-infected participants had higher frequencies of CD206+, CD169+, and CD163+ LN Mφ as compared to HIV-uninfected (CD206+: 0.27 vs. 0.13, p=0.087; CD169+: 0.56 vs. 0.31, p=0.136; CD163+: 0.047 vs. 0.017, p=0.286). CD163+ LN Mφ correlated with lower CD4 counts in blood (r=-0.827, p=0.042) and LN (r=-0.553, p=0.097), as well as lower CD4 CD8 T cell ratios (r=-0.833, p=0.039). CD163+ LN Mφ correlated with more collagen fibrils in LN (r=0.694, p=0.026) and higher plasma levels of fibrosis biomarkers: TGF-β1, r=805, p=0.005; TSP-1, r=0.740, p=0.014; and CICP, r=0.633, p=0.049. CD163+ LN Mφ correlated with higher plasma levels of soluble immune checkpoint receptors (sCTLA-4, r=0.767, p=0.010; sPD-1, r=0.713, p=0.021) and markers of Mφ activation (sCD163, r=0.867, p=0.001; Neopterin, r=0.736, p=0.015).

Conclusion: CD163+ LN Mφ are elevated in ART-treated chronic HIV infection and correlates with limited CD4 T cell reconstitution in blood and LN. CD163+ LN Mφ may play a role in the pathogenesis of LT fibrosis and warrants further study.

239 GUT HOMING DEFECTS AND EXHAUSTION OF BLOOD TH17 AND TH1 CELLS IN HIV INFECTION

Stephanie Dillon[1], Allison J. Christians[1], Kejun Guo[1], Gregory Austin[1], Alan Landay[2], Mario Santiago[1], Cara Wilson[1]
[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [2]Rush University Medical Center, Chicago, IL, USA

Background: HIV infection and depletion of CD4 T helper (Th) cells in gut mucosal tissue are associated with microbial translocation and inflammation. We previously reported more significant depletion of Th17 than Th1 subsets in colon tissue in untreated HIV infection. Altered gut-homing by blood Th cells may be a contributing factor to overall gut Th cell depletion. Here, we investigated the gut-homing potential, activation and exhaustion states of peripheral blood CCR6+ Th17 and CXCR3+ Th1 cells and determined the colonic gene expression of specific chemokines that drive gut Th17 and Th1 homing (CCR6:CCL20; CXCR3:CXCL10).

Methods: Stored PBMC and colon biopsies from 16 untreated, chronic HIV-1-infected study participants (HIV+; median plasma viral load: 66,600 HIV-1 RNA/ml; median CD4 count: 410 cells/µl) and 13 uninfected controls (HIV-) from our previous clinical study (PMID: 24399150) were analyzed with consent. Flow cytometry was used to measure α4+β7+ (gut-homing), CD38+HLA-DR+ (activation) and PD1 expression (exhaustion) of blood CCR6+CCR4+CXCR3- (Th17) and CCR6-CCR4-CXCR3+ (Th1) memory (CD45RA-) CD4 T cells. CCL20 and CXCL10 transcript levels were evaluated in colon tissue by RNAseq. Measures of microbial translocation (plasma bacterial LPS and LTA) were performed as part of our previous study. Non-parametric tests were undertaken.

Results: Expression of α4+β7+ was higher on Th17 (p=0.01) and lower on Th1 (P=0.03) cells in HIV+ persons compared to HIV- persons. Colonic gene expression of CXCL10 was significantly higher (P=0.01) and CCL20 trended lower (P=0.1) in HIV+ versus HIV- persons. Expression of CD38+HLA-DR+ and PD1 were significantly higher on Th17 and Th1 cells in HIV+ persons (all P<0.0001). Th17 activation and exhaustion expression inversely correlated with CD4 count (R=-0.68, P=0.005; R=-0.58, P=0.02 respectively), whereas Th1 activation and exhaustion did not. Exhausted Th17 positively correlated with LPS (R=0.59, P=0.02) and LTA (R=0.64, P=0.01) and exhausted Th1 with LTA (R=0.63, P=0.01).

Conclusion: Gut-homing profiles were altered on blood Th17 and Th1 cells during untreated HIV-1 infection and may result from dysregulated colonic tissue expression of chemokines necessary for their homing. Blood Th17 and Th1 cells displayed features of increased activation and exhaustion that associated with indicators of disease progression and microbial translocation.

240 VARIOUS SUBSETS OF CCR6+ CD4+ T CELLS ARE DIFFERENTIALLY TARGETED BY HIV-1 IN THE GUT

Manon Nayrac[1], Mary Requena[1], Claire Loiseau[1], Fatima L'Faqihi[1], Michelle Cazabat[1], Nicolas Carrere[2], Bertrand Suc[2], Jacques Izopet[1], Pierre Delobel[1]
[1]INSERM, Toulouse, France, [2]CHU de Toulouse, Toulouse, France

Background: HIV-1 persistence in reservoirs under combined antiretroviral therapy precludes virus eradication. HIV-1 DNA levels are higher in gut than in peripheral blood CD4+ T cells of treated HIV-1-infected subjects, suggesting a role for gut CD4+ T cells in HIV-1 persistence. CCR6+ CD4+ T cells are the main mucosal target cells for HIV-1, however, the susceptibility of the various subsets of CCR6+ CD4+ T cells to HIV-1 in the gut mucosal microenvironment remains unknown.

Methods: An ex vivo model of human intestinal mucosa histocultures was used to explore the susceptibility of the various subsets of CCR6+ CD4+ T cells to HIV-1 in intestinal tisue. Small bowel biopsies from healthy subjects were cultured on gelatin sponges and infected by HIV-1 (BaL). At day 5 post-infection, mucosal mononuclear cells were isolated from the mucosal tissue. The phenotype of the CCR6+ cell subsets was characterized by flow cytometry (BD FORTESSA). Mucosal mononuclear cells were sorted by flow cytometry (BD ARIA SORP) in Th17, Th1Th17, and Th22 subsets. Total HIV-1 DNA was quantified in the sorted cells by qPCR (Biocentric; Light cycler 480 Roche). Experiments were repeated on intestinal tissue from five different donors.

Results: All CCR6+ CD4+ T cell subsets express high levels of CCR5 and α4β7 integrin. Most Th1Th17 cells express CCR9 whereas only a few Th17 and Th22 cells did so. Th1Th17 cells (CXCR3+CCR4-CCR6+CD161+), Th17 cells (CXCR3-CCR4+CCR6+CD161+), and Th22 cells (CXCR3-CCR4+CCR6+CD161-CCR10+) were sorted by FACS from mucosal mononuclear cells obtained from infected intestinal histocultures and HIV-1 DNA was quantified in the sorted cells. Gut Th1Th17 cells harbored 12-fold higher levels of HIV-1 DNA than Th17 cells, and 2-fold higher levels of HIV-1 DNA than Th22 cells. Thus Th1Th17 cells appear to be the most susceptible target for HIV-1 among the CCR6+ CD4+ T cell subsets in the gut mucosa.

Conclusion: In the gut microenvironment, the various subsets of CCR6+ CD4+ T cells are differentially targeted by HIV-1. Th1Th17 cells appear more susceptible to HIV-1 infection by an R5 strain than the other CCR6+ cell subsets. Differences in the transcriptional profile of the various CCR6+ subsets could account for their degree of permissivity to HIV-1 infection.

241 SHIV/SIV INFECTION PROMOTES CD8 T CELL VASCULAR INFILTRATION BY CX3CL1 AND IL-15

Bonnie Chen[1], Soumya Panigrahi[1], Jonathan Wyrick[1], Stephen R. Morris[2], Scott F Sieg[1], Nicholas Funderburg[3], David A. Zidar[1], Mirko Paiardini[4], Francois Villinger[5], Souheil A Younes[1], Michael M. Lederman[1], Michael L. Freeman[1]
[1]Case Western Reserve University, Cleveland, OH, USA, [2]Louis Stokes Cleveland VA Medical Center, Cleveland, OH, USA, [3]The Ohio State University, Columbus, OH, USA, [4]Yerkes National Primate Research Center, Atlanta, GA, USA, [5]University of Louisiana at Lafayette, Lafayette, LA, USA

Background: Despite antiretroviral treatment (ART), individuals living with HIV maintain a higher cardiovascular risk than healthy populations, including an increased prevalence of atherosclerosis. Recently, we have shown that aortas

from SIV/SHIV-infected Rhesus macaques (RM) exhibit increased endothelial dysfunction and infiltration of CD8 T cells, and that there is an expansion of activated CD8 T cells that express the vascular endothelium-homing fractalkine receptor CX3CR1 in ART-treated HIV infection. Here we measured IL-15 and fractalkine (CX3CL1) in the aortic endothelium of SIV/SHIV-infected RM and hypothesize that endothelial-T cell interactions promote the activation and trafficking of CD8 T cells to sites of endothelial cell (EC) dysfunction.
Methods: Paraffin embedded descending thoracic aortas from 17 SHIVSF162P3 or SIVmac239 infected and 17 uninfected RM were used for immunofluorescence staining for CX3CL1 or IL-15 and imaged by epifluorescent microscopy. Expression of CX3CL1 and IL-15 was measured in primary human aortic ECs and supernatant by imaging, real-time PCR, and ELISA. Chemotaxis of purified T cells across 3µm collagen-coated transwells was assessed. Purified T cells were treated with recombinant IL-15 (20ng/ml) for 2 or 7 days and analyzed by flow cytometry.
Results: ECs exhibited gene expression, surface localization, and secretion of both CX3CL1 and IL-15 in vitro. CX3CL1 (P=0.005) and IL-15 (P=0.045) expression was significantly increased in the aortic endothelium of RM when compared to levels among uninfected control aortas. CD8 T cells showed increased migration through the transwell membrane toward cultured ECs compared to medium control. IL-15 increased T cell expression of the cytolytic molecules granzyme B and perforin (P=0.039) and also increased surface expression of the tissue-residence receptor CD69 (P=0.016) on CX3CR1+ CD8 T cells (n=8). IL-15 also increased both the percentage of CD8 T cells expressing CX3CR1 (P=0.01) and CX3CR1 density (P=0.002).
Conclusion: Here we show elevated expression of CX3CL1 and IL-15 in SIV/SHIV-infected rhesus vascular endothelium. We demonstrated that ECs can produce CX3CL1 and IL-15 in vitro and enhance CD8 T cell migration. IL-15 promotes cytolytic potential of CD8 T cells and increases their expression of CX3CR1, suggesting that in the setting of HIV infection, an altered endothelium tethers, activates and promotes tissue retention of CD8 T cells that can contribute to vascular dysfunction and damage.

242 SMOKING INHIBITS HIV-1 INDUCED CD8+ T CELL INFILTRATION INTO THE ALVEOLAR SPACE

Bjorn Corleis[1], Josalyn Cho[2], Samantha J. Gates[1], Antonella C. Lisanti[1], Puja Kohli[2], Amy K. Dickey[1], Abigail Schiff[1], Scott R. Harris[2], Benjamin Medoff[2], Douglas Kwon[1]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Massachusetts General Hospital, Boston, MA, USA
Background: HIV-1 infection results in inflammation in the lung and a CD8+ T cell alveolitis. This inflammation is only partially reversed by antiretroviral therapy (ART) and is thought to contribute to an increased risk of chronic obstructive pulmonary disease (COPD) in those living with HIV. Smoking is the single greatest risk factor for development of COPD and is closely associated with CD8+ T cell accumulation in lung tissue. Although 70% of HIV-infected individuals smoke, the lung immune response against HIV-1 in the context of smoking has not been well characterized.
Methods: HIV-infected subjects on ART who were current- and never-smokers underwent bronchoscopy with bronchoalveolar lavage (BAL) and airway brushing. Lung and blood immune cells were analyzed using flow cytometry and mass cytometry by time-of-flight (CyTOF). Monocyte derived macrophages (MDMs) were exposed to cigarette smoking extract (CSE) in vitro and chemotactic attraction of T cells was investigated in a transwell assay. Chemokines in the BAL fluid were measured by Luminex.
Results: We found an HIV-associated increase in the number of CD8+ effector memory T cells in the blood and BAL fluid of never smokers. These CD8+ T cells demonstrated increased expression of the lung homing receptor CXCR3. Among HIV-infected smokers, however, this increase in BAL CD8+ T cells was not observed and there was a corresponding decrease in levels of the CXCR3 ligand CXCL10 in the BAL fluid. However, HIV-infected smokers had an increased frequency of CD69-CD103-non-residenttissue CD8+ T cells in bronchial brushings, suggesting impaired trafficking from circulation into the airspaces. In vitro CSE exposure of MDMs resulted in decreased CXCL10 production and reduced MDM-mediated recruitment of CD8+ T cells in a transwell assay. Blocking CXCL10 signaling with an antibody against its receptor, CXCR3, abrogated CD8+ T cell recruitment by MDMs.
Conclusion: In conclusion, HIV-infected subjects on ART have ongoing recruitment of CD8+ T cells to the airways. Smoking blocks production of the T cell recruiting chemokine CXCL10 in macrophages, which inhibits HIV-1 induced CD8+ T cell recruitment to the airspaces. This may then result in the accumulation of CD8+ T cells in the lung parenchyma, which has been associated with the development of COPD. Our data propose a potential mechanism for the disproportionate risk of COPD observed in smokers living with HIV.

243 INCREASES IN TH17 CELL DENSITY AT MUCOSAL SURFACES IN STATES OF ELEVATED PROGESTINS

Megan Halkett, Ann M. Carias, Thomas Hope
Northwestern University, Chicago, IL, USA
Background: Male to female sexual transmission of HIV contributes to the majority of new infections. There are several known risk factors that increase a woman's chance of acquiring HIV: unprotected sex with an HIV+ male, with IV drug users, with many and/or anonymous partners, as well as previous infection with another STI. An additional risk factor may be high levels of progestins, both exogenous and endogenous. In order to understand a woman's relative risk of infection during times of high progesterone levels, we characterized the changes to HIV target cell populations in the female reproductive tract in response to increased progestins. Th17 cells were the focus of this project as they have been identified as preferentially infected by HIV.
Methods: Eight female pigtail macaques were sacrificed at different phases of the menstrual cycle with vaginal and cervical tissues frozen in OCT. An additional seven rhesus macaques were either treated or not treated with DMPA and tissues were processed in the same manner. Tissues were sectioned and stained for CD3, CD4, CCR6 and DAPI. Deconvolution fluorescence microscopy was used to image the tissue epithelia to identify and phenotype with cell densities determined by cell count per area of epithelium in each image. Th17 cells were defined as cells that are triple positive for CD3, CD4 and CCR6.
Results: High levels of both endogenous and exogenous progestin were associated with a greater density of intraepithelial CD4+ target cells. This trend was also observed in the highly susceptible subset of the CD4+ target cell population, Th17 cells. The increased infiltration of vulnerable immune cells at the mucosal surface increases the availability of target cells to SIV/HIV virions, thus increasing the risk of acquisition.
Conclusion: High progesterone states are a risk factor for increased sexual acquisition of HIV in women. Increased levels of progestins, exogenous or endogenous, result in an increased infiltration of SIV/HIV target cells, particularly Th17 cells, into the epithelium. A greater presence of target cells at this vulnerable mucosal surface increases the probability of interaction with a SIV/HIV virion and subsequent infection.

244 IDENTIFICATION OF NK CELL SUBSETS CORRELATING WITH HIV DNA IN HIV-INFECTED SUBJECTS

Christopher Pohlmeyer[1], Veronica Gonzalez[2], Alivelu Irrinki[1], Ricardo Ramirez[1], Li Li[1], Andrew Mulato[1], Jeffrey Murry[1], Aaron Arvey[1], Rebecca Hoh[3], Steven G. Deeks[3], Garry Nolan[2], George Kukolj[1], Tomas Cihlar[1], Stefan Pflanz[1], Gundula Min-Oo[1]
[1]Gilead Sciences, Inc, Foster City, CA, USA, [2]Stanford University, Stanford, CA, USA, [3]University of California San Francisco, San Francisco, CA, USA
Background: The mechanism of natural immunological control of HIV infection has not been fully elucidated. We characterized NK cells from various populations of HIV-infected subjects to identify novel, non-T cell populations associated with control.
Methods: We used mass cytometry to measure the expression of 25 NK cell surface markers on cells from elite controllers (EC n=13), viremic controllers (VC n=27), non-controllers on suppressive ART (NC n=21), viremic non-controllers (VNC n=12), and seronegative healthy donors (HD n=20). We also quantified total HIV DNA levels in PBMCs as a measure of viral reservoir. We performed linear regression analysis across all subject groups to identify NK cell markers in two primary NK subsets ($CD56^{bright}CD16^{-}$, $CD56^{dim}CD16^{+}$) and 'anergic' NK cells ($CD56^{-}CD16^{+}CD7^{+}$) that correlate with clinical parameters, virus control, and reservoir size. Finally, we assessed NK cell marker repertoire diversity by Simpson's index.
Results: For subjects with detectable viral load, HIV DNA strongly correlated with detectable plasma viremia (p=0.0004). HIV DNA reservoir negatively correlated with Siglec-7 expression on both $CD56^{dim}CD16^{+}$ and $CD56^{-}CD16^{+}CD7^{+}$ cells (p=0.011 and 0.026, respectively). A strong positive correlation was observed between HIV DNA and CD62L expression on $CD56^{dim}CD16^{+}$ cells

(p=0.0011). Using combinatorial gates, we found a positive correlation between the expression of any of the five activating receptors we measured on $CD56^{dim}CD16^{+}$ cells and HIV DNA (OR gate, p=0.037). The diversity of activating receptors was also positively correlated with HIV DNA on both $CD56^{dim}CD16+$ and CD56-CD16+CD7+ cells (p=0.034 and 0.046, respectively).
Conclusion: We confirmed that higher levels of HIV DNA are associated with the loss of Siglec-7 expression, suggesting possible NK cell dysfunction. We also show that higher HIV DNA levels are associated with a greater frequency of CD62L-expressing NK cells, suggesting that these polyfunctional cells are activated and expand in response to HIV infection. The correlations observed between HIV DNA level and both the frequency and diversity of activating NK cell receptors are likely driven by the level of virus replication. Further studies on the functional capacity of Siglec-7+ and CD62L+ NK cells in relation to the control of HIV infection are warranted.

245 CHARACTERIZATION OF NKG2C+ MEMORY NK CELLS IN SIV INFECTION BY FISH-FLOW CYTOMETRY

Daniel Ram, R. Keith Reeves
Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: Recently, we and others have shown that NK cells have memory-like properties against CMV and SIV infections. While the mechanisms of memory-like responses are unclear, it has been shown in humans that expression of the activating receptor NKG2C is elevated on memory NK cells in response to infection with CMV. The role of NKG2C+ NK cells in experimental SIV infection is unclear as previously it has not been technically possible to distinguish NKG2C from its inhibitory counterpart, NKG2A, due to unfaithful antibody cross-reactivity. Because of the crucial role that macaque models play in modeling HIV (SIV) and CMV (rhCMV) new techniques to functionally and phenotypically characterize NKG2C+ NK memory cells are critical.
Methods: Using flow cytometry we phenotyped NK cells from rhesus macaques either chronically infected with SIV (n=8), rhCMV (n=12), or from specific pathogen free (SPF) animals that were negative for both viruses (n=10). Commercial flow cytometry antibodies against rhesus CD3, NKG2A, CD14 and CD20 were used in combination with PrimeFlow (Affymetrix), which combines fluorescence in situ hybridization (FISH) with flow cytometry, allowing for simultaneous detection of NKG2A and NKG2C transcripts (KLRC1 and KLRC2, respectively).
Results: Rhesus macaque NK cells were identified using a standard gating strategy (CD3-CD14-CD20-NKG2a/c+) and NK cell frequencies increased in infected relative to SPF animals. This suggests a virus-specific NK cell increase, though, as expected, inhibitory NKG2A could not be distinguished from activating/memory NKG2C expression. Using RNA probes we identified four different populations within NK cells (KLRC1±KLRC2±). Interestingly, frequencies of KLRC1+ NK cells were higher in the SPF animals, while KLRC2+ NK cells were elevated in infected animals. Levels of CD16 (KLRC1-KLRC2+ population) and CD56 (KLRC1±KLRC2+ populations) were also significantly modulated between infected and SPF groups, and CD2 was globally upregulated on NK cells in infected animals.
Conclusion: Our data suggests that elevated KLRC2 expression and induction of NKG2C+ NK cells is associated with both rhCMV and SIV infection, suggesting these cells could partially delineate memory responses against these pathogens. We expect that this technical advance from combining flow cytometry and FISH will greatly enhance HIV vaccine and cure-related work utilizing the macaque model.

246 INNATE LYMPHOID CELLS IN ENDOCERVICAL MUCOSA OF HIV INFECTED WOMEN

Natasa Strbo, Maria L. Alcaide, Laura Romero, Denisse Garcia, Margaret Fischl
University of Miami, Miami, FL, USA

Background: Dysbiosis of the vaginal microbiome, referred to as bacterial vaginosis (BV) is associated with increased HIV acquisition and transmission. BV increases local inflammation, and activated CD4+ T cells in the female reproductive tract (FRT). Innate lymphoid cells (ILCs), a novel family of immune effector cells, are key regulators of immune defenses at mucosal surfaces, and crucial for maintaining intact mucosal barriers, but have not been evaluated in the (FRT). ILCs are grouped into ILC1, ILC2, and ILC3, which share functional characteristics with Th1, Th2, and Th17 cells, respectively. The genital mucosa is the initial site of viral replication following vaginal HIV-1 infection. We hypothesized that, BV result in increased HIV acquisition and transmission via inflammation-induced disruption to epithelial barrier integrity through dysregulation of ILCs. This is the first report comparing distribution and function of ILCs in endocervical mucosa in HIV+ and HIV- individuals.
Methods: HIV+ (n=7) and HIV- (n=6) pre-menopausal women participating in the WIHS cohort were recruited. Participants underwent vaginal examination with collection of endocervical cytobrushes and peripheral blood. Frequency and phenotype of ILCs were determined in cervical cytobrush samples and peripheral blood by multicolor flow cytometry. BV was determined by Nugent scoring
Results: ILC3 represent the predominant ILCs subset in endocervical intraepithelial cells in HIV- women without BV (BV-). Women with BV (BV+) have lower frequencies of ILC3 than those BV- (BV+ 61 ± 10.01, n=3 vs BV- 77.6 ± 8.647, n=3; p =0.05). In HIV+ women we did not find difference between BV+ and BV- samples, but we found significant decrease of ILC3 in HIV+ women compared to HIV- women (11.2 ± 7.0 n=7 vs 69.6 ± 5.6 n=6; p=0.001).
Conclusion: Composition of the endocervical ILC pool differs between women with and without BV, and is altered by HIV status. Our data suggest a link between dysregulated vaginal microbiome and loss of endocervical ILCs and barrier function, thereby allowing for local immune activation. This highlights the important role played by vaginal microbiome on the endocervical innate immune system and suggest that endocervical barrier integrity and ILCs dysregulation are implicated in HIV acquisition in women with BV.

247 HIV-1 VPR SUSTAINS IL-6 PRODUCTION TO PROMOTE HIV-1 REPLICATION IN MACROPHAGES

Qi Wang, Lishan Su
University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: Persistent inflammation is a hallmark of HIV-1 pathogenesis, but the mechanism that leads to persistent inflammation remains elusive. As one of the abundant HIV-1 virion-associated proteins, Vpr remains the most enigmatic of HIV-1 accessory proteins. Vpr is efficiently incorporated into virus particles to enhance viral replication in macrophage by unclear mechanisms. In addition, the role of virion-associated Vpr in dysregulating inflammatory cytokines remains unclear during HIV-1 infection.
Methods: We utilized different Vpr mutants to determine the proinflammatory cytokines level during HIV-1 infection in primary macrophage. We also utilized a Vpr-deficient HIV-1 and provided Vpr in trans that are packaged into the virions. This system devoids of de novo Vpr production during HIV-1 replication and allows us to exclusively study the role of virion-associated Vpr.
Results: We report here that HIV-1 Vpr enhances IL-6 production, correlated with elevated HIV-1 replication in human monocytic cells via a Vpr activity that is independent of its G2 cell cycle arrest activity. We show that Vpr sustains IL-6 production by reducing binding of TET2 and HDACs to the IL-6 promoter during its resolution phase. We further demonstrate that Vpr-enhanced HIV-1 replication in macrophages partially depends on IL-6 signaling. Blocking IL-6 signaling with IL-6 neutralizing antibody or depleting NF-IL6 significantly reduced the ability of Vpr to enhance HIV-1 replication in human primary macrophages.
Conclusion: First, we have discovered that HIV-1 Vpr enhances IL-6 production, correlated with elevated HIV-1 replication in monocytic cells via an activity that is independent of its G2 cell cycle arrest activity. Second, we demonstrate that Vpr sustains IL-6 production during its resolution phase by preventing binding of TET2 and HDACs to the IL-6 promoter. Third, we demonstrate that Vpr-enhanced HIV-1 replication in macrophages partially depends on IL-6 signaling.

248 T FOLLICULAR HELPER CELLS ARE MAJOR HIV-2 RESERVOIRS AND SUPPORT PRODUCTIVE INFECTION

Ana Godinho-Santos, Ana Antão, Bárbara Tavares, Tiago Ferreira, Ana Serra-Caetano, Paula Matoso, Cheila Rocha, Russell B. Foxall, Ana E. Sousa
Instituto de Medicina Molecular, Lisbon, Portugal

Background: Life-long antiretroviral treatment is currently required for the 36 million people living with HIV in order to restrain persistent viral reservoirs. Follicular helper T cells (Tfh), a CD4+ T cell subset critical for efficient antibody responses, have been shown to be a main HIV-1 reservoir. HIV-2 represents a unique naturally-occurring model to investigate the role of Tfh in HIV/AIDS. Despite reservoir establishment, HIV-2-infected patients feature: 1) low to undetectable viremia throughout disease; 2) slow rate of CD4 decline with limited impact on the survival of infected adults; and 3) high titers of neutralizing antibodies (nAbs). Thus, we reasoned that Tfh might be central

drivers of the HIV-2 benign course, prompting us to investigate here, for the first time, the ability of Tfh to support HIV-2 infection.
Methods: CD4+ T cell subsets from tonsillar tissue were sort-purified based on the expression of CXCR5, PD-1 and ICOS and infected in vitro with HIV-2 and HIV-1 primary isolates with distinct co-receptor tropism. PBMCs were isolated from freshly collected peripheral blood of untreated HIV-2-infected individuals and CD4+ T cell subsets were sort-purified based on CCR7, CD45RA and CXCR5 expression. Viral DNA and mRNA were measured by real-time quantitative PCR. Viral infectivity was assessed using a TZM-bl reporter cell line.
Results: Our data showed that HIV-2 is able to infect Tfh (CXCR5+ICOSbrightPD-1bright). Of note, CXCR4 usage was not associated with higher reservoirs in the case of HIV-2 primary isolates, in contrast with the typical pattern observed in HIV-1. Moreover, Tfh supported productive HIV-2 infection, as attested by the increase in viral DNA levels after TCR stimulation, along with evidence of infectious viruses in culture supernatants. Importantly, sort-purified Tfh from the blood of untreated HIV-2-infected individuals confirmed that this subset is also a main HIV-2 reservoir in vivo. This reservoir was effectively controlled, since these patients featured no detectable plasma viral load.
Conclusion: We reveal that Tfh support productive HIV-2 infection and are a preferential target in HIV-2-infected individuals. Our data are in agreement with a link between Tfh infection and sustained titers of HIV-specific nAbs. Identifying the host factors responsible for the controlled HIV-2 infection will help clarify the mechanisms responsible for the pathogenic nature of HIV-1 and may uncover strategies to achieve a functional HIV cure.

249 NEUTROPHIL EXTRACELLULAR TRAPS PREVENT HIV INFECTION IN THE GENITAL TRACT

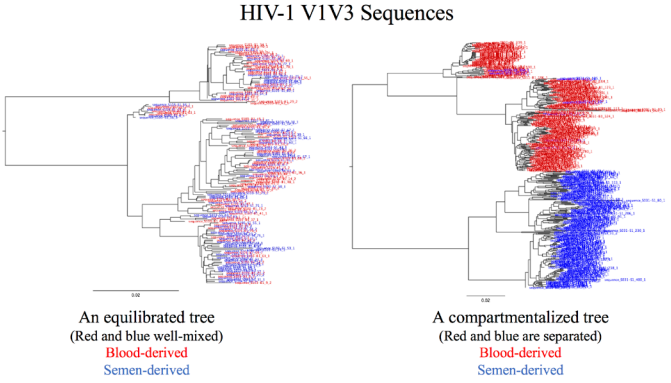
Fiona D. Barr[1], Christina Ochsenbauer[2], Charles Wira[1], **Marta Rodriguez-Garcia**[1]
[1]Dartmouth College, Hanover, NH, USA, [2]University of Alabama at Birmingham, Birmingham, AL, USA

Background: Women worldwide acquire HIV mainly through sexual intercourse. However, the low transmission rate per sexual act indicates that local innate immune mechanisms contribute to HIV prevention. Neutrophils represent 10-20% of the genital immune cells in healthy women. Neutrophils participate in mucosal protection against bacterial and fungal pathogens through different mechanisms, including the release of Neutrophil Extracellular Traps (NETs). NETs are DNA fragments associated with antimicrobial granular proteins. Despite neutrophil abundance and central contributions to innate immunity in the genital tract, their role in protection against HIV acquisition is unknown.
Methods: Genital tract tissues obtained from hysterectomies (ectocervix, endocervix and endometrium) were enzymatically digested to generate mixed cell suspensions and isolate neutrophils. Mixed cell suspensions (immune cells and fibroblasts) or purified neutrophils were stimulated ex-vivo with GFP-tagged HIV viral-like particles (HIV-VLP). NET release was quantified and characterized using time-lapse imaging and confocal microscopy. To measure anti-HIV activity of pre-formed NETs, NETs were induced using calcium ionophore, a known inducer of NETosis. NETs were recovered by centrifugation, and incubated with replication-competent HIV for 1h prior to addition of CD4+ T cells. HIV infection was evaluated after 7 days by flow cytometry and p24 ELISA.
Results: Stimulation of genital neutrophils induced the release of NETs within minutes of viral exposure (P=0.0005). NET release resulted in immediate entrapment of HIV-VLP, which co-localized with extracellular DNA strands, as demonstrated by time-lapse imaging and confocal microscopy. Incubation of HIV with pre-formed NETs resulted in complete inhibition of HIV infection of CD4+ T cells. Viral inactivation was irreversible, given that treatment of HIV-NET complexes with DNAse, to degrade NETs and release potentially infectious virions, did not restore infection. Confocal microscopic analysis of NETs revealed the presence of HNP 1-3, LL-37 and myeloperoxidase, all of which have known anti-HIV activity.
Conclusion: Genital neutrophils recognize and respond to HIV with the release of NETs, which inactivate the virus and prevent the infection of target cells. This could represent a novel mucosal protection mechanism for HIV-acquisition not previously considered. Our findings could open new avenues for research and strategies for HIV prevention.

250 COMPARTMENTALIZED HIV-1 IS FOUND IN THE SEMEN OF MEN WITH AND WITHOUT URETHRITIS

Olivia Council[1], Lihua Ping[1], Chase McCann[1], Gerald Tegha[2], Irving Hoffman[1], Debbie Kamwendo[2], Mitch Matoga[2], Myron S. Cohen[1], Ronald Swanstrom[1]
[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]University of North Carolina Project–Malawi, Lilongwe, Malawi

Background: HIV-1 RNA can be found in the semen of most untreated HIV-infected men and may represent local viral replication or migration of virus or infected cells into the genital tract from the periphery. Inflammation appears to mediate these processes as men with HIV-1 and a concurrent sexually-transmitted infection (STI) have a higher HIV-1 semen viral load. Inflammation likely increases shedding by recruiting CD4+ T cells into the genital tract that are either uninfected and can amplify virus in that compartment or are infected and can release virus from the periphery into the genital tract. In this study, we tested the hypothesis that inflammation due to STI-associated urethritis increases migration of HIV-infected cells into the genital tract, causing HIV-1 in the semen to be genetically similar to virus in the blood (equilibrated). Similarly, we hypothesize that in the absence of inflammation, viral lineages are more likely to replicate independently in the genital tract and become genetically distinct from virus in the periphery (compartmentalized).
Methods: Paired blood and semen samples were collected from HIV-infected, ART-naïve men in Lilongwe, Malawi with and without symptomatic urethritis. HIV-1 RNA was extracted from the samples and cDNA was synthesized. Each cDNA was tagged with a unique 11 nucleotide Primer ID. This Primer ID 'tag' is maintained throughout subsequent amplification steps and reduces PCR and sequencing errors. Approximately 600 bases of the HIV-1 env V1-V3 region were deep sequenced using the MiSeq platform. Phylogenetic trees were then constructed using sequences from the blood and semen and examined for the presence of compartmentalization in the genital tract.
Results: We sequenced samples from men with (n=16) and without (n=8) urethritis. Overall, we observed some degree of viral compartmentalization in the sequences of 7/16 (44%) men with urethritis and in 3/8 (38%) of men without urethritis. Thus, in this cohort, urethritis did not alter the prevalence of HIV-1 compartmentalization in semen.
Conclusion: We observed varying degrees of HIV-1 compartmentalization in the genital tract of approximately 40% of men analyzed, regardless of the presence or absence of urethritis. Deep sequencing with Primer ID revealed compartmentalization in the semen of a surprisingly high fraction of ART-naïve men. The existence of compartmentalized viral lineages in the genital tract has important implications for understanding the biology of transmission.



Representative phylogenetic trees constructed using blood and semen derived HIV-1 V1V3 sequences.

251LB WITHDRAWN

252 FECAL MICROBIOTA FROM HIV-INFECTED SUBJECTS INCREASES INNATE IMMUNE ACTIVATION

Charles P. Neff, Owen Krueger, Sam Li, Nichole Nusbacher, Jennifer M. Schneider, Abigail Armstrong, Catherine Lozupone, Brent E. Palmer
University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Background: 16S rRNA sequence analysis has identified compositional divergence of the enteric microbiota of men who have sex with men (MSM) regardless of HIV status; however, in HIV-infected subjects bacterial translocation contributes to chronic immune activation and drives disease progression. To address if the enteric microbiome of HIV-infected individuals are particularly pro-inflammatory we developed methodology to purify whole fecal bacterial communities (FBC) and test their immunomodulatory properties using healthy PBMC.

Methods: FBCs of 50 individuals with and without HIV infection were isolated by density gradient, enumerated by flow cytometry and verified for composition resemblance to the original fecal sample using 16S rRNA sequencing. The impact of the FBCs on immune cells in peripheral blood was assessed by measuring activation of T cells (HLA-DR and CD38) and monocytes (CD14 shedding and CD80), levels of soluble CD14 and cytokine production (TNF-α, IFN-γ, IL-6) and by blockade assays. Findings were correlated to ex vivo immune parameters.

Results: We demonstrate that FBCs of HIV-infected subjects induce high levels of activated monocytes and T cells in vitro. Monocyte and T cell activation induced by FBCs correlated ($p=0.0006$, $r=0.46$). Blockade of Toll-Like Receptors (TLRs) implicated TLR2 as a primary mediator of activation ($p<0.0001$). FBCs from HIV+ subjects induced TNF-α secretion and TNF-α blockade ameliorated T cell activation ($p<0.0001$). FBC induced T cell activation was correlated with ex vivo T cell activation ($p=0.008$, $r=0.42$), viral load ($p=0.004$, $r=0.78$) and the abundance of two opportunistic pathogens: Terrisporobacter glycolicus ($p=0.002$, $r=0.44$) and Turicibacter sanguinis ($p=0.003$, $r=0.42$).

Conclusion: This study provides insight into the consequence of the alterations in enteric microbiota associated with HIV infection on systemic immune activation. Our findings demonstrate that FBCs from HIV-infected subjects induce monocyte activation and TNF-α production through TLR signaling resulting in T cell activation. This T cell activation correlated with ex vivo T cell activation and viral load in peripheral blood implicating pro-inflammatory enteric microbiota as a driver of disease progression. Collectively, these findings suggest that the enteric microbiome plays a role in HIV disease progression and that modulation of enteric microbiota may provide an effective treatment option.

253 ISOLATION OF TRANSLOCATING BACTERIA IN PROGRESSIVE SIV INFECTION OF RHESUS MACAQUES

Jacob Flynn, Alexandra Ortiz, Jason Brenchley
NIAID, Bethesda, MD, USA

Background: Microbial translocation is commonly observed in HIV-infected humans and is a significant contributor to chronic immune activation and inflammation. In SIV-infected Asian macaques, translocation has been demonstrated to occur across the gastrointestinal barrier; however, translocating bacterial taxa are not representative of the gut microbiota, with Proteobacteria appearing to preferentially translocate. To fully characterize translocating bacterial populations, we isolated systemically translocating bacteria from chronically SIV-infected macaques and identified them subsequent to live culture.

Methods: Liver, mesenteric lymph node, and spleen samples were taken aerobically and anaerobically during necropsy from fifteen, chronically SIV-infected rhesus macaques. Swabs were used on the chest/abdomen of necropsied macaques to sample the skin microbiome as a control for potential contamination. Due to a lack of SIV uninfected macaques being necropsied, samples from these have not been incorporated as a control at this time. Tissue samples were homogenized and plated on: a) Brain Heart Infusion, b) TSA+Tween 80, and c) TSA+5% Sheep's Blood media under aerobic conditions, and d) Brucella Blood and e) CDC Blood media under anaerobic conditions. Isolates were grown at 37°C for 1-7 days, depending on observed density. Colonies were restreaked for pure cultures and identified using MALDI-TOF and 16S rDNA sequencing. Isolates found to be present in tissues but also in the skin microbiome from the same animal were eliminated from consideration.

Results: Eighteen species have been identified thus far, 3 Proteobacteria (all from the family Enterobacteriaceae), 1 Actinobacteria (all Corynebacteriaceae), and 14 Firmicutes (35.7% Lactobacillaceae, 14.3% Streptococcaceae, 14.3% Enterococcaceae, 7.1% Aerococcaceae, 7.1% Eubacteriaceae, 7.1% Leuconostocaceae, 7.1% Planococcaceae, 7.1% Staphylococcaceae).

Conclusion: Although bacterial taxa have been shown to translocate across the gastrointestinal epithelium, translocating taxa do not mirror the composition of the gastrointestinal microbiome, suggesting that translocating bacterial taxa are enriched for motile taxa or are functionally altered. We intend to grow these isolates in the presence of intestinal homogenates and sorted immune cell populations from SIV infected and uninfected macaques in order to measure microbial growth and motility to determine how lentiviral infections may promote preferential translocation.

254 CIRCULATING (1→3)-B-D-GLUCAN AS A MARKER OF MICROBIAL TRANSLOCATION IN HIV INFECTION

Vikram Mehraj[1], Rayoun Ramendra[2], Cecilia Costiniuk[3], Bertrand Lebouché[3], Rosalie Ponte[1], Réjean Thomas[4], Jason Szabo[3], Pierre Coté[5], Roger LeBlanc[6], Jean-Guy Baril[7], Cécile Tremblay[7], Nicole Bernard[1], Don C. Sheppard[1], Jean-Pierre Routy[1]
[1]McGill University Health Centre Research Institute, Montreal, QC, Canada, [2]McGill University, Montreal, QC, Canada, [3]McGill University Health Centre, Glen site, Montreal, QC, Canada, [4]Clinique Médicale l'Actuel, Montreal, QC, Canada, [5]Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada, [6]Clinique OPUS, Montreal, QC, Canada, [7]Centre de Research du Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada

Background: HIV infection is linked to gut damage and translocation of microbial products into the systemic circulation contributing to immune activation. Bacterial products and host acute phase proteins such as LPS, LBP and sCD14 have been used as markers of microbial translocation in HIV infection; however the utility of fungal antigens for the detection of gut damage has not been defined. We therefore sought to determine the relationship of the fungal antigens (1→3)-β-D-glucan (βDG) and galactomannan with markers of microbial translocation, inflammation and disease progression in early (EHI) and chronic (CHI) HIV infection.

Methods: A total of 101 participants without suspicion of fungal infection and/or GI symptoms were assessed in a cross-sectional analysis, including 61 EHI,

22 CHI and 18 uninfected controls. A subgroup of EHI and CHI participants on ART was prospectively assessed. Plasma βDG and galactomannan levels were quantified using Fungitell® and Platelia™ assays, respectively. Plasma βDG levels were compared with age, sex, viral load, CD4 and CD8 T-cell counts, CD4/CD8 ratio, markers of gut damage (I-FABP), microbial translocation (LPS, LBP and sCD14), inflammation (IL1-β, IL-6, IL-8, TNF-α and sCD40L) and Kynurenine/Tryptophan ratio. Univariate and multivariate analyses were conducted at 5% α.
Results: Plasma βDG levels were elevated during EHI (60.5±33.2 pg/mL, p=0.012) and CHI (135.6±48.6 pg/mL, p<0.001) in comparison to controls (30.4±5.3 pg/mL), while galactomannan levels were below level of detection in all participants. βDG levels increased over two year interval in the untreated EHI (100.6±81.2 pg/mL p=0.012) and remained stable in the ART-treated EHI. CHI on 12±4 years of ART had the highest βDG levels (190.7±68.7 pg/mL, p<0.001). A correlation of βDG was observed with viral load (r=0.430; p<0.001) in untreated participants, CD4 T-cell count (r=-0.334; p<0.001), CD4/CD8 ratio (r=-0.286; p=0.003), LBP (r=0.413; p=0.007), sCD14 (r=0.338; p=0.001), IL-6 (r=0.334; p<0.001), IL-8 (r=0.506; p<0.001), sCD40L (r=0.333; p=0.024) and Kyn/Trp (r=0.261; p=0.022). Multivariate analysis showed elevated βDG levels during HIV infection were independent of the effect of age, sex, creatinine, total cholesterol and glucose.
Conclusion: Plasma βDG levels were elevated during early and chronic HIV infection and did not decrease on ART. Elevated βDG levels correlated with the validated markers of microbial translocation and inflammation and can be considered as a marker of HIV disease progression.

255 TRANSFER OF MICROBIOTA AND IMMUNOPHENOTYPES IN HIV-/+ MSM TO MICE BY FECAL TRANSPLANT

Sam Li, Sharon Sen, Jennifer M. Schneider, Nichole Nusbacher, Nancy Moreno-Huizar, Catherine Lozupone, Brent E. Palmer
University of Colorado, Aurora, CO, USA

Background: High-risk men who have sex with men (MSM) have differences in immune activation and gut microbiome composition when compared with men who have sex with women (MSW), even in the absence of HIV infection. Gut microbiome differences that occur with HIV as assessed by 16S rRNA sequencing are relatively subtle. Understanding whether an altered gut microbiome composition drives increased immune activation in MSM and with HIV infection has important implications since immune activation has been associated with both HIV acquisition risk and disease progression.
Methods: Gnotobiotic mice were gavaged with feces from HIV- MSW (n=11), HIV- MSM (n=14), and HIV+ untreated MSM (n=9). At 21 days post-gavage, CD69 and CD103 expression was evaluated on gut T cells, and fecal microbiome composition in the mice was characterized by 16S rRNA gene sequencing. HLADR and CD38 expression on blood T cells and fecal microbiome composition in the human donors were also analyzed and compared with mouse recipients.
Results: We observed increased gut immune activation in gnotobiotic mouse recipients of HIV- MSM feces compared with mouse recipients of HIV- MSW feces. Additionally, several bacterial species significantly correlated with both blood HLADR+ CD38+ CD8+ T cells in human donors (which was significantly higher in MSM, p=0.01) and gut CD69+ CD8+ T cells in mouse recipients. When controlling for MSM, we found no effect of HIV status on gut immune activation or microbiome composition in mouse recipients. Gnotobiotic mice presented some challenges in interrogating MSM-associated gut microbiome differences. The MSM-associated gut microbiome is characterized in part by an increase in the relative abundance of bacteria in the *Prevotella* genus, but *Prevotella* did not colonize the mice. However, principal coordinates analysis (PCoA) revealed that the microbiome of MSM and MSW maintained distinct clustering following transfer to mice that did replicate other differences between MSM and MSW observed in the human donors; mouse recipients of MSM feces had significantly lower abundances of the *Lachnospiraceae* family (p=0.01) and *Blautia* genus (p=0.02) compared with mouse recipients of MSW feces.
Conclusion: Shared microbiome and immunological phenotypes between human donors and mouse recipients support gnotobiotic mice as a model for studying MSM- and HIV-associated microbiome changes. These data suggest that gut microbes influence immune activation in MSM, which may drive what is seen in HIV.

256 ANTIBIOTICS DISRUPT COLONIC MICROBIOTA AND MUCOSAL IMMUNE FUNTION IN RHESUS MACAQUES

Alexander S. Zevin[1], Ryan Cheu[1], **Tiffany Hensley-McBain**[1], Jacob Modesitt[1], Jennifer A. Manuzak[1], Charlene J. Miller[1], Ernesto Coronado[1], Elise Smith[1], Brian Richardson[2], Michael Gale[1], Mark Cameron[2], Jeremy Smedley[3], Nichole Klatt[1]
[1]University of Washington, Seattle, WA, USA, [2]Case Western Reserve University, Cleveland, OH, USA, [3]Washington National Primate Research Center, Seattle, WA, USA

Background: Antibiotics are widely used throughout the world to treat bacterial infections that occur independently or as a result of HIV infection. However, evidence suggests that antibiotic treatments disrupt the composition of the intestinal microbiome. Further, HIV infection is associated with disrupted microbiota and mucosal dysfunction independent of antibiotic use. Intestinal microbiota are critical for maintaining host immune homeostasis and protecting against the expansion of pathobionts. Additionally, microbiota-derived metabolites are key energy sources for colonic epithelial cells and regulate immunity. We hypothesized that antibiotic therapies would disrupt the GI microbiome and host mucosal immunity.
Methods: We administered antibiotics to four groups of healthy female rhesus macaques and collected GI biopsies and stool (Group 1 – enrofloxacin, Group 2 – cephalexin, Group 3 – paramomycin, Group 4 – clindamycin). We tracked bacterial community composition using 16S rRNA gene sequencing and qPCR, evaluated host mucosal immunity in the colon throughout the antibiotic treatment using multicolor flow cytometry, and host gene expression using mRNA-seq. Finally, we quantified plasma biomarkers of mucosal disruption and microbial translocation using ELISA.
Results: The antibiotic treatments disrupted colonic microbiota and led to expansion of facultative anaerobic and potentially pathogenic bacterial taxa as well as quantitative shifts in the bacterial abundance in the colonic mucosa and stool. There also was a significant increase in colonic mucosal neutrophils during the treatment. There also were increased frequencies of Th17 and Th22 CD4+ T-cells after the antibiotic treatment. We further found altered expression of genes involved in cell-cell junctions, cellular metabolism, and inflammatory pathways during and after the antibiotic treatment. Finally, we showed that plasma sCD14 concentrations increased during the antibiotic treatment.
Conclusion: Our data demonstrate that antibiotic therapies alter colonic microbiota, and that these changes were linked to a distinct signature of mucosal inflammation and immune activation, including increased populations of HIV-1 target cells. Thus, in HIV infection, antibiotic use may exacerbate mucosal dysfunction, and resolving bacterial dysbiosis by limiting antibiotic use may be key to maintaining mucosal health.

257 EFFECT OF PROBIOTICS ON GUT MICROBIOTA AND PET/MRI ACTIVITY IN HIV-INFECTED PERSONS

Caroline Arnbjerg[1], **Beate Vestad**[2], Johannes Hov[3], Karin K. Pedersen[1], Sofie Jespersen[1], Helle H. Johannesen[1], Kristian Holm[2], Eva Fallentin[1], Adam E. Hansen[1], Theis Lange[4], Andreas Kjær[1], Marius Troseid[2], Barbara M. Fischer[1], Susanne D. Nielsen[1]
[1]Copenhagen University Hospital, Copenhagen, Denmark, [2]Oslo University Hospital, Oslo, Norway, [3]University of Oslo, Oslo, Norway, [4]University of Copenhagen, Copenhagen, Denmark

Background: Despite combination antiretroviral therapy (cART) with suppressed viral replication, gut microbiota alterations, microbial translocation and low-grade inflammation persist in several HIV-infected individuals. The aim of this study was to investigate the effects of the probiotic strain Lactobacillus rhamnosus GG (LGG) on the gut microbiota composition, microbial translocation and intestinal inflammation.
Methods: The gut microbiota composition (Illumina sequencing of 16s rRNA) and level of microbial translocation (lipopolysaccharide, LPS) were determined at baseline and after probiotic intervention in 45 individuals (15 cART näive and 30 cART-treated). All study participants received 6 x 109 colony-forming units of LGG twice daily for eight weeks. Gut microbial profiles were compared with measurements of intestinal inflammation by 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography/magnetic resonance imaging (18FDG PET/MRI) scans in 15 individuals.
Results: After probiotic intervention, no overall change in microbial translocation (LPS) or microbial alpha diversity could be detected in the study group (observed operational taxonomic units (OTUs); mean change -0.83, 95% CI -2.33 to 0.67, p=0.328, phylogenetic diversity (PD) whole tree;

mean change -10.96, 95% CI -33.33 to 11.41, p=0.270). However, a significant decrease in intestinal inflammation was detected on PET/MRI (-0.3 mean difference in combined activity grade score from six regions, P=0.006), along with a reduction in the bacterial families Enterobacteriaceae (p=0.018) and Erysipelotrichaceae (p=0.037) after probiotic intervention. Comparing individuals with decreased 18F-FDG-uptake on PET/MRI (good responders) with individuals with no change in uptake after intervention (poor responders), there was a significant reduction in the relative abundance of Enterobacteriaceae (p=0.048), but not Erysipelotrichaceae, in the gut microbiome of the good responders.

Conclusion: Reduced abundance of Enterobacteriaceae after probiotic intervention could potentially explain the local anti-inflammatory effect in the gut, as this bacterial family contains several known pathogenic strains. These findings are in line with the measured PET/MRI activity in the gut.

258 INVESTIGATING THE EFFECT OF THERAPEUTICS ON THE MICROBIOME OF PATIENTS WITH HIV/AIDS

Bryn C. Taylor[1], David M. Asmuth[2], Rob Knight[1]
[1]University of California San Diego, La Jolla, CA, USA, [2]University of California Davis, Davis, CA, USA

Background: Here, we investigate the pathways by which maraviroc-treated cohorts experience improved mucosal immunity through changes in host:microbial interactions. We hypothesize that maraviroc therapy-induced improvements in mucosal immunity impacts the microbial mucosal interaction through either a change in the distribution of the microbial communities, their metabolic state, or both.

Methods: We previously performed a three-arm, randomized clinical trial (RCT) that examined the impact of maraviroc alone or combined with raltegravir versus efavirenz (each combined with emtricitabine-tenofovir DF) on gastrointestinal-associated lymphoid tissue (GALT) immune reconstitution. Subjects who were naïve to antiretroviral therapy and with CCR5-tropic virus underwent upper endoscopy and flexible sigmoidoscopy before and 9 months after initiating treatment; plasma and fecal samples were also collected at these time points. We performed 16S rRNA sequencing to look first at the composition of the microbial communities in all samples before and after treatment with the regimens tested in the recently completed RCT. Metabolomic analysis of the stool and plasma was performed to explore whether alterations in the metabolic state of the microbial community is a potential mechanism for altering mucosal immune lymphocyte distribution or immune function as has been suggested for other diseases of the gastrointestinal tract that lead to systemic inflammation.

Results: Analysis of 16S rRNA sequencing of the samples yielded clearly distinct microbial communities between body sites. Interestingly, the microbial communities remained stable in each of the body sites before and after 9 months of each treatment. Despite the overall community stability, with metabolomics analysis we identified distinct functional profiles between treatment groups and over time.

Conclusion: Extensive analysis of the microbial community profiles of the HIV-positive cohort show no community-level differences between treatment groups. Due to the immune reconstitution we see in maraviroc-treated patients, we expected instead to see variation in the functional profile of these microbial communities. We performed metabolomics analysis of these samples to explore the functional output of these stable microbial communities and we determined the metabolic pathways by which maraviroc-treated cohorts achieve improved mucosal immunity.

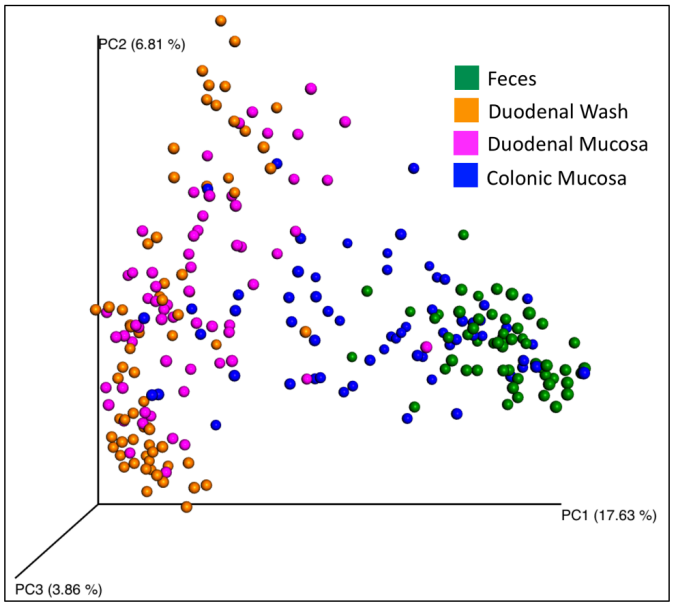


Figure 1. Fecal samples, duodenal mucosal biopsies, duodenal mucosal washes, and colonic mucosal biopsies have distinct microbial community profiles.

259 TLR9 AGONIST MODULATED INTESTINAL GLYCOGENE EXPRESSION IMPACTS MICROBIOME DIVERSITY

Mohamed Abdel-Mohsen[1], Phillip A. Engen[2], Ali Keshavarzian[2], Stefan J. Green[3], Alan Landay[2], Satish K. Pillai[4], Anders K. Dige[5], Jørgen Agnholt[5], Andreas M. Petersen[6], Thomas Benfield[6], Lars Østergaard[5], Line K. Vibholm[5], Ole S. Søgaard[5], Martin Tolstrup[5], Paul W. Denton[5]
[1]Wistar Institute, Philadelphia, PA, USA, [2]Rush University Medical Center, Chicago, IL, USA, [3]University of Illinois at Chicago, Chicago, IL, USA, [4]Blood Systems Research Institute, San Francisco, CA, USA, [5]Aarhus University Hospital, Aarhus, Denmark, [6]University of Copenhagen, Copenhagen, Denmark

Background: An emerging paradigm suggests that the gut-associated glycome is critical to the maintenance of a homeostatic relationship between the host and its gut microbiota. In HIV infection, alterations in glycan metabolism may contribute to HIV-mediated intestinal damage, microbial translocation, and chronic inflammation. Given that we recently found that the TLR9 agonist lefitolimod (MGN1703, Mologen AG) increased microbiome diversity in HIV-1 infected individuals at multiple phylogenetic levels in Shannon and Simpson indices (PMID: 28766555), we hypothesized that lefitolimod-mediated changes in the gut glycome promoted changes in microbiome diversity.

Methods: Sigmoid biopsies and stool samples were collected (at baseline and after the last dose) from 8 HIV+ adults on suppressive antiretroviral therapy who received lefitolimod (60 mg s.c.) twice weekly for 4 weeks. Ribosomal RNA gene amplicon libraries from fecal samples were sequenced, and all datasets were rarefied to 14,500 reads for calculations of both beta and alpha diversity. Sigmoid tissue was digested and percoll-enriched intestinal mononuclear cells were obtained. The tissue expression of 424 glycosylation-associated genes (glycogenes) was measured using RNA-sequencing. False-discovery rate (FDR) was used to correct for multiple comparisons.

Results: Overall, we found 51 unique gut-associated glycogenes that significantly correlated with 122 microbiome classifications (FDR<0.05). When we filtered the data to only the glycogenes that were significantly modulated by lefitolimod, we identified 10 glycogenes with diverse functions including: mucin-type O-glycosylation synthesis (N-acetyl-galactosaminyltransferases); mannose synthesis and metabolism; and anti-microbial C-type lectin-mediated innate immunity (p<0.05). The changes in these glycogenes correlated strongly (FDR<0.05) with the longitudinal changes in microbiome diversity in multiple

taxa including Alphaproteobacteria (Proteobacteria), Paraprevotellaceae (Bacteroidetes) and several species of Firmicutes.

Conclusion: The degree of glycosylation in the gut directly impacts the ability to maintain a functional mucus layer and healthy intestines. Our analyses identified a gut glycomic signature associated with lefitolimod treatment that may influence intestinal homeostasis by modulating alpha diversity of the gut microbiome. Our data highlight that host glycomics is an important tool for evaluating impact of novel HIV interventions, particularly within the context of HIV eradication.

260 EVOLUTION OF THE GUT MICROBIOME FOLLOWING ACUTE HIV-1 INFECTION

Muntsa Rocafort[1], Marc Noguera-Julian[1], Javier Rivera[1], Lucia Pastor Palomo[2], Yolanda Guillén[1], Jost Langhorst[3], Mariona Parera[1], Inacio Mandomando[2], Jorge Carrillo[1], Bonaventura Clotet[1], Julià Blanco[1], Denise Naniche[2], Roger Paredes[1]
[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [2]Universitat de Barcelona, Barcelona, Spain, [3]University of Duisburg-Essen, Essen, Germany

Background: The early events following acute HIV-1 infection might be critical to shape the long-term interaction between the human gut microbiome and the host. In previous studies in non-human primates, SIV infection was followed by expansion of the enteric virome but had a limited impact on the gut bacteriome. Human data are scarce.

Methods: We prospectively evaluated 103 subjects who attended the outpatient clinic of the Manhiça District Hospital in Mozambique with fever, and were either diagnosed with primary HIV-1 infection (PHI, n=49) or were HIV-1-negative (n=54) (baseline). Longitudinal fecal samples were collected over the first year starting at month 1, and were compared with single fecal samples from 98 chronically HIV-1-infected (CHI) subjects, 27 on ART and 71 ART-naïve. The fecal bacteriome was characterized with MiSeqTM 16S rDNA sequencing. Metagenomic Shotgun sequencing (MGS) was also performed in month 1, 4 and 9 samples in 13 subjects with PHI and 8 HIV-negative individuals. Presence of fecal Adenovirus (ADV), Cytomegalovirus (CMV), Enterovirus (ETV), and Human Herpes Viruses (HHV) 6A, 6B and 8 was evaluated by commercial real time PCR. Linear mixed models were used to assess longitudinal changes bacterial abundance and microbial richness.

Results: At baseline, 49%, 14%, 14% and 23% PHI subjects were at Fiebig 3, 4, 5, and 6 stages, respectively. HIV-1 infection was associated with virus expansion: ADV were detected in >50% of PHI subjects, as well as in CHI individuals; CMV and ETV were mostly found in ART-naïve CHI subjects (Table). No HHVs were detected at all. Both PHI and HIV-neg groups showed reduced taxonomic (16S) and genetic (MGS) richness at month 1. Whereas both parameters recovered in HIV-neg, genetic richness remained low in PHI. Recovery in taxonomic richness in PHI was concomitant to increases in anti-inflammatory bacteria (Odoribacter, Rikenellaceae and Barnesiellaceae) alongside decreases in Proteobacteria.

Conclusion: Primary HIV-1 infection is associated with virome expansion, transient loss of bacterial taxonomic richness and long-term reductions in microbial gene richness, all of which occur during hyperacute phases of HIV-1 infection.

Detection of eukaryotic viruses in human feces (% of positive RT-PCR)

	PHI	CHI_noART	CHI_ART	HIV_neg
ADV	53.2**	50.7**	44.4**	20.4
CMV	6.1	12.7**	11.1	1.8
ETV	2.4	20*	4.2	4.4
HHV 6A, 6B & 8	0	0	0	0

*p <0.1; **p<0.05, Fisher's pairwise comparisons relative to HIV-1 negative. Only the first fecal sample available is used for comparison.

261 HIV-ASSOCIATED CHANGES OF THE GUT MICROBIOME IN ARV-TREATED, UNTREATED, & CONTROLLERS

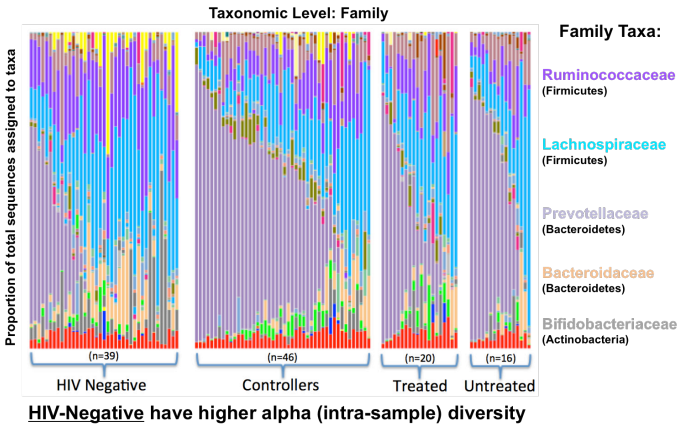
Jesus M. Luevano, David B. Gootenberg, Zoe Rogers, Jeff Paer, Douglas Kwon
Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

Background: HIV infection is associated with gut microbiome alterations, enteropathy, and intestinal translocation of microbial products. It is unclear what HIV associated changes in the gut microbiome occur in HIV-infected individuals who control the disease immunologically without treatment, but they provide a unique model to investigate the effects of HIV infection.

Methods: Our Boston cohort (n=183), the largest of its kind, includes HIV-uninfected controls and three HIV-infected sub-groups: anti-retroviral treated (ART), chronic untreated with high viral loads, and immunologic controllers that maintain low viral loads without ART. Fecal microbial composition was determined by 16S amplicon sequencing. Serum inflammatory markers were measured by immunological assay. These data were analyzed with cohort metadata and clinical data, including dietary micronutrients and macronutrients. Candidate bacteria of significance were selected for an in vitro transepithelial resistance (TER) co-culture assay with Caco-2 cells to determine the epithelial cell response to potential commensals and pathogens associated with HIV infection.

Results: HIV infection was the predominant correlative factor, with significant differences between the bacterial communities of uninfected and HIV-infected individuals regardless of ART or immunologic control. HIV infection was associated with loss of alpha diversity, relative decrease in the phyla Firmicutes and families Bifidobacteriaceae and Bacteroidaceae, and expansion of the family Prevotellaceae. This shift correlated with serum levels of sCD163, an inflammatory marker, in HIV-infected patients. However, controllers uniquely had serum levels of sCD14, a bacterially mediated inflammatory marker, similar to healthy controls despite elevations in other HIV-infected subgroups. Diet, micronutrient, and clinical cohort data were not significant correlative factors. Initial Caco-2 TER assay demonstrated that bacteria significantly enriched by HIV infection have a mixed effect on epithelial integrity.

Conclusion: Our findings demonstrate a complex model for how HIV may alter the gut microbiome and human host health. Our data suggests that bacterial communities, irrespective of means of HIV control, and inflammatory responses, with nuances, could be driven by HIV infection and baseline microbial community structure. However, this alone does not prove that the bacteria enriched in HIV infection elicit a pathogenic effect on the host and colonic epithelium as was previously presumed.



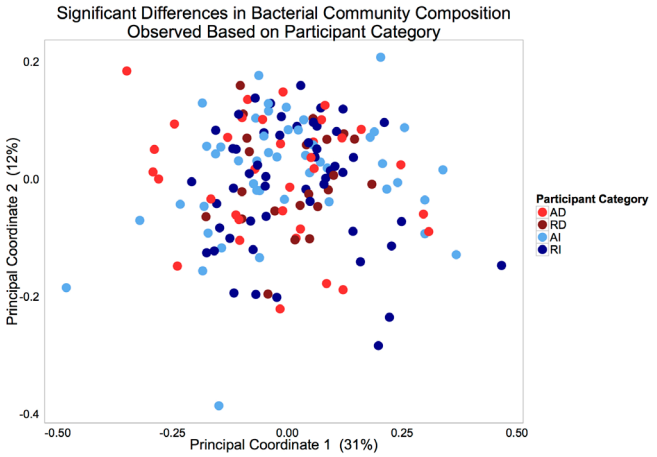
262 TIME BETWEEN HIV ACQUISITION AND ART INITIATION IMPACTS GI MICROBIOME

Douglas Fadrosh[1], Susan V. Lynch[1], Javier R. Lama[2], Ricardo Alfaro[3], Delia Pinto-Santini[4], Rachel A. Bender Ignacio[4], Peter W. Hunt[1], Jessica Rios[3], Ann Duerr[4]
[1]University of California San Francisco, San Francisco, CA, USA, [2]University of Washington, Seattle, WA, USA, [3]Asociacion Civil Impacta Salud y Educacion, Lima, Peru, [4]Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: Recent data suggests that initiation of ART early in infection confers several benefits on HIV-related morbidity and clinical outcomes. Because initiation of ART during acute infection is not currently a viable public health strategy, it is important to investigate the relative long-term benefits of starting ART at different times during early infection. We evaluated how timing of ART initiation impacts the gastrointestinal microbiome during early infection in a subset of the Sabes study, a randomized clinical trial in Peru.

Methods: HIV-infected MSM and transgender women who were diagnosed while sero-negative (acute HIV, A), or were sero-positive and 90 days or less from last negative RNA test (recent HIV, R) were randomized within strata to receive standard-of care ART immediately (I) or after 24 weeks deferral (D). Cryopreserved stool samples collected from enrollment to 24 wks, including 1, 2, 4,8 and 16 wks, were analyzed in 29 participants who started ART in acute infection (AI, N=8), recent infection (RI, N=12), or after 24 weeks deferral (AD, N=4; RD, N=5). The V4 hypervariable region of the 16S rRNA gene was

sequenced on the Illumina Nextseq and the resulting microbiota profiles were analyzed. Differences in bacterial community composition were assessed both longitudinally and cross-sectionally using weighted UniFrac; statistical significance was determined using Linear Mixed Effects Models (LME) and permutational multivariate ANOVA (PERMANOVA), respectively.
Results: Using repeated measure analyses, significant differences in the bacterial community composition (beta diversity scores) were observed in the AD group compared to either of recent infection groups (LME, p=0.009 and 0.007 for the RI and RD groups, respectively). Significant differences in bacterial community composition based on a 4-way comparison (groups AI, AD, RI, RD) were also observed at the 1 (p=0.035), 2 (p=0.007) and 24 (p=0.025) week collections with trends toward significant differences at enrollment (p=0.142) and the 4 (p=0.133) week collection.
Conclusion: Our pilot data indicate that time of ART initiation after HIV acquisition is associated with significant differences in gut microbiota composition of HIV-infected patients. Microbiome analysis of samples from HIV uninfected and chronically infected controls, as well as analysis of the microbiome, latent HIV reservoir, and immunologic function in this cohort during long-term follow-up (up to 4.5 years after diagnosis) is ongoing in the MERLIN study.



263 COMPLEXITIES OF GUT MICROBIOME DYSBIOSIS IN HIV INFECTED AND HIGH RISK POPULATIONS

Abigail Armstrong, Michael Shaffer, Nichole Nusbacher, Thomas Campbell, Brent E. Palmer, Catherine Lozupone
University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Background: Gut microbiome composition in HIV-infected populations has been shown by our lab and others to be significantly different from that of HIV negative individuals, even with effective Antiretrovoral Therapy (ART). However, understanding compositional changes associated specifically with HIV infection and immune dysfunction is hindered by several confounding factors including factors unrelated to HIV disease itself such as gender, geography, diet, and sexual behavior. These confounding factors in addition to the complexity of HIV disease itself such as degree of immune suppression and ART usage highlight the need for large cohorts in order to perform well controlled analysis.
Methods: In this study, 16S rRNA targeted sequencing was performed to characterize the fecal microbiome of the largest concurrently analyzed cohort to date for understanding compositional changes that occur in HIV-infected populations, including samples from 217 individuals from Colorado, USA. The analyses controlled for sexual behavior and diet to further characterize gut microbiome attributes that are associated with HIV infection and ART, and show unique HIV-associated changes in men versus women.
Results: We confirmed previous reports that Prevotella-rich microbiomes with increased alpha diversity characterize men who have sex with men (MSM) regardless of their HIV infection status. However, stratified analysis in women and in MSM show significant alterations in microbiome taxa in treated and untreated HIV infection. Furthermore, several taxa changes may be associated specifically with ART usage in both our cross-sectional and longitudinal samples. Lastly, analyses of immune activation in ART-naïve HIV-infected individuals revealed several taxa associated with decreased immune activation as well as increased viral load.
Conclusion: This study provides an in-depth characterization of microbiome differences that occur in a US population infected with HIV and the degree to which these differences may be driven by lifestyle factors, ART, and HIV infection itself. This understanding will help to guide efforts to investigate the functional implications of these differences to ultimately target the microbiome to improve the health of this population.

264 ELEVATED FECAL INFLAMMATORY BIOMARKERS IN HIV-/+ MSM ASSOCIATE TO GUT MICROBIOTA

Jennifer M. Schneider, Sam Li, Charles P. Neff, Nichole Nusbacher, Nancy Moreno-Huizar, Catherine Lozupone, Brent E. Palmer
University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Background: HIV replication and bacterial translocation associate with inflammatory biomarkers in the blood, however less is known about the gut. To more directly assess the effect of HIV and gut microbiota on GI inflammation and barrier integrity we measured inflammatory biomarkers in feces. Recent studies have shown pronounced differences in gut microbiome composition between HIV- men who have sex with women (MSW) and HIV- men who have sex with men (MSM), but the effects of this altered gut microbiome in MSM on gut inflammation are not understood. Using MSM as a control allows for investigation of contributions of HIV and/or the HIV-associated gut microbiome to gut inflammation by eliminating differences driven by sexual behavior.
Methods: Fecal samples were collected from 73 subjects from: HIV- low risk (HIV-LR), high risk (HR) MSM, HIV+ ART treated (HIV+ART+) and HIV+ ART naïve (HIV+ART-) subjects. 30 biomarkers of inflammation, innate cell activation and intestinal barrier integrity were measured by ELISA either from the feces itself or water extracted from 2 grams of stool.
Results: There were no significant differences between any of the biomarkers measured in HR-MSM and HIV+ subjects. However, 12 biomarkers, primarily inflammatory cytokines (e.g. IL-1b (p=0006), IL-12/p23p40 (p<0.0001)) and calprotectin (p=0.009), were elevated in HIV+ART- compared to HIV-LR subjects. Except for ICAM-1 (p=0.03), there were no significant differences between HIV+ subjects on or off ART. Seven biomarkers were elevated in HR-MSM such as IL-12/23p40 (p=0.001), ICAM-1 (p=0.0003) and sCD14 (p=0.008) compared to HIV-LR subjects. Fecal IL-12/23p40 (p=0.001) and ICAM-1 (p=0.0005) were elevated in HR-MSM and further increased in HIV+ART- subjects (p<0.0001, p<0.0001) which correlated to viral load (IL-12/23p40, r=0.42, p=0.015) and CD8+/HLA-DR+/CD38+ T-cells (ICAM, r=0.48, p=0.003) in peripheral blood. We found fecal IL-12/23p40 in HIV- subjects correlated with Peptococcus, while in HIV+ subjects associated with Prevotella from the Paraprevotellacaea family.
Conclusion: These data show that gut inflammation is elevated in MSM, and by some measurements exacerbated with HIV infection. Similar to gut microbiome phenotypes, these inflammatory phenotypes are primarily associated with HR-MSM, suggesting that gut inflammation is more impacted by sexual behavior and associated gut microbiome differences than by HIV infection itself. These data highlight the importance of including HIV- MSM controls in GI inflammation studies.

265 EFFECTS OF SUBSTANCE USE AND SEXUAL BEHAVIOR ON THE INTESTINAL MICROBIOME IN HIV

Jennifer A. Fulcher[1], Ryan Cook[1], Fan Li[1], Shehnaz K. Hussain[2], Nicole Tobin[1], Amy Ragsdale[1], Steven Shoptaw[1], Pamina Gorbach[1], Grace M. Aldrovandi[1]
[1]University of California Los Angeles, Los Angeles, CA, USA, [2]Cedars–Sinai Medical Center, Los Angeles, CA, USA

Background: HIV-1 infection alters the human intestinal microbiome; however, the factors driving these changes remain poorly defined. In this study, we examine the effects of substance use and sexual behavior on the intestinal microbiome during chronic HIV-1 infection in men who have sex with men (MSM).
Methods: Samples were obtained from an ongoing cohort (The mSTUDY) examining the effects of substance use on HIV-1 transmission and pathogenesis in young MSM. Rectal swabs, urine drug testing, and substance use and sexual behavior questionnaires were obtained from HIV-positive participants at baseline and 6-month follow-up visits (n=37). Microbiome profiling was performed using 16S rRNA gene sequencing and data processed using QIIME v1.9.1. Associations between substance use and sexual behavior variables and

microbiota abundance were examined for each visit separately (n=74) using zero-inflated negative binomial regression (ZINB). Further analysis of selected variables of interest was performed using propensity scores (PS) to better account for multiple confounders.

Results: Using permutational multivariate analysis of variance (PERMANOVA) with Bray-Curtis distances we found the most significant drivers of microbiome variation were the individual (P=0.001), methamphetamine use (P=0.04), and oral semen exposure (P=0.003). Microbiome composition varied with sexual behavior; oral sex and receptive anal intercourse (RAI) displayed overlapping associations, likely attributable to multiple sex acts. Drug use similarly influenced microbiome composition, with drugs often used concurrently clustering together (prescription drugs, ecstasy, party drugs). Marijuana and methamphetamine displayed unique associations, most notable for increased *Prevotella* with methamphetamine. Further analysis using PS to better account for multiple confounders revealed clearer associations. Methamphetamine use was associated with increased *Prevotella*, *Campylobacter*, and *Peptostreptococcus* while marijuana use decreased *Paraprevotella* and *Gemella*. Recent RAI was associated with increased *Gemella*, *Mycoplasma* and *Veillonella*, with decreases in *Parabacteroides*, *Blautia*, and *Ruminococcus*.

Conclusion: Drug use and sexual behavior influence intestinal dysbiosis during chronic HIV-1 infection among MSM, with specific inflammatory changes associated with methamphetamine use. This study highlights the importance of these factors in HIV-associated dysbiosis.

266 LIVER BACTERIAL DYSBIOSIS PERSISTS DURING ANTIRETROVIRAL THERAPY IN SIV+ MACAQUES

Bridget Fisher[1], Cole Fisher[1], Matthew Wood[1], Melanie Gasper[2], Elise Smith[3], Richard Green[3], Connor Driscoll[3], Michael Gale[3], Guido Silvestri[4], Ann Chahroudi[5], Nichole Klatt[6], Donald Sodora[1]

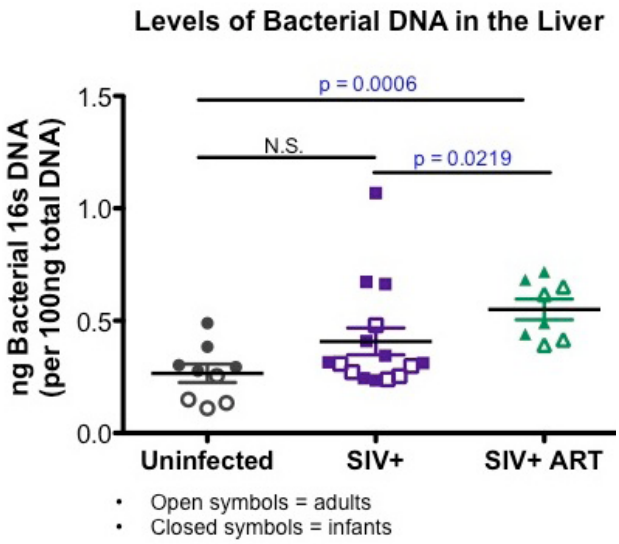
[1]Center for Infectious Disease Research, Seattle, WA, USA, [2]Seattle Children's Research Institute, Seattle, WA, USA, [3]University of Washington, Seattle, WA, USA, [4]Yerkes National Primate Research Center, Atlanta, GA, USA, [5]Emory University, Atlanta, GA, USA, [6]Washington National Primate Research Center, Seattle, WA, USA

Background: Even during combination antiretroviral therapy (cART), liver disease is a significant contributor to morbidity and mortality in HIV+ individuals. Here, we present evidence in a SIV-macaque model that treatment with cART does not reduce bacteria levels or microbial dysbiosis in the liver, which may contribute to hepatic dysfunction and impact disease outcome.

Methods: Liver tissue was acquired at necropsy from infant and adult rhesus macaques that were uninfected (n=7/4, infant/adult), SIV+ (n=9/6), or SIV+/cART-treated (n=4/6). LPS-binding protein (LBP) levels were quantified in plasma (ELISA) and 16s bacterial DNA was quantified by in the liver (qPCR). The liver microbiome composition was evaluated by 16s microbial sequencing with operational taxonomic units determined by QIIME analysis. Dysbiotic liver bacteria were tested for the ability to induce liver-specific hepatocyte inflammation (gene expression analysis) and systemic immune activation using whole blood assays (flow cytometry).

Results: An increase in bacterial translocation was identified via elevated plasma LBP levels in both SIV+ and SIV+cART macaques. Assessment of liver bacterial 16s DNA levels determined elevated bacterial load was present in SIV+cART macaques (compared to uninfected) (p=0.0006). Liver microbiome assessment of SIV+ macaques revealed an abundance of bacteria generally associated with HIV dysbiosis in the gut (e.g. Gammaproteobacteria) and an enrichment of Mycobacteria, which persisted during cART. Using multi-gene sequencing, the liver-associated Mycobacteria was identified as M. smegmatis, an opportunistic pathogen. In vitro experiments demonstrated that M. smegmatis stimulates monocytes to produce high levels of TNFa, even more potently than other species of Mycobacteria (BCG, M. tuberculosis). Importantly, M. smegmatis also induced inflammatory responses in hepatocytes through an upregulation of inflammation-associated genes (e.g. CRP, IL-6, IFNb, CCL2),

Conclusion: Our findings indicate that cART does not sufficiently reduce bacterial translocation as demonstrated by elevated levels of LBP in plasma and bacterial DNA in the liver. In addition, an abundance of Mycobacteria was observed in the liver that was associated with inflammatory responses in both monocytes and hepatocytes. These findings provide mechanistic insights regarding the factors that influence the high prevalence of liver disease in HIV+cART-treated individuals.



267 PREGNANCY ASSOCIATED VAGINAL PROTEOME ALTERATIONS LINKED TO HIV ACQUISITION RISK

Christina Farr Zuend[1], **Nicole Tobin**[2], Kenzie Birse[1], Laura Noël-Romas[1], Lani Kotyrba[1], Trisha Vera[1], Sarah Mutch[1], Max Abou[3], Stuart McCorrister[3], Garrett Westmacott[3], Grace M. Aldrovandi[2], Adam Burgener[1]

[1]University of Manitoba, Winnipeg, MB, Canada, [2]University of California Los Angeles, Los Angeles, CA, USA, [3]Public Health Agency of Canada, Winnipeg, MB, Canada

Background: Pregnant women are at increased risk of HIV acquisition, due to both behavioral and biological factors, but the mechanisms are not well understood. Immunological, structural and bacterial changes during pregnancy may all lead to increased HIV susceptibility. Here we assessed host immune pathways and bacterial differences in the vaginal mucosa of pregnant and non-pregnant women using a metaproteomics approach to identify potential mechanisms of HIV susceptibility.

Methods: Cervicovaginal lavage (CVL) samples collected from 23 pregnant and 25 non-pregnant women were analyzed by mass spectrometry. Microbial abundance and taxa identifications were determined using non-homologous bacterial proteins. Differential protein expression was determined by t test and bacterial taxa by Mann-Whitney test. Functional information was assigned using the KEGG ontology and IPA knowledge databases. Gene set enrichment analysis (GSEA) was utilized to compare pregnancy-associated signatures with HIV acquisition risk using a proteomic dataset generated from 701 women, 63 of which were pre-seroconversion CVL samples.

Results: 550 human proteins and 376 bacterial proteins from 9 genera were identified. Two major bacterial groups were identified, Lactobacillus dominant or non-Lactobacillus dominant. All pregnant women were Lactobacillus dominant (100%), compared to only 79% of non-pregnant women (p=1.66E-2). Pregnancy also associated with changes to the functional microbiome, including increases to carbohydrate metabolism (p=3.66E-2) and metabolism of cofactors and vitamins (p=3.95E-2). Host proteome analysis indicated 56 human proteins (10%) were differentially abundant (p<0.05) between pregnant and non-pregnant women, including alterations to complement (p=3.63E-3), leukocyte extravasation signaling (p=1.45E-2), blood vessel formation (3.36E-3) and tissue permeability (p=1.27E-4). GSEA analysis indicated that pregnant women with ectopy had the strongest overlap (p=0.003, p<0.001) to host proteome signatures predicting increased risk for HIV acquisition.

Conclusion: Pregnant women, particularly those with cervical ectopy, have alterations to mucosal proteome pathways related to immune system, blood vessel formation and mucosal barrier function. The overlap of certain pregnancy-associated pathways with increased HIV acquisition risk in an independent cohort provides a plausible role of these functions in HIV susceptibility during pregnancy.

268 VAGINAL MICROBIOTA AND HIV ACQUISITION RISK AMONG AFRICAN WOMEN

Sujatha Srinivasan[1], Barbra A. Richardson[2], Jacqueline Wallis[1], Tina L. Fiedler[1], Charlene S. Dezzutti[3], Z. Mike Chirenje[4], Edward W. Livant[5], David N. Fredricks[1], Sharon L. Hillier[3], Jeanne Marrazzo[6]
[1]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [2]University of Washington, Seattle, WA, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA, [4]University of Zimbabwe, Harare, Zimbabwe, [5]Magee–Womens Research Institute, Pittsburgh, PA, USA, [6]University of Alabama at Birmingham, Birmingham, AL, USA

Background: Recent studies have identified vaginal bacterial community types and species associated with HIV acquisition risk. However, results have not been consistent, perhaps reflecting different study populations and methods. We aimed to define associations between concentrations of vaginal bacterial species and genera with risk of HIV acquisition among women participating in the VOICE study, a randomized placebo-controlled trial of daily oral vs. vaginal tenofovir-based pre-exposure prophylaxis for HIV.

Methods: Vaginal swabs were collected routinely at 6 month intervals or when pelvic examination was indicated. Cases and controls were matched by study arm and site. Concentrations of nine bacterial taxa previously shown to be associated with increased HIV risk, and one associated with protection, were measured using quantitative PCR. Each taxon was analyzed as a four-category exposure including undetectable, 1st, 2nd, and 3rd tertiles of concentrations, and relationship between bacterial concentrations and HIV risk assessed using Generalized Estimating Equation models. A Benjamini-Hochberg False Discovery Rate of 0.05 was applied. Models were adjusted for age, contraception method, number of sex partners, frequency of sex, and report of condom use.

Results: The relationship between vaginal bacteria and HIV acquisition at 177 HIV pre-seroconversion visits from 150 women who acquired HIV (cases), and 531 visits from 436 women who remained HIV uninfected (controls) was examined. Six taxa were significantly associated with increased HIV acquisition including *Eggerthella* sp. Type 1 (p=0.011), *Gemella asaccharolytica* (p=0.002), *Leptotrichia/Sneathia* spp. (p=0.021), *Megasphaera* sp. Type 2 (p<0.001), *Mycoplasma hominis* (p<0.001), and *Parvimonas* sp. Type 2 (p=0.01). *Prevotella bivia*, previously linked with higher risk in South African women, was not significant in the adjusted model (p=0.055). *Megasphaera* sp. Type 1 (p=0.66) and *Parvimonas* sp. Type 1 (p=0.16) were not associated with increased risk. Women with the highest tertiles of *Lactobacillus crispatus* had a decreased risk of HIV acquisition (p=0.034).

Conclusion: Concentrations of specific vaginal bacteria are consistently associated with HIV acquisition risk in African women. Bacterial targets may serve as biomarkers of HIV risk or protection. Antibacterial therapy could be explored as one approach to reduce HIV risk in women.

269 THE VAGINAL MICROBIOME IN PREGNANCY DIFFERS BY HIV STATUS, ART EXPOSURE, AND CLASS

Charlotte-Eve S. Short, Richard Brown, Rachael A. Quinlan, Robin J. Shattock, Phillip R. Bennett, Graham P. Taylor, David A. MacIntyre
Imperial College London, London, UK

Background: The vaginal microbiome during healthy pregnancy is characterised by increased Lactobacillus spp. dominance and reduced diversity. Increased diversity or early dominance by Lactobacillus iners associates with preterm birth (PTB) risk. The composition of vaginal bacterial communities in HIV–infected pregnant women is yet to be described despite their increased risk of PTB. This study characterises and compares the vaginal microbiome of HIV-infected pregnant women with uninfected pregnant women delivering at term, and explores associations with PTB and antiretroviral therapy (ART).

Methods: Pregnant women were prospectively recruited from 10 London antenatal clinics to 2 cohorts: HIV-infected with a CD4 cell count >350 cells/mL (n=53) and uninfected controls (n=30). HIV infected women were further classified as pre ART (no therapy(12)), on PI–based ART(16) and non PI-based ART(25). High vaginal swabs were obtained at 14-22 weeks. MiSeq sequencing of 16S rRNA gene amplicons was used to characterise the microbiome. Multivariate modelling was performed to explore associations with bacterial genus/species and clinical data.

Results: HIV-infected mothers (median age 35yrs), 81% were of Black ethnicity and 14% had PTB. In contrast 50% of controls were Caucasian (median age 33yrs). HIV infection was associated with higher frequency of vaginal microbial dominance by L. iners (45 v 23%, p<0.001) and G. vaginalis (17 v 7%, p<0.001), whereas L. crispatus dominance was associated with healthy controls (45 v 15%, p<0.001). HIV-infected mothers delivering at term had higher mean abundance of Gardnerella (18 v 3%, p=0.003) and Prevotella species (4 v 0.1%, p=0.002) and lower levels of Lactobacillus species (70 v 93%, p=0.009) compared to uninfected controls. Amongst HIV-infected women, PTB was associated with increased G. vaginalis (p=0.04) and Prevotella species (p=0.05) compared with term births. Women conceiving on ART had a higher abundance of Atopobium vaginae, Snaethia and Ureaplasma parvum than women pre ART initiation (p <0.05). Women receiving PI-based ART had a higher abundance of U. parvum than women pre ART (p=0.02), not withstanding correction. No difference was observed by non PI ART or nucleoside backbone.

Conclusion: Vaginal bacterial communities of HIV-infected pregnant women are characterised by increased dominance by L. iners and G. vaginalis. The associations of higher abundance of anaerobic pathogens observed with HIV, PTB and PI-exposure at conception warrant further investigation.

270 BACTERIAL VAGINOSIS ASSOCIATED MICROBES INDUCE ALTERED INNATE IMMUNE PROFILES

Ryan Cheu[1], Tiffany Hensley-McBain[1], Avid Mohammadi[2], Jennifer A. Manuzak[1], Alexander S. Zevin[1], Charlene J. Miller[1], Mark Yudin[2], Rupert Kaul[2], Nichole Klatt[1]
[1]University of Washington, Seattle, WA, USA, [2]University of Toronto, Toronto, ON, Canada

Background: Bacterial vaginosis (BV) is associated with inflammatory responses and an increased transmission rate of HIV, however, the mechanism(s) underlying this are unknown. BV is characterized by a change from a predominantly Lactobacillus spp. environment to a more diverse community, including Gardnerella vaginalis. Inflammatory cells such as neutrophils are critical for innate immune responses, but can also contribute to barrier damage and inflammation. Currently, the role of neutrophils in HIV transmission and BV status is unknown. Here, we hypothesize that BV-associated bacteria will induce neutrophil activation and prolonged life, promoting neutrophil accumulation in the female reproductive tract (FRT), thereby potentially promoting tissue damage.

Methods: In order to elucidate the mechanisms for the negative consequences of BV, we collected cervicovaginal cytobrushes from 6 women with BV (Nugent >7), and without BV (Nugent <5). We used flow cytometry to assess phenotype and functionality of neutrophils, and performed in vitro whole blood co-cultures with bacteria associated with BV (*G. vaginalis*), healthy commensals such as *L. iners* and *L. crispatus*, media alone (negative control) and lipopolysaccharide and peptidoglycan (positive controls).

Results: We demonstrated increased neutrophil activation via CD62L downregulation (p=0.0022) and prolonged lifespan via decreased caspase-3 expression (p=0.0022) in the cytobrushes with women with BV. Similarly, in our co-culture experiments we observed more neutrophil activation (p<0.0001) and prolonged lifespan (p=0.079) in cultures with G. vaginalis similar to our positive controls. Of interest, women without BV had reduced inflammatory immune responses similar to our in vitro experiments with cultures containing Lactobacillus spp. that maintained immune cell phenotypes similar to negative controls.

Conclusion: Here, we demonstrate that BV-associated bacteria induce neutrophil activation and delay apoptosis as a potential mechanism for promoting tissue damage. Women without BV, that have healthy vaginal mucosal bacterial communities (Lactobacillus) may support the balance between antimicrobial function of neutrophils and do not induce inflammation, whereas women with BV and dysbiotic vaginal communities (G. vaginalis) potentially lead to neutrophil accumulation and tissue damage. Thus, this study provides potential mechanistic insights into how BV may lead to FRT inflammation and increased HIV transmission.

271 MICROBIOME-ASSOCIATED EPITHELIAL DISRUPTION MODIFIES HIV ACQUISITION RISK IN WOMEN

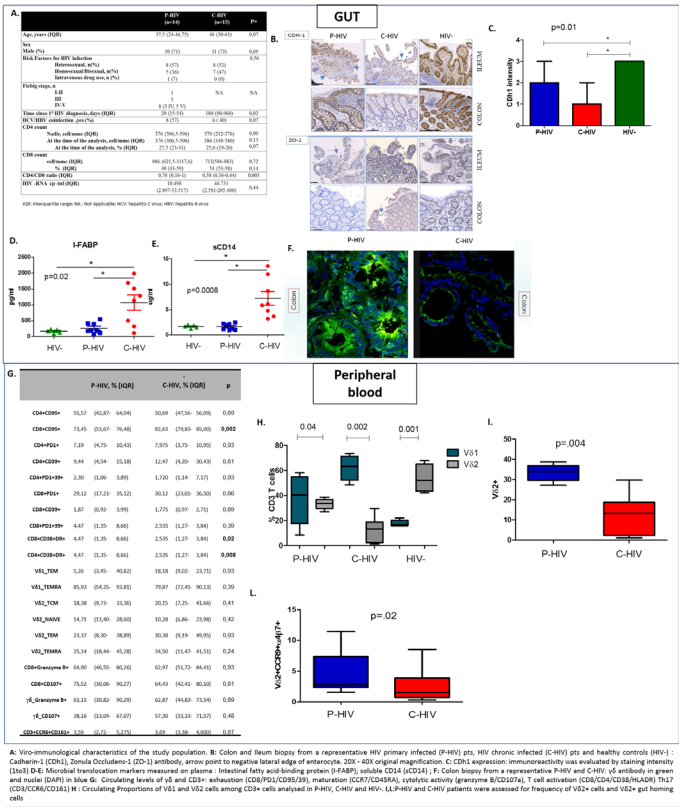
Laura Noël-Romas[1], Michelle Perner[2], Alicia Berard[2], Ann M. Carias[3], Kenzie Birse[2], John Schellenberg[2], Melissa Lemke[4], Annelie Tjernlund[5], Garrett Westmacott[1], Douglas Lauffenburger[6], Kristina Broliden[5], Lyle McKinnon[2], Kelly Arnold[4], Thomas Hope[3], **Adam Burgener**[2]
[1]Public Health Agency of Canada, Winnipeg, MB, Canada, [2]University of Manitoba, Winnipeg, MB, Canada, [3]Northwestern University, Chicago, IL, USA, [4]University of Michigan, Ann Arbor, MI, USA, [5]Karolinska University Hospital, Stockholm, Sweden, [6]MIT, Cambridge, MA, USA

Background: Understanding the biological correlates of HIV susceptibility in young women is critical for prevention efforts, but these are not well defined. Here we utilized a metaproteomics approach to identify cervicovaginal host and bacterial factors underlying HIV acquisition risk in women from the CAPRISA 004 trial, and examined functional relationships using rhesus macaques (RM) and in vitro models.
Methods: Cervicovaginal lavage samples from last HIV negative time point in 63 women who acquired HIV within the trial (cases), and 638 women who remained uninfected, were analyzed by mass spectrometry. A total of 5,335 host and bacterial proteins were identified. Cox PH models and hierarchical clustering were used to determine relationships to risk of HIV infection. Bacterial co-cultures were used to study bacteria-proteome interactions. In vivo immunofluorescense and RNAseq data of early infectious foci was collected from vaginal mucosal tissues of dual-reporter SIV/SIV challenged RM's.
Results: Twenty proteins were differentially abundant in cases (P<0.05, HR>1.6, FD>1). Eleven downregulated proteins best classified cases from controls by cluster analysis (OR: 3.7 (2.1-6.6), P=2.21E-6). These localized to the upper vaginal epithelium signifying epithelial barrier disruption (EBD). Women with EBD had similar baseline characteristics to those without EBD, and adjustments for STI's, contraceptive usage, sexual behaviors, and other criteria did not impact these findings. In vaginal tissue of SIV-challenged RM, GSEA and immunofluorescence showed HIV risk proteins could distinguish virus susceptible from non-susceptible sites (NES=1.95, P<0.0001). EBD was most frequent in women with vaginal community state type (CST) IV bacteria (Prevotella, Mobiluncus, others) (OR: 4.57 (2.45-8.64), P=8.5E-07). CST-IV bacteria reduced EBD protein expression in vaginal epithelial cells in vitro (P<0.05). HIV risk with EBD was exacerbated by CST-IV bacteria (Interaction P=0.0393); women with both EBD and CST-IV bacteria were the highest risk group identified, with a 8.9-fold increase compared to women without EBD and CST-I bacteria (L. crispatus) (HR=9.89 (4.01-24.37), P=1.4E-4).
Conclusion: This study identifies a high-risk phenotype and provides evidence that epithelial disruption exacerbated by vaginal bacteria increases HIV acquisition risk in young women, which may represent vulnerable tissue sites favorable for virus. Strategies reducing bacteria-associated EBD may decrease HIV acquisition in young women.

272 IMPAIRED GUT TIGHT JUNCTION BUT PRESERVED ΓΔ AND MICROBIAL TRANSLOCATION IN ACUTE HIV

Elvira S. Cannizzo, Giuseppe Ancona, Delfina Tosi, Federica Savi, Camilla Tincati, Antonella D'Arminio Monforte, Giulia Marchetti
University of Milan, Milan, Italy

Background: Disruption of gastrointestinal integrity and subsequent microbial translocation (MT) are hallmarks of chronic HIV infection (C-HIV). Likewise, γδ T-cells are deeply affected in number and function. Despite their pivotal role in mucosal immunity, few data are available on gut-associated γδ T-cells during HIV. Thus, we aimed to comparatively investigate circulating and gut-associated γδ T-cells in primary (P-HIV) and C-HIV infection and their possible association with gut Junctional Complexes (JC) and MT.
Methods: In 14 P-HIV patients (pts, Fiebig I-V), 15 C-HIV and 10 age-matched healthy controls (HC) we measured in peripheral blood (PB): (i) γδ frequency (CD3+panγδ+Vδ1+Vδ2+), (ii) γδ and CD3+ exhaustion (CD8/PD1/CD95/39), maturation (CCR7/CD45RA), cytolytic activity (granzyme B/CD107a), gut-homing (α4β7/CCR9/CD103) (Flow Cytometry, FC) (iii) T-cell activation (CD8/CD38/HLADR) (iv)Th17 (CD3/CCR6/CD161) (FC); (iv) plasma MT (I-FABP, sCD14, EndoCAb) (ELISA). On colon/ileum biopsies: (i) tight junction (TJ) proteins (CDh1, ZO-1) (Immunohistochemistry, IHC), (ii) T-cell count (CD3, CD4, CD8) (FC); (iii) γδ quantification (FC and IHC). Chi-square, Mann-Whitney test were used.
Results: Fig. 1A shows the clinical characteristics of P-HIV and C-HIV pts. Compared to HC, C-HIV and P-HIV displayed equally contracted ileum/colon CD4+ and CDh1 and ZO-1, with TJ immunostaining being distributed only at the basolateral cell surface and not around the entire epithelial surface (Fig.1B-C). Despite the CDh1/ZO-1 zonal loss, P-HIV featured lower circulating I-FABP and sCD14 vs C-HIV, comparable to HC (Fig.1D-E), suggesting contained gut damage and MT. Interestingly, gut γδ T frequency seemed conserved in P-HIV vs C-HIV (Fig. 1F). In PB, P-HIV showed heightened activated CD8+/CD4+CD38+HLA-DR+, lower exhausted CD95+CD8+ and similar Th17-like CD3+CD161+CCR6+ vs C-HIV (Fig.1G). Both P-HIV and C-HIV displayed a higher Vδ1 vs Vδ2 cells, in contrast with Vδ2 predominance in HC (Fig. 1H), consistent with an inversion of the physiologic Vδ2/Vδ1 ratio. Moreover, P-HIV featured higher Vδ2 cells (p=0.004) (Fig.1I) with gut homing phenotype (p=0.02) (Fig.1L).
Conclusion: Despite the damaged JC, early-infected HIV pts still contain MT, possibly due to an enrichment in gut-associated γδ cells known to positively regulate mucosal homeostasis. Further, the inverted plasma Vδ2/Vδ1 ratio with outgrowth of gut-homing Vδ2, confirms subverted γδ balance with ongoing gut recruitment.



A: Viro-immunological characteristics of the study population. B: Colon and Ileum biopsy from a representative HIV primary infected (P-HIV) pts, HIV chronic infected (C-HIV) pts and healthy controls (HIV-) : Cadherin-1 (CDh1), Zonula Occludens-1 (ZO-1) antibody, arrow point to negative lateral edge of enterocyte. 20X - 40X original magnification. C: CDh1 expression: immunoreactivity was evaluated by staining intensity (1to3) D-E: Microbial translocation markers measured on plasma : Intestinal fatty acid-binding protein (I-FABP); soluble CD14 (sCD14) ; F: Colon biopsy from a representative P-HIV and C-HIV. γδ antibody in green and nuclei (DAPI) in blue G: Circulating levels of γδ and CD3+ exhaustion (CD8/PD1/CD95/39), maturation (CCR7/CD45RA), cytolytic activity (granzyme B/CD107a), T cell activation (CD8/CD4/CD38/HLADR) Th17 (CD3/CCR6/CD161) H : Circulating Proportions of Vδ1 and Vδ2 cells among CD3+ cells analysed in P-HIV, C-HIV and HIV-. I,L:P-HIV and C-HIV patients were assessed for frequency of Vδ2+ cells and Vδ2+ gut homing cells

273 MICROBIAL DYSBIOSIS DOES NOT ALTER DISEASE PROGRESSION IN SIV-INFECTED ASIAN MACAQUES

Alexandra Ortiz[1], Sarah DiNapoli[1], Jacob Flynn[1], Carly Elizabeth C. Starke[1], Stephen Lai[1], Mackenzie Long[1], Ornella Sortino[1], Carol Vinton[1], Joseph Mudd[1], Jacob D. Estes[2], Jason Brenchley[1]
[1]NIH, Bethesda, MD, USA, [2]NCI, Rockville, MD, USA

Background: Progressive HIV infection is associated with systemic immune activation that is not fully ameliorated with effective antiretroviral therapy. Measures of immune activation – including elevated concentrations of circulating pro-inflammatory cytokines, low frequencies of intestinal TH17 cells, and exacerbated T-cell activation – have been shown to correlate with the enrichment of disease-associated intestinal microflora, namely an expansion of bacteria within the phylum Proteobacteria at the expense of the Firmicutes and Bacteroidetes. Although several studies have indicated that the therapeutic administration of probiotic, or commensal species may significantly improve disease progression in non-human primate models of HIV infection, an empirical assessment of the contribution of microbial dysbiosis to disease progression has not yet been executed.
Methods: To assess the contribution of microbial dysbiosis to untreated lentiviral disease progression, we administered vancomycin (10 mg/kg p.o.; 5 doses/month) to 7 rhesus macaques prior to and throughout SIV infection. Prior to infection, vancomycin treatment resulted in a significant increase in the frequency of fecal Proteobacteria and Fusobacteria and a concordant decrease in Bacteroidetes and Firmicutes, as compared to 6 control animals. We infected all animals with SIVmac239 and routinely measured lymphocyte frequency and function by polychromatic flow cytometry, viral loads by SIV-Gag qRT-PCR, and fecal microbial frequencies by 16S sequencing by Illumina.
Results: Fecal microbial instability was evident throughout SIV infection, with increased frequencies of Deltaproteobacteria and Gammaproteobacteria, and

decreased frequencies of Bacteroidales and Clostridia. Despite evidence for progressive and high levels of dysbiosis, no significant differences in viremia, immune activation, or systemic microbial translocation were noted between the experimental groups throughout SIV infection. Clinical indices of disease progression including survival curves did not reveal any evidence for enhanced disease progression in the dysbiotic animals.

Conclusion: Our results demonstrate that microbial dysbiosis does not significantly influence host or viral dynamics during untreated SIV infection and may suggest that observed dysbioses in untreated HIV infection may be ancillary to disease progression.

274 EFFECTS OF PROBIOTIC VISBIOME ES ON COLONIC MUCOSAL CD4 CELLS: RESULTS FROM A5352S

Rachel Presti[1], Douglas W. Kitch[2], Adriana Andrade[3], Alan Landay[4], Jeffrey Jacobson[5], Cara Wilson[6], Eunice Yeh[2], Jacob D. Estes[7], Claire Deleage[7], Karin L. Klingman[8], Netanya S. Utay[9], Edgar T. Overton[10], Jason Brenchley[8], Brett Williams[4]

[1]Washington University St Louis, St Louis, MO, USA, [2]Harvard University, Cambridge, MA, USA, [3]Johns Hopkins University, Baltimore, MD, USA, [4]Rush University Medical Center, Chicago, IL, USA, [5]Drexel College of Medicine, Philadelphia, PA, USA, [6]University of Cologne, Cologne, Germany, [7]National Cancer Institute, Frederick, MD, USA, [8]NIAID, Bethesda, MD, USA, [9]University of Texas at Galveston, Galveston, TX, USA, [10]University of Alabama at Birmingham, Birmingham, AL, USA

Background: HIV infection in the GI tract results in CD4 cell depletion, especially Th17 cells, and neutrophil (PMN) infiltration, characterized by myeloperoxidase (MPO) activity. This results in impaired mucosal barrier function and systemic inflammation. ART fails to fully restore GI mucosal CD4 cells. In non-human primate models, probiotics improve GI CD4 T cell recovery during ART. In A5352s, ART-suppressed HIV-infected individuals were randomized to probiotic Visbiome ES or placebo to determine whether probiotic administration reconstitutes mucosal CD4 cells & Th17 cells and decrease PMN activity. Here, we present results from immunohistochemistry (IHC) on colonic biopsies.

Methods: At entry and after 24 weeks of intervention, participants underwent flexible sigmoidoscopy with 10 punch biopsies. Immunohistochemistry (IHC) staining was performed using antibodies to CD4, IL-17, and MPO. Stained slides were scanned using the ScanScope CS System (Aperio Technologies, Inc.); quantitative image analysis was performed to measure area of lamina propria occupied by CD4 cells, IL-17+ cells, or MPO. Changes from baseline to week 24 were calculated and arms were compared by exact Wilcoxon test.

Results: Of 42 participants enrolled, 30 had paired biopsy specimens for analysis (15 in each arm). Mean age was 48 yrs (range 25,64); 27 males; median CD4 count 718 c/mm^3 (range 263,1839). At baseline, the median % positive staining for CD4 in the placebo arm was 2.1 and 2.0 in the Visbiome ES arm. Median % CD4 decreased to 1.65 in the placebo arm, but only to 1.74 in the Visbiome ES arm, with a median change of -0.21 for placebo, and change of -0.03 in Visbiome (p=0.089). IL-17 staining was highly variable, but demonstrated no median change over 24 weeks (p=0.65). MPO minimally decreased in placebo from 0.18 to 0.11, with a median change of -0.04, while it increased in Visbiome from 0.14 to 0.18 for a median change of 0.05 0.18 over 24 weeks(p=0.081).

Conclusion: Although CD4 cells staining appeared to be more stable in the Visbiome arm when compared to placebo, similar to non-human primate studies, we failed to detect significant differences in CD4, IL-17 or MPO alterations between arms. This may be due to no effect of Visbiome, small study size, diverse nature of HIV and ART history, or short course of probiotic administration. Future analyses will assess measures of systemic inflammation and GI permeability.

Table 1: Changes in % Area Colonic Lamina Propria for CD4, IL-17, and MPO Staining. *P-value by exact Wilcoxon test.

Stain by IHC	Placebo Arm (n=15)			Visbiome ES Arm (n=15)			P value*
	Median % (Q1, Q3) Week 0	Median % (Q1, Q3) Week 24	Median change (Q1, Q3)	Median % (Q1, Q3) Week 0	Median % (Q1, Q3) Week 24	Median change (Q1, Q3)	
CD4	2.14 (1.39, 2.90)	1.65 (1.21 2.14)	-0.20 (-1.03, 0.05)	2.04 (1.30, 2.21)	1.74 (1.43, 3.64)	-0.03 (-0.37, 1.02)	0.089
IL-17	1.50 (0.71, 2.55)	2.16 (0.70, 2.75)	-0.01 (-1.33, 0.89)	0.97 (0.86, 2.56)	1.60 (0.20, 3.13)	0.00 (-0.60, 1.39)	0.653
MPO	0.18 (0.06-0.34)	0.11 (0.03-0.31)	-0.04 (-0.17, 0.04)	0.14 (0.09-0.67)	0.18 (0.09, 0.44)	0.05 (-0.03, 0.30)	0.081

275 THE IMPACT OF SYNBIOTICS IN ADVANCED HIV DISEASE: A RANDOMIZED CLINICAL TRIAL

Sergio Serrano-Villar[1], Maria Lagarde[2], Nadia Madrid[1], Jose I. Bernardino[3], Alejandro Vallejo[1], Carolina Gutiérrez[1], Alfonso Cabello[4], Mariano Matarranz[2], Judit Villar[5], Alberto Díaz de Santiago[6], Jose-Ramón Blanco[7], Talía Sainz[3], Federico Pulido[2], Santiago Moreno[1], Vicente Estrada[8]

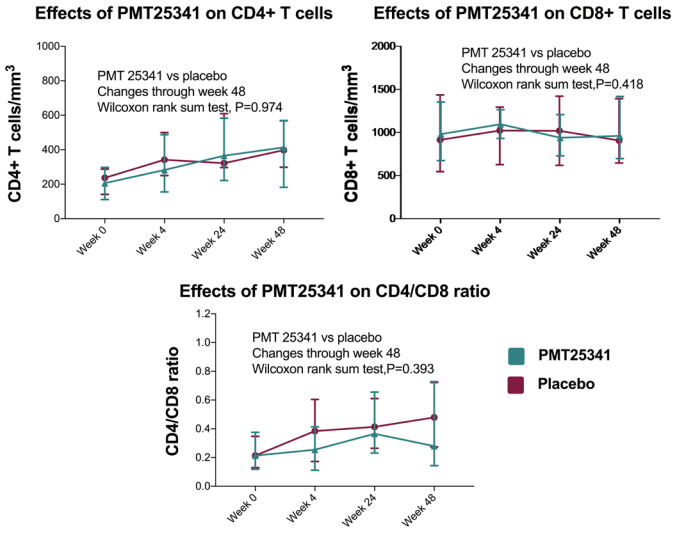
[1]Hospital Ramón y Cajal, Madrid, Spain, [2]Hospital Universitario 12 de Octubre, Madrid, Spain, [3]Hospital La Paz Institute for Health Research, Madrid, Spain, [4]Fundacion Jimenez Diaz, Madrid, Spain, [5]Hospital del Mar, Barcelona, Spain, [6]Hospital Puerta de Hierro, Madrid, Spain, [7]Hospital San Pedro, La Rioja, Spain, [8]Hospital Universitario Clínico San Carlos, Madrid, Spain

Background: Late diagnosis of HIV infection is associated with impaired immunological restoration during ART and poor prognosis. While nutritional interventions with prebiotics and probiotics seem to exert immunological effects, the clinical implications in this key population remain unclear.

Methods: Pilot multicenter randomized placebo-controlled, double blind clinical trial in which 73 HIV-infected ART-naive subjects with <350 CD4 T cells/mm3 or AIDS were randomized (1:1) to either daily nutritional supplementation with the synbiotic mixture PMT25341 or placebo for 48 weeks, each in combination with first-line ART. We performed an intention to treat analysis. Primary endpoints were change in CD4 T-cells and CD4/CD8 ratio levels from baseline to week 48 and safety. Secondary endpoints were changes in markers of inflammation, bacterial translocation and T cell activation and senescence (Clinicaltrials.gov: NCT00870363).

Results: Fifty-nine patients completed the follow-up, mean (SD) age 37 (11 years), 92% men, 83% MSM, CD4 T cells 221 (108)/ul, CD4/CD8 ratio 0.27 (0.19), 10% diagnosed with an AIDS-defining condition. All patients initiated triple ART (61% with integrase inhibitors) and 94% had undetectable plasma HIV RNA at week 48. Baseline characteristics were balanced between arms. PMT25341 was well tolerated, and no grade 3-4 adverse effects attributable to the intervention were identified. Compared to placebo-treated subjects, PMT25341-treated subjects did not experience any significant change in the median change of CD4+ T cells (196 cells/ul vs. 206, P=0.974), CD8+ T cells (-28 cells/ul vs. 120, P=0.418), CD4/CD8 ratio (0.31 vs. 0.24, P =0.393), %HLADR+CD38+ CD4+ T cells (-5.5 vs. -5.4, P=0.356), %HLADR+CD38+ CD8+ T cells (-9.6 vs -7.3, P=0.522) or %CD28- CD8+ T cells (-6 vs. -8.3, P=0.299). Similarly, we did not detect differences between treatment arms in the median fold change of sCD14 (0.85 vs. 0.86, P=0.910), sCD163 (0.58 vs. 0.59, P=0.757), CRP (0.75 vs. 0.71, P=0.843) or LTA (0.51 vs. 0.52, P=0.847) plasma levels.

Conclusion: After 48 weeks of dietary supplementation with a synbiotic mixture aimed at ameliorating the gut microbiota and mucosal immunity, we did not detect an impact on CD4 or CD8 T cell counts, inflammation, bacterial translocation or immune activation. Our data suggest that the clinical benefit of nutritional strategies targeting the gut is very limited in HIV-infected patients initiating ART at advanced disease.



276 SIGNATURES OF PROTECTIVE SIV-SPECIFIC CD8+ T CELLS

Carly Elizabeth C. Starke, Jason Brenchley
NIH, Bethesda, MD, USA

Background: Simian immunodeficiency virus (SIV)-specific CD8+ T lymphocytes can reduce SIV replication, slowing disease progression. However, SIV-specific CD8+ T cells are incapable of reducing viral replication to low levels for the lifespan of most SIV-infected rhesus macaques (RM) and the majority of animals progress to simian AIDS. Recent studies demonstrate that SIV persists in lymphoid follicles, infecting CD4+ follicular helper T (TFH) cells. In rare elite controller Asian macaques, SIV replication is spontaneously controlled and may be attributed to the unique ability of some CD8+ T cells to penetrate into lymphoid follicles and reduce SIV infection of TFH cells.

Methods: To determine whether there are signatures of tissue-resident SIV-specific CD8+ T cells associated with increased virologic control, we analyzed molecular and immunological characteristics of SIV-specific CD8+ T cells in lymphoid and gastrointestinal tract tissues of SIV-infected viremic controller (≤10,000 copies/mL) and noncontroller (>10,000 copies/mL) RM. MHC-I tetramers loaded with SIV epitopes were used to identify SIV-specific CD8+ T cells and flow cytometric, gene chip, and T cell receptor (TCR) clonotypic analyses were used to measure phenotypic and functional qualities.

Results: While we found no differences in the magnitude of SIV-specific T cell responses based upon the ability to control viral replication, RM controllers exhibited increased CXCR5 expression in lymphoid tissues compared to RM noncontrollers. Additionally, frequencies of SIV-specific CD8+ T cells correlated with CD4+ T cell count and frequencies of CXCR5+ SIV-specific CD8+ T cells negatively correlated with plasma RNA viral load and viral DNA within TFH cells. TCRβ clonotypic analysis revealed that CDR3 length distribution was biased towards CDR3s with a length of 14aa, including all public clonotypes, and the TCR repertoire of controllers was more diverse than that of noncontrollers with public clonotypes and some V and J gene segments appearing more frequently.

Conclusion: Our data suggest that inherent functionality and particular trafficking of SIV-specific CD8+ T cells may be important for virologic control. The increased CXCR5 expression by SIV-specific CD8+ T cells of RM controllers may suggest an ability of CD8+ T cells to enter the follicle and reduce viral loads. Understanding the role of SIV-specific CD8+ T cells and the mechanisms that underlie viral control in SIV pathogenesis may lead to improved vaccine and therapeutic development.

277 TCF-1 EXPRESSION IS ASSOCIATED WITH HIV-SPECIFIC CD8+ T CELL PROLIFERATIVE CAPACITY

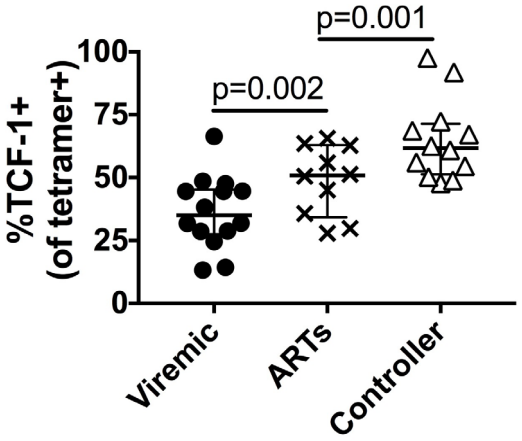
Rachel L. Rutishauser[1], Christian Deo T. Deguit[1], Rebecca Hoh[1], Michelle A. Hough[1], Melissa Krone[1], Rafick-Pierre Sekaly[2], Frederick M. Hecht[1], Christopher D. Pilcher[1], Jeffrey N. Martin[1], Steven G. Deeks[1], Joseph M. McCune[1], Peter W. Hunt[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]Case Western Reserve University, Cleveland, OH, USA

Background: Many HIV cure strategies propose to elicit HIV-specific CD8+ T cell responses to control and/or eradicate the virus, but they will not be effective if they do not prevent or reverse CD8+ T cell exhaustion. A loss in proliferative capacity is a key feature of exhaustion, but little is known about how this capacity is regulated in these cells. The purpose of this study was to explore the connection between TCF-1, a Wnt-signaling transcription factor, and proliferative capacity in HIV-specific CD8+ T cells.

Methods: Cryopreserved PBMCs were sampled from Viremic (VL>8,000 copies/mL; n=14), ART-suppressed (VL<40 copies/mL on stable ART for a median of 2 years; n=10), and Controller (VL<40 copies/mL not on ART; n=12) HIV-infected individuals. Using flow cytometry, HIV-specific CD8+ T cells were identified by staining with Gag, Pol, or Nef-specific MHC Class I (HLA-A*02, *03, *24, or -B*07)-restricted tetramers. Tetramer+ cells were characterized for the expression of transcription factors (TCF-1, Tbet), effector molecules (Granzyme B, Perforin), and surface proteins (PD-1, CD127, CCR7). Proliferation of the tetramer+ population was measured after 6-day in vitro peptide stimulation of CellTraceViolet (CTV)-labeled cells.

Results: HIV-specific tetramer+ CD8+ T cells from Controllers compared to Viremic individuals had greater proliferative responses (%CTVlo 89% vs. 16%; p=0.05; measured in a subset of individuals), were more likely to express CD127 (26% vs. 7%; p=0.0001), and were less likely to express PD-1 (60% vs. 95%; p<0.0001). Median TCF-1 expression was highest in tetramer+ cells from Controllers, followed by ART-suppressed and then Viremic individuals (62% vs. 51% vs. 35%; p<0.0001). TCF-1 expression in these cells was associated with higher CCR7 and CD127, and lower PD-1, Granzyme B, and Tbet expression. Strikingly, expression of TCF-1 (but not PD-1) strongly correlated with proliferative capacity amongst Viremic and Controller individuals (r=0.83, p=0.0008), and was inversely correlated with HIV VL in Viremic individuals (r=-0.85, p=0.02).

Conclusion: TCF-1 expression marks subpopulations of less terminally differentiated tetramer+ HIV-specific CD8+ T cells whose abundance correlates with enhanced proliferative capacity. Whether preservation of TCF-1+ cells is required to prevent HIV-specific T cell exhaustion remains to be investigated, but these data provide a rationale for future studies to evaluate TCF-1 as a target to enhance the efficacy of CD8+ T cell-based HIV cure strategies.



* As 4 participants contributed to Viremic and ART-suppressed groups, linear mixed models were used for p values.

278 LONGITUDINAL T CELL RESPONSES IN HIV-EXPOSED INFANTS WITH CONGENITAL CMV INFECTION

Pamela M. Odorizzi[1], Rachel L. Rutishauser[1], Ruth Cortado[2], Margaret Feeney[1], Trevor Burt[1], Karin Nielsen-Saines[2], Deborah Persaud[3], Yvonne Bryson[2], Joseph M. McCune[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]University of California Los Angeles, Los Angeles, CA, USA, [3]Johns Hopkins University, Baltimore, MD, USA

Background: Congenital CMV (cCMV) infection has a significant impact on pediatric health and affects 0.5-2% of live-born infants worldwide. The rate of cCMV infection is higher amongst children born to HIV-infected mothers, including those who are HIV-exposed but uninfected (HEU). HEU infants are also at higher risk of morbidity from other severe infectious diseases. While many factors likely contribute to this increased risk, the impact of cCMV infection on immune responses in HEU infants is unknown. The goal of this study was to determine how cCMV in HEU infants impacts global CD4+ and CD8+ T cell responses over the first 3 months of life.

Methods: Cryopreserved PBMCs were obtained from HEU infants who were either diagnosed with cCMV at birth (CMV detected by PCR in the urine, HEU:CMV+) or who were CMV-negative at birth (HEU:CMV-; n=6 infants per group). Longitudinal samples from three time points (2, 6, and 12 weeks of age) were evaluated. CD4+ and CD8+ T cells were stained and evaluated by flow cytometry to determine the expression of effector-memory markers (CD45RA, CCR7). The expression of effector proteins (e.g., Tbet, Granzyme B) and chemokine receptors that delineate CD4+ T cell subsets (e.g., Th1, Th17, Treg) was characterized on non-naïve T cells.

Results: Compared to HEU:cCMV- infants, 2 week old HEU:cCMV+ infants form a large population of non-naïve effector CD8+ T cells that express Tbet (66% vs. 15%; p=0.002) and Granzyme B (62% vs. 1%; p=0.002). This profound effector-differentiated CD8+ T cell response is stably maintained at 6 and 12 weeks. While there is less of an effect on CD4+ T cell responses, cytotoxic non-naïve CD4+ T cells are also found at higher frequency at 2 weeks of age in HEU:cCMV+ compared to HEU:cCMV- infants (%Granzyme B+ non-naïve CD4+ T cells: 0.75% vs 0.006%; p=0.002).

Conclusion: cCMV infection in HEU infants induces the generation of a effector-differentiated CD8+ T cells and, to a lesser extent, CD4+ T cells that

persist over time. This suggests that an adult-like "set-point" in the T cell compartment is established early in life by cCMV infection. These results provide rationale for future studies to correlate immunologic findings with infant clinical outcomes, including cCMV clearance, vaccine responses, and rates of febrile illness. Collectively, these studies will add to our current understanding of immune development in the setting of congenital infection and provide critical information to inform CMV therapy and vaccine design in infants.

279 PHOSPHORYLATED HIV-1 AS POTENTIAL CYTOTOXIC T LYMPHOCYTE (CTL) TARGETS

Fatema Z. Chowdhury[1], Shivaali Maddali[1], Matthew J. Szucs[2], Rushdy Ahmad[2], John Sidney[3], Alessandro Sette[3], Pratikkumar Rathod[4], Emmanuel J. Chang[4], Mathias Lichterfeld[1], Xu G. Yu[1]

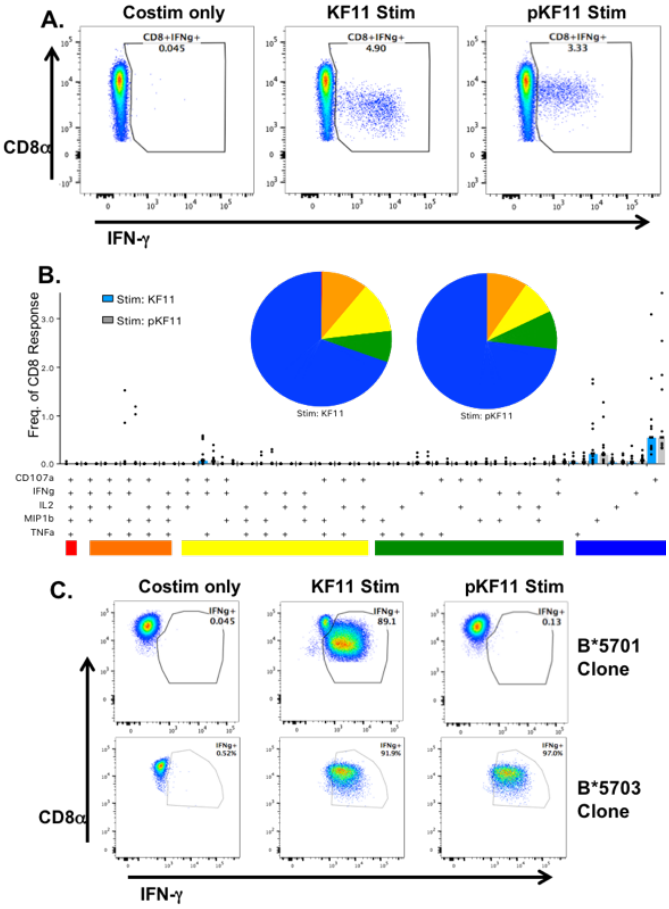
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Broad Institute of MIT and Harvard, Cambridge, MA, USA, [3]La Jolla Institute for Allergy and Immunology, La Jolla, CA, USA, [4]City University of New York, New York, NY, USA

Background: As a small retrovirus, HIV-1 depends on the host cell machinery to support its life cycle. Host kinases can phosphorylate HIV-1, which can influence functional states of viral proteins and may influence viral replicative fitness. How HIV-1 phosphorylation affects viral immune recognition by cytotoxic T cells is unknown at present. Notably, recognition of phosphorylated epitopes by CD8 T cells is well documented in the context of lymphoma and melanoma.

Methods: In vitro infected CD4 T cells (n=4) and cell-free HIV-1 isolated from culture supernatants (n=3) were subjected to LC-MS/MS mass spectrometry. Selected identified phosphorylated HIV-1 peptides were synthesized and tested for HLA class I binding. PBMCs from HIV-1 infected patients were stimulated with phosphorylated and non-phosphorylated peptides, followed by flow-cytometric analysis of antigen-specific effector response (Fig A, B).

Results: We identified 30 unique and largely novel site-specific phosphorylation in HIV-1, the majority of which were located in the Gag, Pol, and Rev proteins. Of 74 optimal CTL epitopes within Gag, 34 contained identified phosphorylated sites, suggesting that phosphorylation may influence immune recognition by CTLs. Out of six CTL epitopes with detectable phospho-residues selected for further analysis, three phosphorylated epitopes were recognized by CTLs from HIV-1 infected patients in direct ex-vivo assessments. Although CTL responses to these phosphorylated peptides were polyfunctional, the magnitude and cross reactivity of these phospho epitope-specific CTL varied with both epitope and HLA background (Fig A, B). Specifically, while both B*5701 and B*5703 patients responded to phosphorylated version of the immunodominant KF11 epitope, these responses were lower in magnitude and functional avidity when compared with the non-phosphorylated KF11 (Fig A). Cloning of KF11-specific CTLs indicated that cross-reactivity between the phosphorylated and the corresponding non-phosphorylated epitope were mediated by single TCRs (Fig C).

Conclusion: Host kinases can phosphorylate HIV-1 at immunogenic regions. Multiple phosphorylated CTL epitopes can be recognized by HIV-1-specific CTLs, and TCRs able to cross-recognize phosphorylated epitopes are naturally recruited, suggesting that presentation of phosphorylated epitopes may occur in vivo. Phospho-epitope specific T cell responses may modulate the efficacy of antiviral cellular immune responses.



280 EVALUATING THE LINK BETWEEN MITOCHONDRIAL STATE & HIV-SPECIFIC CD8+ T CELL EXHAUSTION

Christian Deo T. Deguit[1], Michelle A. Hough[2], Rebecca Hoh[2], Melissa Krone[2], Christopher D. Pilcher[2], Jeffrey N. Martin[2], Steven G. Deeks[2], Joseph M. McCune[2], Peter W. Hunt[2], Rachel L. Rutishauser[2]

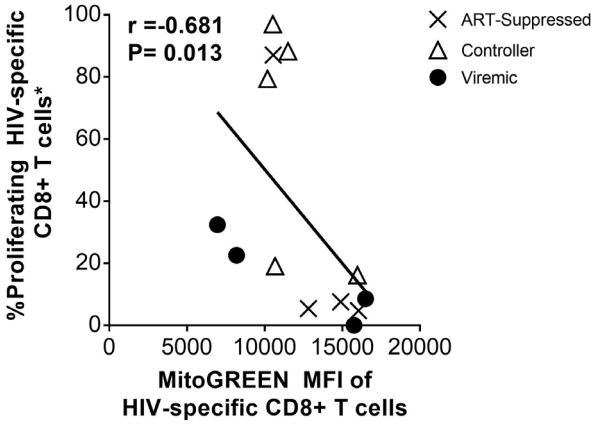
[1]University of the Philippines Manila, Manila, Philippines, [2]University of California San Francisco, San Francisco, CA, USA

Background: Antigen-specific CD8 T cell exhaustion, marked by poor proliferative and effector capacity, occurs in HIV disease and other settings of persistent antigen stimulation such as other chronic infections and cancer. Distinct metabolic features, such as increased mitochondrial mass (MM), decreased mitochondrial membrane potential (MMP), and increased reactive oxygen species (ROS) content are related to greater antigen-specific exhaustion. Yet, the contribution of these pathways to HIV-specific CD8 T cell exhaustion has not been explored. We hypothesized that HIV-specific CD8 T cells with features of exhaustion (e.g. cells from viremic individuals, with increased PD-1 expression and/or with poor proliferative capacity) have a distinct mitochondrial state that is linked to their dysfunction.

Methods: Cryopreserved PBMC samples were obtained from 20 HIV-infected individuals in 3 clinical groups: Viremic (VL>2000 copies/mL, ART-naïve, n=6), ART-suppressed (VL<40 copies/mL on stable ART for a median of 11 years, n=8), and Controllers (VL<40 copies/mL, n=6). Using flow cytometry, we evaluated the MM, MMP, and ROS content of MHC Class I tetramer+ HIV-specific CD8 T cells in these individuals. We also characterized the tetramer+ cell expression of co-inhibitory receptors, effector molecules, and proliferative capacity after 6-day in vitro peptide stimulation.

Results: Although the mitochondrial state of HIV-specific tetramer+ CD8 T cells did not vary by clinical group, we found significant differences within tetramer+ subsets identified by PD-1, CD127, and/or CD45RA expression. Total tetramer+ cells expressing PD-1 have greater ROS content ($p<0.001$) and MM ($p=0.007$) and lower MMP ($p=0.027$) than PD-1- cells, but for tetramer+ PD-1+ CD45RA- cells, CD127 expression was associated with decreased ROS content

(p=0.033), MM (p<0.001), and MMP (p=0.024). The MM of the tetramer+ cells was also found to negatively correlate with their capacity to proliferate after stimulation (r=-0.681, p=0.013), even after adjustment for %PD-1+ or %CD127+ tetramer+ CD8 T cells (p≤0.025) or for clinical group (p=0.046).
Conclusion: These findings suggest that PD-1+ HIV-specific cells have a state of metabolic stress, which is associated with poor proliferative capacity, that may be attenuated by CD127 expression. While it remains unclear if metabolic stress is a cause or consequence of PD-1 or CD127 expression, these findings highlight a potential role of metabolic stress in HIV-specific CD8 T cell exhaustion.



Note: Proliferation data not available for all participants studied

281 S100A14, NOVEL NK CROSS TALK PROTEIN FOR MONOCYTE-NK ACTIVATION IN HESN-IDU SUBJECTS

Krystal Colon-Rivera[1], Costin Tomescu[1], David Metzger[2], David W. Speicher[1], Luis Montaner[1]
[1]Wistar Institute, Philadelphia, PA, USA, [2]University of Pennsylvania, Philadelphia, PA, USA

Background: High-risk HIV-exposed uninfected individuals that share needles (HESN-IDU) have increased NK cell activation/function when compared to no-risk no-drug user controls and to low-risk no-sharing IV-drug users (NS-IDU). Using proteomic analysis of NK cells from HESN-IDU and controls, it was demonstrated that HESN-IDU have an increased expression of S100A14 and other members of the S100 family, along with other Interferon-induced proteins. These findings lead to hypothesize that S100A14 may be part of an immune mechanism of resistance in HESN-IDU.
Methods: Plasma levels of S100A14 in HESN-IDU were measured using ELISA. Recombinant S100A14 was added to isolated PBMCs obtained from normal donors. Lysates were collected after 18hrs stimulation with S100A14. We measured CD69 to assess NK activation. To measure monocytes activation, PBMCS were stimulated for 5hrs then TNF-alpha was measured using flow cytometry. NK cells and monocytes were isolated by negative selection using magnetic beads. For ensuring the highest purity, the NKs enriched preparation was further sorted for CD56+ cells. Expression of MX1 in PBMCs was measured using western blot. TAK-242, a TLR4 inhibitor, was used to determine the signaling pathway of S100A14 in monocytes.
Results: Increased levels of S100A14 were found in the plasma of HESN-IDU (n=15) in comparison with controls (n=10; p<0.01) and NS-IDU subjects (n=15; p<0.05). When added in vitro, S100A14 caused increased expression of CD69 in NKs (n=9; p<0.01) and increased expression of TNF-alpha in monocytes (n= 5; p<0.01). S100A14 induced the activation of isolated monocytes but not isolated NKs, but when in co-culture with monocytes, NKs activation was induced. S100A14 did not increase the expression of MX1, an IFN-induced gene, in PBMCs. S100A14 effects were inhibited when TAK-242 was added to PBMCs (n=7; p<0.001).
Conclusion: Identified as over-expressed in NK in HESN-IDUs, S100A14 is now identified as increased in HESN-IDU sera as well as able to induce TLR-4-dependent monocyte responses that modulate NK cell activation. An increase of NK-derived S100A14 is a novel positive feedback protein identified in HESN-IDUs with direct monocyte cross talk potential to further re-engage NK immune activation in HESN-IDU subjects.

282 FUNCTIONAL MECHANISMS OF MEMORY-LIKE NK CELLS IN SIV-INFECTED MACAQUES

Spandan Shah[1], Cordelia Manickam[1], Daniel Ram[1], R. Keith Reeves[2]
[1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]Harvard University, Cambridge, MA, USA

Background: Burgeoning evidence indicates a broader functional repertoire for NK cells beyond innate immunity including memory and other memory-like functions. One recent example is memory-like NK cells identified by lack of the FcR intracellular γ-signaling chain (FcRΔg-NK cells) which still require antibody to grant antigen-specificity, but are pre-sensitized and capable of rapid mobilization and more robust responses against viral antigens. Interestingly, FcRΔg-NK cells are initially expanded by CMV infection as part of innate-priming but execute memory-like killing against other pathogens through incompletely understood mechanisms.
Methods: Fifty-three rhesus macaques were used: twenty-one specific pathogen-free, rhCMV–; ten rhCMV+ but otherwise experimentally naïve; and twenty-two chronically SIVmac-infected macaques. NK cell analyses were performed using polychromatic, functional, and phospho-flow cytometry assays.
Results: FcRΔg-NK cells were systemically distributed in mucosal and secondary lymphoid organs, but increased two- and four-fold in CMV+ and HIV/SIV-infected individuals. FcRΔg-NK cells displayed little difference in binding affinity to virus-antibody immunocomplexes compared to traditional NK cells, but exhibited two-fold more robust IFN-γ secretion and cytotoxicity, suggesting disparate signaling or activation could account for improved function. To that end, FcRΔg-NK cells showed significantly reduced expression of Helios and Eomes and clustered independently from traditional NK cells in multidimensional t-SNE. The γ-chain adaptor, Syk, was reduced or inactively dephosphorylated in FcRΔg-NK cells, but the expression of active ζ-chain, phosphorylated by increased adaptor Zap70, was significantly upregulated, suggesting these cells may exploit the ζ-chain/Zap70 pathway in the absence of γ-chain/Syk to achieve greater functional potency.
Conclusion: Collectively, our work presents the first description of a combinatorial mechanism of innate-priming and alternative signaling cascade to explain the functional potency of memory-like NK cells. This mechanism could explain, at least in part, the improved functional potency of NK cell-mediated ADCC in rhCMV+ animals and impaired functions observed in chronic HIV/SIV infections. Future studies targeted at harnessing these pathways could open up new modalities for vaccine and curative therapy.

283 IFN-ALPHA ENHANCES NK CELL AND CD8+ T CELL MEDIATED SUPPRESSION OF HIV REPLICATION

Abena Kwaa, Joel Blankson
Johns Hopkins University, Baltimore, MD, USA

Background: Current shock and kill strategies have shown evidence of blips of viremia but no decrease in the size of the latent reservoir. One possible explanation for this is that the immune system is incapable of killing infected cells following the reversal of latency. Furthermore, some studies have suggested that certain latency reversing agents may inhibit CD8+ T, and NK, cell responses. In this study, we asked whether pulses of IFN-alpha could improve the function of NK and CD8+ T cells, in elite suppressors (ES) and chronic progressors (CPs).
Methods: NK or CD8+ T cells were isolated from 10 ES PBMCs, pulsed for 6hrs with varying concentrations of IFN-alpha, washed, then co-cultured with autologous CD4+ T cells infected with GFP expressing pseudotyped virus. Viral suppression (determined by reduction of GFP expression) was quantified by flow cytometry at 72 hours. To bypass our inability to perform this suppression assay in CPs due to residual antiretroviral drugs in their CD4+ T cells, we employed a surrogate assay. Briefly, NK and CD8+ T cells were isolated from 9 CP PBMCs, treated with IFN-alpha as above, and then stimulated with K562 cells or anti-CD3/28 antibodies respectively. The effector function of the cells was then assessed by CD107a, MIP-1-beta, IFN-gamma, TNF-alpha and IL-2 production.
Results: IFN-alpha treatment enhanced the HIV suppressive capacity of ES NK cells (0.012≤ p ≤0.043) and CD8+ T cells (0.007≤ p ≤0.035). In the surrogate assays, IFN-alpha treatments resulted in significant increases in CD107a (0.0001≤ p ≤0.0006), MIP-1-beta (0.0003≤ p ≤0.0032) and IFN-gamma (0.0003≤ p ≤0.0073) expression by CP NK cells. Furthermore, CP CD8+ T cells produced significantly more CD107a (0.0005≤ p ≤0.0022), MIP-1-beta (0.0001≤

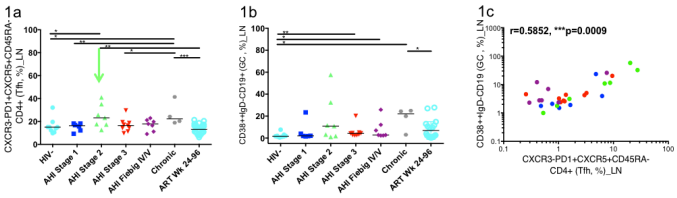
p ≤0.0074), IFN-gamma (0.0001≤ p ≤0.0007) and TNF-alpha (0.008≤ p ≤0.017) following incubation with IFN-alpha.
Conclusion: In vitro treatment with IFN-alpha enhanced the suppressive capacity of ES NK cells and CD8+ T cells. Furthermore IFN-alpha treatments enhanced the production of cytokines by CP NK cells and CD8+ T cells in response to K562 cells and anti-CD3/28 antibodies respectively. Clinicians have a lot of experience using IFN-alpha. Treatment with this cytokine may therefore represent a way of potentiating NK cell and CD8+ T cell control of viral replication in HIV eradication studies.

284 FREQUENCIES AND DISTRIBUTION OF ENV-SPECIFIC B CELLS IN BLOOD VERSUS LYMPH NODES

Alessandra Noto[1], Andrew McDavid[2], Phu Van[2], Madeleine Suffiotti[1], Agostino Riva[3], Jean-Marc Corpataux[1], Song Ding[4], Craig Fenwick[1], Raphael Gottardo[2], Giuseppe Pantaleo[1]
[1]Lausanne University Hospital, Lausanne, Switzerland, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]ASST Fatebenefratelli, Milan, Italy, [4]EuroVacc Foundation, Amsterdam, Netherlands
Background: The large majority of the studies on B cells in HIV-1 infection have been performed in blood. Limited information is available on B cell populations from lymph nodes and on the association with the functional profile of T follicular helper (Tfh) cells.
Methods: We have investigated the distribution and frequencies of Env-specific B cells in lymph nodes and blood of 14 HIV-1 infected viremic individuals and 11 aviremic ART treated individuals using flow and mass cytometry. Lymph node mononuclear cells (LNMC) were stained with Env probes together with a B cell panel of 32 isotope-conjugated antibodies. LNMCs were stimulated with PMA/ionomycin for 6h and stained with a panel of 32 markers defining the phenotype and function of Tfh cells.
Results: The frequency of Env-specific B cells was increased in LNs as compared to blood (1.5% vs 0.5%, p<0.0001) and in LNs of viremics as compared to treated (1.73 fold). In blood, Env-specific B cells were contained within the resting memory and activate memory phenotype while the majority of LN Env-specific B cells were contained within the Germinal Center (GC) (55% in viremics and 20% in treated) and switched memory (35% in viremics and 75% in treated) B cells. The percentage of Env-specific B cells within the GC directly correlated with viral load and with the number of total GC B cells. LN Env-specific B cells from viremics expressed decreased levels of BCL-2, CXCR4 and CXCR5 and increased levels of CD95, KI67, BCL6, FCRL4, CXCR3 and T-bet. In viremics, we found a significant increase (2-3 fold) in the Tfh cells defined by the CXCR3+T-bet+ phenotype and IFN-γ production along with a significant decrease (2-3 fold) in Tfh cells expressing CCR4, CCR6 and producing IL-4. The CXCR3/T-bet/IFN-γ signature of Tfh cells was strongly associated with the appearance of Env-specific B cells expressing CXCR3 and T-bet. In vitro experiments demonstrated IFN-γ as the causative factor inducing the differentiation of the CXCR3+T-bet+ memory B cells and as a strong suppressive factor of antibody production.
Conclusion: The differences in composition of Env-specific B cells between blood and LN and the identification of Th1-like Tfh cells and IFN-γ as the main mechanisms affecting Env-specific B cell maturation will provide novel insights into strategies to develop optimal antibody responses in HIV infection and following vaccination.

285 T AND B CELL ALTERATIONS IN PERIPHERAL BLOOD AND LYMPH NODE IN ACUTE HIV INFECTION

Supranee Buranapraditkun[1], Hiroshi Takata[2], Carlo Sacdalan[3], Sopark Manasnayakorn[1], Suthat Chottanapund[3], Pattarawat Thantiworasit[1], Peeriya Prueksakaew[3], Khunthalee Benjapornpong[3], Bessara Nuntapinit[4], Timothy Schacker[5], Merlin L. Robb[6], Nelson L. Michael[7], Jintanat Ananworanich[6], Lydie Trautmann[2]
[1]Chulalongkorn University, Bangkok, Thailand, [2]HJF, Silver Spring, MD, USA, [3]SEARCH, Bangkok, Thailand, [4]Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, [5]University of Minnesota, Minneapolis, MN, USA, [6]HJF, Bethesda, MD, USA, [7]Walter Reed Army Institute of Research, Silver Spring, MD, USA
Background: Both cellular and humoral immunity are important for the controlling HIV infection. However, little data is known about immune cells in different compartments in very early acute HIV infection (AHI). The RV254 Thai study captures participants in AHI from prior to viral load (VL) peak (Fiebig 1 and 2), at peak VL (Fiebig 3) and during VL decay (Fiebig 4/5).
Methods: Frozen matched peripheral blood mononuclear cells (PBMC) and lymph node (LN) cells of 29 acute HIV-infected Thais (wk.0), 29 antiretroviral therapy (ART)-treated, chronically infected and uninfected Thais (n=13) were studied. The immune cells of CD4, CD8 and B cells were characterized by flow cytometry.
Results: Frequencies of resting memory (RM) B cells (CD21+CD27+IgG+CD20+) were significantly decreased whereas frequencies of tissue-like memory (TLM) B cells (CD21-CD27-IgG+CD20+) were significantly increased during AHI in PBMC but not in LN. However, frequencies of RM and TLM B cells were not restored as the same level in healthy donors after ART. Frequencies of plasmablast (IgD-CD38hiCD20+) B cells were evaluated in PBMC at all AHI stages but not in LN. Importantly, in LN, frequencies of CD4 Tfh cells (CXCR3-PD1+CXCR5+CD45RA-CD4+) were not elevated compared to controls and significantly lower than in chronic infection except for a transient increase at Fiebig 2 (Fig.1a), suggesting that CD4 Tfh cells are depleted or not generated in AHI after Fiebig 2 impacting B cell maturation. Germinal Center (GC) B cells (CD38++IgD-) showed a similar transient increase in Fiebig 2 in LN that did not persist in later AHI stages (Fig.1b) suggesting that GC formation is impaired in AHI. Interestingly, frequencies of CD4 Tfh cells were associated with frequencies of GC B cells (p=0.0009) (Fig.1c). Moreover, both CD4 and CD8 T cell subsets showed activated effector (Ki67+Bcl-2lo) cells as early as Fiebig 1 in PBMC and Fiebig 2 in LN followed by an increase in later stages of AHI in both compartments. Interestingly, frequencies of effector CD4 and CD8 T cells and HIV-specific CD8 T cells correlated between PBMC and LN. In contrast, other immune subsets exhibited decreasing frequencies in blood during AHI while remaining stable in LN.
Conclusion: The phenotypes of immune cells are unique in blood vs. LN. Understanding the immune cells alteration in these compartments during AHI may help defining the mechanisms leading to lack of immune control in natural HIV infection.



286 CYTOLYTIC CD4+ T CELLS WITH FOLLICULAR HOMING PROPERTIES IN CHRONIC HIV INFECTION

Enrico Richter[1], Johanna Eberhard[2], Marek Korencak[1], Bruce T. Schultz[1], Britta Flach[1], Stefan Esser[3], Julian Schulze zur Wiesch[2], Hendrik Streeck[1]
[1]Institute for HIV Research, Essen, Germany, [2]University Hospital Hamburg–Eppendorf, Hamburg, Germany, [3]University Hospital Essen, Essen, Germany
Background: It has been demonstrated that the lymphoid B cell follicle is an important HIV reservoir capable of harboring high levels of virus even when HIV is undetectable in the periphery. It is believed that the B cell follicle is an immune privileged site which blocks HIV-specific CTLs from entering, while allowing T follicular helper cells to pass freely in and out of the follicle. Here, we describe a population of HIV-specific cytolytic CD4+ T cells that have the ability to enter the B cell follicle and may be harnessed to reduce the follicular viral burden.
Methods: We analyzed PBMCs from chronic HIV+ ART-naïve, HIV+ ART-treated and HIV- individuals, as well as lymphatic tissue from tonsils and lymph nodes of HIV+ and HIV- individuals. We used multicolor flow cytometry and immunofluorescence microscopy to determine the phenotype, frequency and functional properties of these cells. Furthermore, we assessed the plasticity of these cells in an in vitro culture and determined their ability to inhibit viral replication.
Results: In the peripheral blood, we identified a CD4+ CXCR5+ T cells population expressing granzyme B and perforin that showed the ability to degranulate (CD107a) after stimulation. This cellular subset was significantly expanded in chronic HIV infection and contracted upon antigen reduction by ART. In response to Gag stimulation we found that a substantial portion of these cytolytic CD4+ T cells with follicular homing properties (TFC) were HIV-specific and further secreting interferon-γ. We next determined their frequency in

lymph nodes and also found a substantial frequency of CD4+ CXCR5+ effector T cells in samples from HIV+ individuals. Importantly, the expansion of these cells after SEB stimulation was elevated in comparison to TFCs in lymph nodes and tonsils from healthy controls or blood samples from chronic HIV+ individuals. Using immunofluorescence microscopy we determined an enrichment of TFCs in the B cell follicle confirming their follicular homing. We next determined their ability to kill virally infected cells and found that similar to regular CTL CD4+ T cells, these cells showed enhanced ability to recognize and kill infected cells.
Conclusion: In conclusion, we demonstrate a novel subset of cytolytic CD4+ T cells with follicular homing properties that can be found in the B cell follicle and shows enhanced viral inhibitory activity. Harnessing this cellular subset through therapeutic intervention may provide a novel strategy for HIV eradication attempts.

287 TFC CELLS INTERACT WITH OTHER FOLLICULAR T CELLS TO CONTROL SIV VIREMIA

Mohammad Arif Rahman[1], Katherine M. McKinnon[1], Tatiana S. Karpova[1], David A. Ball[1], David Venzon[2], Wenjin Fan[3], Guobin Kang[3], Qingsheng Li[3], Marjorie Robert-Guroff[1]
[1]NIH, Bethesda, MD, USA, [2]NIH, Rockville, MD, USA, [3]University of Nebraska–Lincoln, Lincoln, NE, USA

Background: B cell follicles, which may not be accessible to ART or antiviral CD8+ T cells, are considered an immune privileged site for HIV/SIV replication. However, recent evidence suggests follicular cytotoxic T cells (Tfc) can locate to B cell follicles of secondary lymphoid tissue and might contribute to viremia control. Here we aimed to clarify the role of viral-specific Tfc cells in lymph nodes (LNs) over the course of SIV infection in rhesus macaques.
Methods: LN biopsy specimens were collected from naïve and acutely and chronically (low viral load, LVL; and high viral load, HVL) SIV-infected rhesus macaques. Assays performed to clarify the interaction of Tfc cells with other LN follicular T cells and assess their impact on disease course included: immunohistochemistry to localize Tfc and Tfh cells; flowcytometry to determine the frequency of Tfc, Tfh and T follicular regulatory (Tfreg) cells and SIV-specific cytokine production; ELISPOT using sorted cells to quantify SIV-specific Tfc; a flowcytometry based killing assay to evaluate the functionality of sorted Tfc cells.
Results: Tfc and Tfh cells were localized in LN B cell follicles. Positive correlations between percentages of these cells were observed in acute ($r=0.55$, $p=0.022$) and LVL ($r=0.60$, $p=0.0073$) but not HVL animals. SIV-specific Tfc cell frequencies were comparable between HVL and LVL animals, however, LVL animals tended to express more Gag-specific granB, exhibited greater killing than HVL animals ($p=0.008$), and their Tfc cell frequencies negatively correlated with viremia ($r=-0.63$, $p=0.04$). In LVL but not HVL animals, Tfh and Tfc cells correlated directly ($r=0.63$, $p=0.04$). Env- and Gag-specific IL-21+Tfh of LVL but not HVL macaques negatively correlated with viral load ($r=-0.65$, $p=0.036$; $r=-0.67$, $p=0.028$, respectively), suggesting better provision of T cell help to Tfc. In LVL animals Tfreg and Tfc cells were positively correlated ($r=0.74$, $p=0.013$) and negatively correlated with viremia ($r=-0.81$, $p=0.0033$), perhaps due to suppression of chronic inflammation. In contrast, Tfreg and Tfc cell frequencies of HVL macaques tended to negatively correlate ($r=-0.57$, $p=0.071$). A positive correlation was seen between Tfreg cell number in HVL macaques and viremia ($r=0.65$, $p=0.034$), suggesting dysfunction and suppression of an effective Tfc immune response.
Conclusion: Our results indicate that control of virus-infected cells in B cell follicles not only depends on Tfc cell cytotoxicity but also on Tfc cell interaction with Tfh and Tfreg.

288 CHARACTERIZATION OF THE NEUTRALIZING ANTIBODY RESPONSE IN A LINKED HIV SUPERINFECTION

Deogratius Ssemwanga[1], Nicole Doria-Rose[2], **Andrew D. Redd**[3], Andrea R. Shiakolas[2], Andrew Longosz[3], Rebecca N. Nsubuga[1], Gershim Asiki[4], Janet Seeley[4], Amy Ransier[2], Sam Darko[2], Daniel Douek[2], Stephen Porcella[2], Thomas C. Quinn[3], John R. Mascola[5], Pontiano Kaleebu[4]
[1]Medical Research Council, Entebbe, Uganda, [2]NIAID, Bethesda, MD, USA, [3]NIAID, Baltimore, MD, USA, [4]MRC Uganda Virus Research Institute, Entebbe, Uganda, [5]Vaccine Research Center, NIAID, Bethesda, MD, USA

Background: HIV-superinfection (HIV-SI) occurs when an infected individual acquires a new HIV strain that is phylogenetically distinct from their existing viral population. HIV-SI provides an opportunity to examine the potential role of pre-existing HIV-specific neutralizing antibodies (NAb) in protecting against a subsequent HIV challenge.
Methods: Virally unlinked HIV+ individuals in monogamous (n=15) and polygamous relationships (n=6) from the Rural Clinical Cohort (RCC) in southwest Uganda were tested for occurrence of HIV-SI using a previously validated next-generation sequencing (NGS) assay of three viral genomic regions (gag, pol, gp41). One case of linked HIV-SI was identified, and for this case serum samples from before and after the time of the HIV-SI event for both the female, and her husband, were subjected to single-genome amplification (SGA) to generate full-envelope sequences. Full-length Env amplicons from SGA were used to generate pseudoviruses that were tested for their neutralization susceptibility to their homologous serum, as well as their partner's heterologous serum from before and after HIV-SI.
Results: The linked HIV-SI occurred in a polygamous relationship in which an HIV-infected uncircumcised male superinfected one of his four wives who were all HIV-positive. The male had no indication of HIV-SI in any of the sequences examined. Full-length viral envelope sequences were obtained from the female partner immediately before HIV-SI (Month 0, n=21) and when HIV-SI was first detected three months later (Month +3, n=10). Three of the viral sequences from this later sample were phylogenetically linked to the male's viruses, thus representing the superinfecting strain. The female's serum samples prior to HIV-SI displayed moderate NAb activity against her homologous virus. However, her serum prior to HIV-SI, and immediately post HIV-SI, contained no detectable NAb activity to the superinfecting strain. Ten months post HIV-SI, the female had developed a moderate response to the superinfecting strain.
Conclusion: A linked HIV-SI event occurred in a chronically infected female who had moderately potent and broad anti-HIV NAb responses. Despite this, she possessed no detectable NAb response to the superinfecting strain during the estimated HIV-SI window, which potentially could have protected her. This unique case highlights the exciting amount of potential information that even a small number of these linked HIV-SI events could provide.

289 BROAD SPECTRUM OF NEUTRALIZATION-ENHANCEMENT BY NOVEL CD4MIMIC COMPOUND YIR-821

Shokichi Takahama[1], Kazuki Tanaka[1], Hasan Zahid[1], Alam Muntasir[2], Takeo Kuwata[1], Ami Masuda[3], Kohei Takahashi[3], Takuya Kobayakawa[3], Takuya Yamamoto[4], Tomoyuki Miura[5], Liye He[6], Hirokazu Tamamura[3], Shilei Ding[7], Andrés Finzi[7], **Shuzo Matsushita**[1]
[1]Kumamoto University, Kumamoto, Japan, [2]International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh, [3]Tokyo Medical and Dental University, Tokyo, Japan, [4]National Institutes of Biomedical Innovation, Health and Nutrition, Osaka, Japan, [5]Kyoto University, Kyoto, Japan, [6]Institute for Molecular Medicine Finland, Helsinki, Finland, [7]Centre de Research du Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada

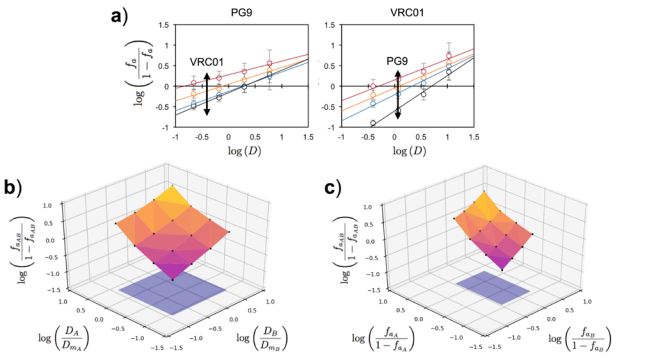
Background: CD4 mimic compounds (CD4mc) that inhibit the interaction of gp120 with CD4 are expected as an entry inhibitor. Furthermore, CD4mc induce structural changes in gp120 trimer through binding to the CD4 binding (Phe43)-cavity of gp120. We recently developed YIR-821, a novel CD4mc, which showed more potent and less cytotoxic activities than original CD4mc NBD-556. Here we examined anti-HIV-1 activities of YIR-821 including enhancing activities for neutralization and ADCC (antibody-dependent cellular cytotoxicity) against a variety of viruses.
Methods: We used pseudovirus panels of HIV-1 strains (standard panel B/panel C/global standard panel) to investigate the spectrum of YIR-821 for neutralization/binding enhancement as well as activities as an entry inhibitor. Synergistic effects in neutralization were examined for antibodies targeting V3/CD4bs/CD4i regions and calculated by R package "SynergyFinder". To evaluate ADCC, CEM-NKR-CCR5-luc T-cell line infected with HIV-1 BaL was prepared as target and incubated with antibodies and effector cells (CD16 expressing KHYG-1 NK cell line) for 8 hours, then relative luminescent activity was measured.
Results: We found broad and potent anti-HIV-1 activities of YIR-821 as an entry inhibitor against panels of subtype-B and C virus. YIR-821 induced exposure of conformational epitopes on gp120 was observed not only in subtypes B and C, but also subtypes A and B/C, which were relatively resistant to the inhibitory activity by YIR-821. Interestingly, YIR-821 treatment alone is not effective against JR-FL (subtype B, but uniquely YIR-821 resistant strain), but the combination of YIR-821 with anti-V3/CD4i antibodies showed synergistically neutralization, suggesting some difference in the process of these two anti-HIV

mechanisms. Moreover, we observed potent enhancement for ADCC activity of anti-V3/CD4i antibodies against HIV-1 infected cells in the presence of YIR-821.
Conclusion: These data taken together suggest that YIR-821 has enhancing activity to ADCC with an excellent property of neutralization-enhancing activities for broad spectrum of HIV-1 in vitro. Combinational use of YIR-821 and anti-V3/CD4i antibodies represents a promising candidate for prevention or treatment of HIV-1 infection.

290 A 2-DIMENSIONAL APPROACH TO ANALYZING BROADLY NEUTRALIZING ANTIBODY COMBINATIONS

Nicholas E. Webb, Colin M. Sevaried, Nicole Tobin, Grace M. Aldrovandi
University of California Los Angeles, Los Angeles, CA, USA

Background: Broadly neutralizing antibodies (bnAbs) show great promise for HIV treatment and prophylaxis. Immunotherapies involving combinations of bnAbs (BNACs) will be necessary to prevent transmission and the emergence of resistant variants. Current methods for evaluating BNACs use a constant dose ratio, which may not represent an ideal combination. These approaches focus on identifying synergy, with experimental and analytical methods that depend on combinatorial models. The models impose specific assumptions about the interactive mechanics of the system under study and their applicability to BNACs has never been formally determined. For example, the most commonly used model, Loewe Additivity, is explicitly invalid for assessing BNACs whose components exhibit different curvatures, or slopes, which are characteristic features of bnAb activity.
Methods: We employed a two-dimensional matrix experimental strategy, where neutralization curves of one antibody are generated in the presence of a constant concentration of another antibody, for two-member permutations of PG9, VRC01, 10E8 and PG16. The neutralizing activity of the combination is then mapped as a two-dimensional surface, which can be analyzed empirically, without imposing any mechanistic assumptions. Because the primary target of neutralizing antibodies, the HIV-1 envelope (Env), is extremely variable, we characterized these BNACs across a panel of clade C, mother-to-child-transmitted Env isolates.
Results: Combinatorial activity was assessed from both a dose and effect-based perspective, reflecting the two major combinatorial models, Loewe Additivity and Bliss Independence, respectively (see figure). Inclusion of a PG9/PG16 BNAC provided mechanistic insight, as this BNAC represents an ideal Loewe combination. Unlike other approaches, this method also measures combinatorial activity across a range of dose ratios, allowing us to assess clinical potential across a wider range of parameters.
Conclusion: The matrix/surface approach is significantly more informative for evaluating BNACs, both clinically and mechanistically, than more common, fixed-ratio methods.



Combinatorial Surface Analysis. (**a**) Median effect plots of neutralization for PG9 across four concentrations of VRC01 (left) and for VRC01 across four concentrations of PG9 (right). (**b**) Activity of PG9/VRC01 combo (z-axis) with respect to IC_{50} dose ratios of PG9 (left axis) and VRC01 (right axis). (**c**) Combinatorial activity (z-axis) with respect to the expected singular effect of PG9 (left axis) and VRC01 (right axis). Data shown are average and standard deviation of triplicates.

291 OPTIMIZING HIV-1 VIRUS TEST PANELS FOR EFFECTIVE DETECTION OF NEUTRALIZATION BREADTH

Claus Kadelka[1], Peter Rusert[1], Roger Kouyos[2], Huldrych F. Günthard[2], Alexandra Trkola[1]
[1]*University of Zurich, Zurich, Switzerland,* [2]*University Hospital Zurich, Zurich, Switzerland*

Background: Potent broadly neutralizing antibodies (bnAbs) are a key focus of HIV-1 vaccine and therapy development but are only elicited at low frequency in natural infection. The identification of bnAb responses requires virus screening panels that effectively capture neutralization breadth. Varying procedures and thresholds to define breadth are applied in the literature calling for standardization efforts to enable unbiased assessment of vaccine responses. The Swiss 4.5K Screen, a systematic survey of bnAb activity in 4,484 HIV-1 infected individuals, identified 239 bnAb inducers (Rusert, Kouyos Nat Med 2016), which provided an ideal set of patients to investigate the composition of optimized virus panels for the detection of HIV-1 neutralization breadth.
Methods: The Swiss 4.5K Screen was based on a multi-clade panel of 8 HIV-1 strains. 729 plasma samples, which showed >80% inhibition of at least one of these viruses, were screened against 15 additional viruses thus yielding neutralization information for a total of 23 viruses. For 162 plasma samples with the highest predicted bnAb activity (based on the 23-virus panel), we obtained ID50 values against a multi-clade 40-virus panel. The median ID50 served as a proxy for true neutralization breadth. Spearman correlations, Fisher's exact test and the area under the ROC curve were used to evaluate virus screening panels of different size and composition.
Results: A larger screening panel generally led to more accurate neutralization breadth predictions (see Figure). However, the gain in predictive strength decreased with the number of included viruses. A comparison of various transformation functions for the % inhibition values revealed max(value – 10%, 0) as best, yielding significantly better predictions than the frequently used 20-50-80 rule. As expected, virus panels of diverse subtypes performed better than single-clade panels. Intriguingly, inclusion of certain viruses like TRO clone11 led to consistently better average predictions than others, independent of panel size. General neutralization sensitivity of the 23 viruses had no impact on our findings.
Conclusion: Collectively, our systematic survey of virus screening panels for the detection of HIV-1 neutralization breadth provides important information on the optimal design of test panels. This data provides a basis for a standardization of neutralization breadth assessment and prediction methods, which will be particularly important in the evaluation of forthcoming vaccine efficacy trials.

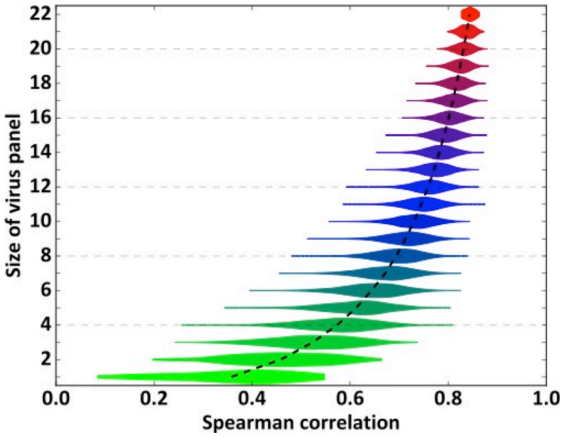


Figure: Distribution of the predictive strength for different panel sizes
For each panel size, the distribution of the predictive strength of 1000 tested virus panels is shown. The function max(value – 10%, 0), identified as best transformation function of the measured neutralization activity, is used to transform the % inhibition values. The dashed black line shows the average predictive strength.

292 HIV RECEPTOR USAGE IMPACTS SENSITIVITY TO V1-V3 LOOP BROADLY NEUTRALIZING ANTIBODIES

Ludy Registre[1], Yvetane Moreau[2], Sila Ataca[1], Manish Sagar[2]
[1]*Boston University, Boston, MA, USA,* [2]*Boston Medical Center, Boston, MA, USA*

Background: Broadly neutralizing antibodies (bnAbs) are being investigated as a potential therapeutic. BnAbs target a relatively limited number of conserved HIV-1 envelope glycoprotein (env) structures, including glycans in and around the variable loop 1 – 2 (V1/V2) and 3 (V3) domains. Changes in the env V1/V2 and V3 loops are also known to dictate the use of either the CCR5 or CXCR4 chemokine receptor for cell entry.

Methods: Full length envs (n =47) were isolated using single genome amplification and incorporated into isogenic backbones to construct replication competent viruses, which were then phenotypically characterized for coreceptor usage. Neutralization sensitivity of CCR5- and CXCR4- utilizing viruses was examined using the TZM-bl assay. Robetta online server, Pcons metaserver, and Pymol software was used for structural modeling studies of the interaction between HIV-1 env and bnAbs. Chimeric envs were generated to validate the structural modeling predictions.

Results: Viruses that exclusively use CXCR4 (X4) from 8 individuals as compared to variants that only use CCR5 (R5) from 9 subjects were around 5 fold less sensitive to anti-V3 antibodies PGT121 (p=0.02) and 10-1074 (p=0.04). X4-using viruses were less neutralization sensitive to V1/V2 loop directed antibodies, PG9 and PG16, as compared to R5-using viruses, although this difference was not statistically significant. Multiple co-circulating X4 (median=4, range=1-5) as compared to R5 envs (5 per subject) isolated from 4 subjects also demonstrated decreased sensitivity to V1-V2 and V3 directed bnAbs although these differences were subject specific. Both intra and inter individual R5 and X4 variants did not have significant neutralization susceptibility differences to CD4 binding site (VRC01) and membrane proximal external region (10E8) directed bnAbs. Structural modeling suggested that the envs with resistance to V3 directed bnAbs had V1/V2 loops that sterically interfered with antibody binding to known PGT121 and 10-1074 epitope. PGT121 susceptibility increased when the V1/V2 loop of an env insensitive to PGT121 was replaced with the V1/V2 loop from an env sensitive to PGT121 and vice versa.

Conclusion: Neutralization susceptibility to V1-V2 and V3-directed bnAbs associates with coreceptor usage. Structural modeling predicts that V1-V2 loop mediated steric hindrance prevents V3-directed bnAb – env interactions. Our structural modeling techniques may be used as a tool to predict neutralization susceptibility to bnAb based therapies.

293 USE OF PROMISCUOUS GLYCAN AT V3 REGION CORRELATES WITH ELITE NEUTRALIZATION RESPONSE

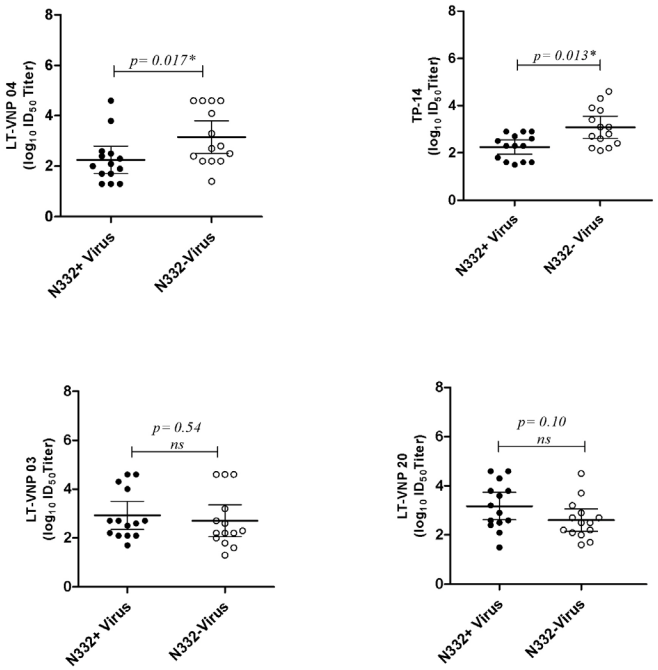
Nandagopal Paneerselvam[1], Jayantha Bhattacharya[2], Aylur K. Srikrishnan[1], Rajat Goyal[3], Chinnambedu Ravichandran Swathirajan[1], Shilpa Patil[2], Shanmugam Saravanan[1], Suprit Deshpande[2], R Vignesh[1], Sunil S. Solomon[4], Nikhil Singla[3], Joyeeta Mukherjee[3], Kailapuri G. Murugavel[1]
[1]*YR Gaitonde Center for AIDS Research and Education, Chennai, India,* [2]*HIV Vaccine Translational Research Laboratory, Faridabad, India,* [3]*International AIDS Vaccine Initiative, New York, NY, USA,* [4]*Johns Hopkins Hospital, Baltimore, MD, USA*

Background: Broadly neutralizing antibodies to HIV provide important leads for vaccine design and may be valuable in therapy. Defining the sites of vulnerability can inform the choice of immunogens and immunization strategies to induce broadly neutralizing antibodies through vaccination. Here we report on the epitope specificity of elite neutralizers with subtype C infected individuals in India

Methods: In this study, plasma samples from a cohort of 70 ART-Naïve HIV-infected individuals with various stages of disease progression were tested against Tier-2 global virus panel (n=11) which includes subtype A, B, C, G, AC, BC & AE. Subjects with < 50 % neutralization breadth were defined as non-broadly cross-reactive neutralization group (Non-BCN) and those with >50 % neutralization breadth was defined as the broadly cross-reactive neutralization group (BCN) were then tested against an extended virus panel (n=19) to find Elite neutralization. Elite neutralizers are those able to neutralize >70% of viruses tested with geometric mean ID50> 500.Comprehensive neutralization, binding and competition analysis were performed to map the epitope of elite neutralizers.

Results: Out of 70 samples screened, 28 (40%) of them neutralized >50% of the global virus panel and 8(11%) of these plasma have broad and potent antibody response when tested with extended virus panel.we were able to identify 4 elite neutralizers with geometric mean ID50 titer between 500 and 700. Epitope mapping of those elite neutralizers were not specific to known targets like V2, V3, CD4bs and MPER region. Interestingly, two of the elite neutralizers (Figure.1; LT-VNP04;p=0.010 &TP-14, p=0.013) show enhanced significant sensitivity towards viruses that lacks N332 glycan. In addition to that, rest of the elite neutralizers (Figure.1; LT-VNP03;p=0.54 & LT-VNP20,p=0.10) does not depend on either presence or absence of N332 glycan.

Conclusion: Elite neutralization response was associated with the absence of N332 glycan. This may be due to utilization of promiscuous glycan at the high mannose patch of V3 region that favours the development of neutralization breadth among elite neutralizers. These data suggest promiscuous glycan are the potential target region for the development of immunogen that elict broad and potent antibody response.



294 ENV STRUCTURE IS EVOLVING AT DIFFERENT RATES IN DIVERSE CLADES OF HIV-1

Raghavendranath Kandula, Hagit Hodis, Yunxia O'Malley, Kallin Khan, **Hillel Haim**
University of Iowa, Iowa City, IA, USA

Background: The Envelope glycoproteins (Envs) of viruses from diverse HIV-1 clades show different patterns of recognition by broadly neutralizing antibodies (BNAbs). We recently analyzed BNAb binding patterns of clade B Envs circulating in a defined region in the United States and observed significant changes during the past 30 years (DeLeon, Hodis, O'Malley et al., PLOS Biology 2017). BNAb epitopes are present in a decreasing proportion of circulating strains. The population decay rate of each epitope is distinct and remained constant over the course of the pandemic. Interestingly, epitopes that show higher rates of historic decay also exhibit higher rates of in-host divergence and higher levels of variance among strains that co-circulate in the individual at any time point (a parameter we designate volatility). We sought to compare the decay rates of epitopes in different HIV-1 clades and the relationship with their volatilities.

Methods: To calculate BNAbs epitope integrity based on sequence, we utilized sequence-phenotype datasets to learn the relative contribution of each residue and position that composes an epitope to antibody binding. These values were then applied to large historic sequence datasets from clades B, C, D and CRF01_AE to determine changes in epitope integrity. Measured decay rates were compared with the mean volatility of the epitope in patients infected by virus from the same clade.

Results: Many BNAb epitopes demonstrated different decay rates in the above clades. Domains that showed major differences include the glycan patch of gp120, the MPER of gp41 and quaternary structure-dependent epitopes.

In some cases, structural diversification of the clades appears to be relatively recent; epitopes were similarly distributed in the 1980's but then decayed at different rates during the next three decades. The in-host volatility of each epitope was clade-specific and correlated strongly with its rate of population decay in the same clade.

Conclusion: HIV-1 Env structure is highly dynamic in the population. Epitopes appear to have defined and clade-specific longevities. The in-host volatility of structural features guides their longitudinal divergence and accounts for their population-level diversification patterns over the course of the pandemic. The conserved clade-specific rates of diversification help us to predict the future distribution of epitopes, to guide design of population-targeted immunogens.

295 OPENPRIMER, A PRIMER DESIGN TOOL FOR AMPLIFYING B CELL CDNA ENCODING HUMAN ANTIBODIES

Matthias Döring[1], Christoph Kreer[2], Nathalie Lehnen[2], Nico Pfeifer[3], Florian Klein[2]

[1]Max Planck Institute for Informatics, Saarbrücken, Germany, [2]Cologne University Hospital, Cologne, Germany, [3]Max Planck Institute for Infection Biology, Berlin, Germany

Background: Deciphering the human antibody response requires the amplification of cDNA from B cells using multiplex polymerase chain reaction (mPCR), which necessitates primers targeting a variety of immunoglobulin gene segments with or without additional somatic mutations. Broadly neutralizing antibodies (bNAbs) against HIV-1 carry high levels of somatic mutations, which can impede the successful amplification of their cDNA. Therefore, we set out to design novel primers that target the putatively less mutated immunoglobulin leader region in order to enhance the probability of covering antibody genes even with high levels of somatic mutations.

Methods: To design novel sets of primers, we developed a primer design algorithm with three stages: (1.) Construction of a degenerate set of primers by computing consensus sequences of hierarchically-clustered target region substrings, (2.) filtering of the initial primer set by applying constraints on up to eleven physicochemical properties, and (3.) optimization of the remaining primer candidates by solving an instance of the set cover problem using either a greedy algorithm or an integer linear programming formulation. The theoretical significance of the designed primer sets was computed by applying Fisher's exact test on the constraint fulfillment matrix. The designed primer sets for the heavy chain were validated by performing mPCR on individual clones of germline immunoglobulin cDNA and comparing in silico and in vitro coverage events.

Results: We have designed novel primer sets that bind with at most one mismatch to the leaders of IGHV (n=14), IGKV (n=7), and IGLV (n=8) such that all antibody variants are covered (Figure 1). The newly designed primer sets fulfilled significantly more physicochemical constraints than existing primer sets from the literature (p-values of 3.2e-22, 7.7e-12, and 7.5e-14, respectively). The experimental validation of the designed primer sets showed that in silico and in vitro coverages agreed well, with both sensitivity and specificity exceeding 80%.

Conclusion: We have developed *openPrimeR*, an open-source computational tool for designing, evaluating, and comparing primer sets for mPCR. Using the tool, we constructed primer sets that could facilitate the discovery of new bNAbs. Since the tool is very general, it could be used to analyze and design primer sets in many other application scenarios. *openPrimeR* (http://openprimer.mpi-inf.mpg.de) will be available in Bioconductor release 3.6.

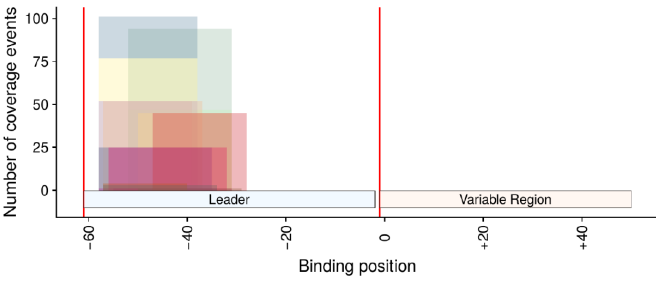


Figure 1: Primer binding sites of the newly designed primers for amplifying the variable region of cDNA originating from the human heavy chain locus IGH. The width of individual bars indicates the binding region of the primers, while the height of the bars shows the number of template sequences that are covered.

296LB STRUCTURE-GUIDED IMPROVEMENT OF HIV-1 BROADLY NEUTRALIZING ANTIBODIES

Qingbo Liu, Yen-Ting Lai, Peng Zhang, Peter D. Kwong, Paolo Lusso

NIAID, Bethesda, MD, USA

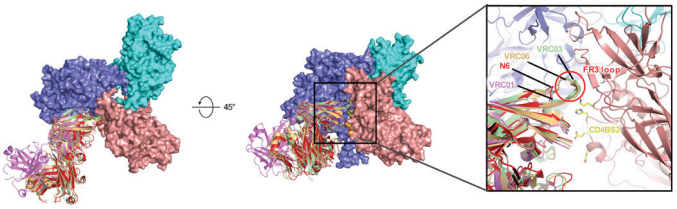
Background: Broadly neutralizing antibodies (bNAb) are a promising alternative to antiretroviral drugs for prevention and treatment of HIV-1 infection. We recently reported the identification of a second, quaternary CD4-binding site (CD4BS2) on the native HIV-1 Env trimer spike, and found that some anti-CD4BS NAbs like VRC03 and VRC06 mimic the quaternary binding mode of CD4, establishing contacts with a neighboring gp120 protomer through the extended framework 3 (FR3) loop of their heavy chain. In contrast, some bNAbs like N6 and VRC01 contain a shorter FR3 loop and interact with only a single gp120 protomer. The aim of this study was to investigate if bNAbs like N6 and VRC01 could benefit from establishing quaternary contacts and if this could be achieved by elongation of their FR3 loop.

Methods: All wild-type (WT) and mutated antibodies were expressed in 293FS cells and purified by protein-A columns; trimer binding was measured by ELISA and surface plasmon resonance (SPR); the crystal structure of antibody-trimer complex was solved by x-ray diffraction and molecular replacement; neutralization was determined by the TZM-bl assay against a global panel of HIV-1 isolates.

Results: The key role of the FR3 loop in the quaternary interaction of VRC03 and VRC06 was confirmed by FR3-loop truncation and testing on CD4BS2 mutants. Thus, we employed structure-based engineering to engraft the long FR3 loop of VRC03 into several potent CD4-supersite antibodies. Three of 4 chimeric antibodies (derived from VRC01, VRC07 and N6) showed enhanced neutralizing capacity against the majority of HIV-1 strains tested. Binding of chimeric antibodies to the Env trimer was also increased. SPR analysis showed that the quaternary contact stabilized the interaction between the modified antibody and the Env trimer by prolonging their dissociation rate. The crystal structure of one engineered antibody, N6 70-03, was solved in complex with the BG505 SOSIP.664 trimer, showing that the FR3 loop of chimeric N6 70-03 interacts both with CD4BS2 and with the V3-loop base in the neighboring gp120 protomer.

Conclusion: Engraftment of the FR3 loop enabled potent anti-CD4BS antibodies to establish quaternary contact with a neighboring protomer of the HIV-1 Env timer, leading to increased potency. These modified bNAbs are potential candidates for application in HIV-1 therapy and prevention.

Antibodies That Establish Quaternary Interaction with the CD4-Binding Site Possess Unique Extended FR3 Loops



297 THE CODEVELOPMENT OF ANTIBODY GLYCOSYLATION AND FUNCTIONALITY IN HIV INFECTION

Madeleine Jennewein[1], Jennifer Mabuka[1], Bruce D. Walker[1], Thumbi Ndungú[2], Galit Alter[1]

[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]KwaZulu-Natal Research Institute for TB and HIV, Durban, South Africa

Background: Increasing evidence points to a role for antibody-mediated effector function in preventing and controlling HIV infection. Antibody effector functions are regulated both by changes in antibody subclass/isotype selection and changes in antibody glycosylation. However, it us unknown how antibody effector function evolves following infection, nor how the humoral immune response naturally is tuned to recruit the antiviral activity of the innate immune system.

Methods: Using a set of unique hyper-acute HIV-infection samples from 15 South-African women who were identified within 48 hours of infection (the FRESH cohort), systems serology was performed to evaluate both the functional and biophsycial changes in p24-, gp120-, and gp41- specific antibody responses

at days 30, 90, 180, 270 and 360 following infection. Over 100 biophysical, functional and clinical parameters including glycosylation, subclass distribution, phagocytosis, NK degranulation, cytokine release and viral set point were included in the analysis.
Results: Significant changes were observed in both the functional and biophysical characteristics of the evolution of humoral immune response following acute HIV infection. Antibody glycosylation matured dramatically during infection, transitioning from a highly functional (highly galactosylated) profile, to a less functional (highly agalactosylated) profile, typically associated with increaded inflammation and characteristic of chronic HIV infection. Fc functionality increased over infection, with increases in antibody-mediated phagocytosis, NK degranulation and complement in a highly antigen-specific manner. p24-specific functional activity evolved more modestly over time compared to gp120- and gp41-specific response. Both antibody subclass changes and glycosylation drove changes in the evolution of antibody effector activity, highlighting the natural modifications in the humoral immune response that enable the directed recruitment of the innate immune system to target and control HIV.
Conclusion: Antibody functionality evolves rapidly following acute HIV infection in an antigen-specific manner, pointing to specific antibody effector functions in the early control of HIV infection.

298 GP41–SPECIFIC ANTIBODIES MEDIATE POTENT ANTIBODY–DEPENDENT CELLULAR CYTOTOXICITY

Megan M. Stumpf[1], Katherine L. Williams[1], Nicole Naiman[1], Meghan Garrett[1], Nitya Ramadoss[2], Peter Kim[2], Julie Overbaugh[1]
[1]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [2]Stanford University, Stanford, CA, USA

Background: HIV-specific antibodies (Abs) are capable of limiting viral infection by neutralizing cell-free virus and/or targeting infected cells for destruction. The latter process is referred to as antibody-dependent cellular cytotoxicity (ADCC). ADCC-mediating Abs have been identified as a correlate of protection from HIV in the RV144 Phase III HIV vaccine trial as well as in experimental vaccine studies in non-human primates. High levels of passively acquired ADCC-mediating activity has also been correlated with improved clinical outcome in HIV-infected infants. Due to requirements for fusion and entry, certain regions of gp41 are highly conserved. However, little is known about antibodies that target these conserved regions and whether they mediate FcR-dependent effector activity, like ADCC.
Methods: HIV-specific B cells were sorted from PBMC samples obtained from a subtype-A infected Kenyan woman 914 days post-infection. Following sequence amplification and protein expression, the Abs were tested for HIV binding by ELISA and in a rapid and fluorometric ADCC (RF-ADCC) assay. We used the following four coating antigens: a clade B gp41 protein, a clade C gp41 ectodomain protein, a clade A gp140 protein which includes the extracellular domain of gp41, and a six-helical mimetic gp41 protein which consists of the conserved HR1 and HR2 regions in a continuous trimer. Competition ELISAs were performed to further characterize the individual epitopes.
Results: We identified four gp41-specific ADCC-mediating Abs from unique B cell lineages that target two distinct regions of the gp41 ectodomain. Abs QA255.006 and QA255.016 bind the heptad-repeat regions whereas QA255.067 and QA255.072 target the C-C loop of gp41. QA255.006 and QA255.016 both mediated strong ADCC activity against all four gp41 antigens tested in the RF-ADCC assay, including the gp41 mimetic. In contrast, QA255.067 and QA255.072 maintained strong activity against the other three gp41 antigens but did not demonstrate any measurable ADCC activity against the mimetic antigen.
Conclusion: Here we describe four new ADCC-mediating antibodies, isolated from one individual that are derived from distinct B cell lineages, that target gp41. Two of these antibodies recognize the trimeric post-fusion conformation mimetic containing the conserved HR1 and HR2 regions. Further characterization of these novel functional antibodies may inform the design of a broad and effective HIV vaccine.

299 DISSECTING THE PHENOTYPE AND TRANSCRIPTOME OF IGG3+ B CELLS

Saheli Sadanand, Wen-Han Yu, Dario Garcia-Dominguez, Galit Alter
Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

Background: HIV-specific IgG3 antibodies (Abs) have been established as a key signature associated with robust humoral immune activity in the context of both natural HIV infection and the efficacious RV144 vaccination trial. While highly functionally potent, IgG3 Abs are short-lived and not abundant. An improved understanding of the mechanism(s) by which IgG3+ B cells are actively induced and preserved could suggest strategies for eliciting highly potent and stable IgG3 Abs. It is unclear whether intrinsic factors are important for selection and maintenance of IgG3-secreting B cells. We hypothesized that IgG3+ B cells have a distinct phenotype and transcriptome that preserves IgG3 subclass expression.
Methods: Peripheral B cells from HIV negative donors and HIV positive donors (elite controllers, viremic controllers and treated chronic progressors) were phenotypically profiled using multicolor flow cytometry. For RNA-sequencing, peripheral non-naïve bulk isotype-specific B cells were sorted into lysis buffer and whole transcriptome amplification was performed using a modified SMART-Seq2 protocol. For *in vitro* stimulations, resting memory B cells were stimulated with anti-IgG or anti-IgM along with CpG and soluble CD40 ligand for four days.
Results: IgG3+ peripheral B cell frequencies are similar in HIV negative and HIV positive donors. We evaluated expression of markers associated with B cell-T cell interactions and homing to the germinal center. IgG3+ B cells have a unique and intermediate phenotype that is independent of HIV disease status (Figure). Transcriptional analyses of peripheral non-naive IgM+, IgG3+ an IgG1+ B cells further revealed that IgG3+ B cells were more similar to IgM+ B cells than to IgG1+ B cells. Notably, both IgM+ and IgG3+ B cells had higher expression of genes involved in class-switch recombination. Finally, preliminary *in vitro* data suggest that upon stimulation IgG3+ B cells significantly modulate expression of over 600 genes, including some involved in DNA repair and BCR signaling.
Conclusion: Collectively, the phenotypic and transcriptional profile of IgG3+ B cells likely promotes germinal center reentry as opposed to plasmablast differentiation. Our data suggest B cell-T cell interactions and genes that may be useful targets for blocking further class-switch recombination, thereby skewing activated IgG3+ B cells towards plasmablast differentiation and leading to more production of highly potent IgG3 Abs.

300 DEFINING CORRELATES OF ANTIBODY-POLYFUNCTIONALITY IN RV144 VACCINEES

Stephanie Fischinger[1], Todd J. Suscovich[1], Hendrik Streeck[2], Galit Alter[1]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Institute for HIV Research, Essen, Germany

Background: Results from the RV144 trial pointed to a potentially important role for non-neutralizing but functional antibodies in protection against HIV acquisition. Importantly, while ADCC activity was primarily associated with protection in the case-control study, RV144 vaccine induced antibodies were able to recruit a broader range of antiviral functions including antibody-dependent cellular phagocytosis (ADCP), neutrophil phagocytosis (ADNP), activation of natural killer cells (NK), and the recruitment of complement. However, the specific antibody modifications that permitted the induction of this polyfunctional response are incompletely understood but may provide critical insights to enhance protective immunity.
Methods: Systems serology profiling was therefore performed in plasma samples from 300 RV144 vaccinees including both functional and biophysical profiling of the humoral immune response against both the priming (MN-cladeB) and boosting (A244-cladeAE) HIV envelope immunogens.
Results: Heterogeneous responses for antibody mediated monocyte phagocytosis, antibody mediated neutrophil phagocytic, activation of antibody-dependent complement deposition (ADCD) and NK cell-activating activity were observed across the vaccinees and across the two antigens. The functional responses to prime- and boost-antigen were highly correlated in the overall cohort. Levels of IgG3 against either antigen, which was shown to be a correlate of protection was strongly correlated with ADCP, ADNP, ADCD and IFN-γ release by NK cells. Polyfunctionality was associated with IgG3 levels, but more strongly associated with antigen-specific IgG1 levels, pointing to a potentially critical role for altered IgG1 glycosylation in driving antibody polyfunctionality within this vaccine trial.
Conclusion: The data argue for a synergistic role for both IgG3 and particularly modified IgG1 antibodies in the induction of polyfunctional antibody effector profiles, pointing to novel correlates of antiviral immunity that may be leveraged to drive enhanced antibody effector function in future vaccine design.

301 DEFINING CORRELATES OF HUMORAL IMMUNE PROTECTION AGAINST EBV

Christina B. Karsten[1], Sally A. Shin[1], Howard M. Heller[2], Kumaran Kolandaivelu[3], Jaap M. Middeldorp[4], Bruce D. Walker[1], Boris Julg[1], Galit Alter[1]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]MIT, Cambridge, MA, USA, [3]MIT Institute for Medical Engineering & Science, Cambridge, MA, USA, [4]VU University Medical Center, Amsterdam, Netherlands

Background: Epstein-Barr virus (EBV)-associated cancers including Burkitt, Hodgkin and non-Hodgkin lymphoma pose a deadly health threat, especially among HIV-1 infected populations. However, a protective vaccine to prevent EBV infection and or limit disease has yet to be developed. While previous vaccine efforts have focused on the induction of either neutralizing antibodies or CD8+ T-cell responses to prevent or kill infected cells, mounting evidence points to a potentially critical role for cytotoxic antibodies, able to deploy the antiviral activity of the innate immune system, in the control and clearance of EBV. Thus, here we aimed to define whether non-neutralizing antibody functions, able to recruit a broad array of innate immune effector functions, might selectively evolve following EBV infection.

Methods: Systems serology profiling was performed in a cohort of 12 EBV-infected patients that were enrolled during the acute stage of infection and sampled for a year. Both functional and biophysical assays were performed to define cross-sectional and longitudinal differences in the humoral immune response against acute- and latency- associated EBV antigens.

Results: As anticipated, IgG1 and IgG3 antibody subclasses, known to drive enhanced antiviral function, predominated the IgG immune response to the EBV viral envelope protein (gp350/220), capsid antigen (p18), early antigen (p47/54) and latent protein (EBNA 1). However, variability was observed among infected subjects suggesting the existence of different responder groups or patterns. While all EBV protein-specific antibodies were unable to recruit monocyte-dependent phagocytosis, p18-specific antibodies induced low levels of phagocytosis by neutrophils (ADNP) early in infection (0-2 weeks post enrollment; average median fold over background response (SD)= 2.33±0.16). Moreover, ADNP was associated with p18-specific IgM antibodies, indicating that an IgM, rather than an IgG response to this target, may be largely responsible for this antiviral function ($r=0.77$, $p=0.044$). Further, EBNA 1-specific IgMs were found to correlate more strongly ($r=0.99$, $p= 0.000013$) with the severity of EBV symptoms than the previously described p18-specific IgA suggesting a potential role of IgMs in the pathogenesis of EBV infection.

Conclusion: Our systems serology approach identified ADNP as a first antibody mechanism of action against EBV with the potential to be exploited for future treatment and vaccine strategies.

302 LEVERAGING NEUTROPHILS TO CONTROL HIV VIA IGA

Nickita Mehta, Magdalena Sips, Jishnu Das, Marina Krykbaeva, Anne-Sophie Dugast, Fernanda Cerqueira, Galit Alter
Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

Background: Neutrophils are the most abundant white blood cell and are rapid responders to infections. Neutrophils are also the most potent mediators of Fc-effector functions and in addition to phagocytosis, neutrophils degranulate and can kill through the formation of extracellular traps. However, little is known about the role of neutrophils in antiviral control of HIV. Thus, here we aimed to define the role of neutrophil-recruiting antibodies in antiviral control of HIV.

Methods: Because neutrophils express both an IgA and IgG Fc-receptor, both IgA and IgG were purified from HIV infected patient serum and compared to healthy controls. The functional activity of these antibodies were compared for phagocytic, degranulation, NET formation, and release of elastase activity.

Results: Elevated levels of all neutrophil recruiting antibody subclasses and isotypes were observed in spontaneous controllers of HIV including higher HIV-specific IgG3, IgA1 and IgA2 titers. Moreover, while both IgA and IgG induced HIV-specific neutrophil phagocytosis, IgA1 drove enhanced phagocytosis compared to IgG or IgA2. Conversely, IgA2 induced enhanced degranulation and NET formation, which were not induced by IgA1. Additionally, IgA2 synergized with IgG1 and IgG3 to recruit neutrophil functions. However the depletion of IgA significantly reduced neutrophil activation, despite the presence of IgG1 and IgG3.

Conclusion: These data suggest that HIV-specific IgA responses are not only enriched among spontaneous controllers of HIV, but may be selectively enriched to drive robust and rapid recruitment of neutrophils to clear and destroy HIV infected cells. Surprising differences in functionality were observed among the IgA subclasses, each poised to leverage distinct innate immune effector functions. Overall, these data point to a potentially critical immunoprotective role for IgA via the recruitment of the tremendous anti-viral potential of neutrophils.

303 THE DEVELOPMENT OF A NOVEL MACHINE-LEARNING-GUIDED HIV IMMUNOGEN DESIGN

Wen-Han Yu[1], Galit Alter[1], Christina B. Karsten[1], Douglas Lauffenburger[2], Daniel Lingwood[1], Dan Barouch[3]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]MIT, Cambridge, MA, USA, [3]Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: HIV envelope glycoprotein (Env) is the major target for broadly neutralizing antibodies (bNAbs). Both the underlying protein and glycan shield represent antigenic determinants for many potent bNAbs. Several state-of-the-art protein-engineering approaches have been developed to generate HIV immunogens, among which the native-like trimer (SOSIP.664) has shown promise in inducing NAb responses against autologus tier-2 viruses. However, the roadmap for HIV vaccine development remains hampered by the inability to drive broad NAb responses to heterologous tier2 and 3 viruses. While several stragies have focused on improving SOSIP.664 or developing scaffolds to selectively induce mature/gemline bNAb, via immunofocusing approach, these immunogens do not take sequence and glycan diversity into account.

Methods: To address this challenge, we developed a machine-learning model, aimed at deeply learning the complexity of the HIV sequence/glycan diversity linked to bNAb neutralization sensitivities, to guide an in silico rational immunogen design aimed at selectively inducing bNAbs while simultaneously blocking non-bNAb binding. Specifically, this Bayesian Support Vector Regression (SVR) model were based on 6,886 Env sequences, glycan occupancy and bNAb neutralization sensitivities (IC50). The predictive model was next used to guide a de novo sequence evolutionary algorithm. The algorithm imitated the process of natural selection to iteratively evolve a given trimeric gp140 Env sequence. The final convergent immunogen was designed to enhance/impair specific bNAb/non-bNAb binding without compromising structural stability and sequence conservation.

Results: This machine-learning models were able to predict total 130 bNAb and non-bNAb IC50 profiles, and 80% of the predictive models showed a robust prediction performance (average correlation R-square between predicted and actual IC50 profile larger than 0.9), and the feature signature that enhances bNAbs, while simultaneously occluding non-bNAb binding was observed. This design approach has produced novel proof-of-principle immunogens that successfully skew binding of bNAbs PGT121 or PGT128 in vitro, with design of an enhanced PGT121 and/or PGDM1400 immunogen in process.

Conclusion: This approach provides an innovative design strategy, rooted in deep learning of glycobiology and large sequence data, to predictably modulate NAb binding aimed at focusing the humoral immune response to sites of vulnerability.

304 DEFINING THE COMMON CORRELATES OF HIV VACCINE TRIALS CROSS-PREDICTS VACCINE EFFICACY

Wen-Han Yu[1], Dan Barouch[2], Douglas Lauffenburger[3], Margaret Ackerman[4], Caitlyn Linde[1], Thomas Broge[1], Galit Alter[1]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Beth Israel Deaconess Medical Center, Boston, MA, USA, [3]MIT, Cambridge, MA, USA, [4]Dartmouth College, Hanover, NH, USA

Background: Over the last decade, several different HIV vaccine candidates have shown robust protection against SIV challenges in non-human primate (NHP) models, and immunological correlates of protection have often been identified. However, as these correlates are frequently different for each of the vaccine regimens, a major hurdle has been the ability to translate these data sets into a computational model in order to accurately cross-predict protective efficacy in future human vaccine trial.

Methods: To address this, we used Systems Serology to comprehensively profile the biophysical and functional properties of the humoral immune response in two independent NHP trials. In the first trial, NHPs were primed with adenovirus (Ad) vectors expressing SIV Env/Gag/Pol, and then boosted with Ad or SIV Env gp140 proteins. The second trial was performed under the similar vaccine regimens, but the SIV antigens were substituted by HIV proteins. The

multivariate models were further developed to define the common correlates from the comprehensive antibody profiles.
Results: Using a unsupervised multivariate analysis, we observed the distinct humoral profiles induced by different vaccine regimens, and the evolution of the humoral profiles skewing along vaccine priming and boosting. To connect between elicited antibody-mediated responses and protective efficacy, the immunological correlates that associated to vaccine protection in each of the NHP trials were defined by a supervised multivariate analysis. Importantly, we further developed a multiple-string model which ranked the antibody features from each of the studies, and defined the common correlates shared between two studies, including antibody polyfunctionality and breadth, indicating a potential core humoral response mechanism linked to protective efficacy, regardless of different antigens vaccinated in the two trials. Significantly, based on the communal correlates, the supervised multivariate model was able to robustly cross-predict the protective efficacy in these two independent trials with > 80% accuracy.
Conclusion: Taken together, this predictive model built based on robust immunological correlates provides the first framework to evaluate protective immunity and define novel immunological correlates for the development of future human HIV vaccine trials.

305 VACCINATION WITH MF59 INDUCES DISTINCT VACCINE-SPECIFIC ANTIBODY FUNCTIONALITY

Carolyn Boudreau, Todd J. Suscovich, Galit Alter
Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

Background: In the search for an HIV vaccine, novel adjuvants such as MF59 provide a promising strategy boost vaccine responses, both through their capacity to improve antibody titers but also by improving antibody antiviral activity. Analyses of RV144 vaccinees showed that high IgG3 antibody responses, with links to antibody functions like antibody-dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and complement deposition (ADCD) were correlates of protection from HIV infection. However, whether adjuvants can boost both the neutralizing activity and Fc-functional activity of the vaccine-induced immune response remains unclear. In the imminent phase 2/3 RV144-follow up vaccine trial (HVTN702) underway, adjuvants MF59 and alum will be compared. Thus, understanding the humoral immune effects of MF59, an oil-in-water emulsion, will provide vital clues related to the specific opportunities by which antibodies may provide resistance to HIV infection.
Methods: Using Systems Serology, we evaluated the impacts of MF59 and alum on antibody effector profiles in an influenza vaccine study, using a potential pandemic influenza strain to which few individuals have pre-existing immunity.
Results: Strikingly, MF59 induced remarkably distinct antibody effector profiles compared to alum-based vaccination. MF59 induced higher levels of ADCP, neutrophil phagocytosis (ADNP), natural killer cell degranulation, and ADCD. MF59 also induced longer lasting antibodies capable of inducing ADCP and ADCD. Moreover, this increase in functional humoral response was linked to an increase in the most functional subclass of antibodies, IgG3, previously linked to protection from HIV acquisition in the RV144 vaccine trial.
Conclusion: Thus, these results from a pandemic influenza vaccine trial indicate that MF59 is an attractive adjuvant to boost both protective immune responses and functional antibody subclasses that may drive enhanced immunity to HIV.

306 ADDITIONAL BOOST OF AIDSVAX B/E FURTHER INCREASED RV305 IGG BUT NOT IGA ANTIBODIES

Siriwat Akapirat[1], Sandhya Vasan[2], Supachai Rerks-Ngarm[3], Punnee Pitisutthithum[4], Kirsten S. Smith[1], Surawach Rittiroongrad[1], Jiraporn Puangkaew[1], Sanjay Phogat[5], Faruk Sinangil[6], Nelson L. Michael[7], Jean-Louis Excler[8], Jerome H. Kim[8], Nicos Karasavvas[9], Robert J. O'Connell[1]
[1]Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, [2]US Military HIV Research Program in Thailand, Bangkok, Thailand, [3]Ministry of Pubic Health, Nonthaburi, Thailand, [4]Mahidol University, Bangkok, Thailand, [5]Sanofi Pasteur, Swiftwater, PA, USA, [6]Global Solutions for Infectious Diseases, San Francisco, CA, USA, [7]US Military HIV Research Program, Silver Spring, MD, USA, [8]International Vaccine Institute, Seoul, South Korea, [9]Walter Reed Army Institute of Research, Silver Spring, MD, USA

Background: The late boosts with AIDSVAX B/E with or without ALVAC-HIV (RV305) induced higher HIV binding antibody responses in RV144 vaccine recipients who completed the primary vaccination series 6-8 years earlier. We studied HIV binding antibodies in HIV-uninfected RV305 vaccine and placebo recipients who received additional boost of AIDSVAX B/E 18-30 months post RV305 vaccinations.
Methods: ELISA IgG and IgA to HIV gp120 A244gD- (CRF01_AE) and MNgD- (subtype B), and gp70V1V2 scaffold proteins 92TH023 (CRF01_AE) and CaseA2 (subtype B) were assessed in plasma at weeks 0, 1, 2 and 24 post additional boost of AIDSVAX B/E.
Results: At the pre-additional boost timepoint, geometric mean titers (GMT) of IgG to gp120 A244gD- and MNgD- were detected in all groups (ALVAC-HIV/AIDSVAX B/E [Gr1]-AIDVAX B/E [Gr2]-ALVAC-HIV [Gr3]-Placebo [PLB]/A244gD-=1459-1313-105-67; MNgD-=1925-1767-105-84), indicating durability of RV305 IgG binding antibodies. IgG GMT to gp70V1V2 scaffolds ranged from 50-115 at the pre-additional boost timepoint in all groups. IgG GMT to all proteins were significantly increased 2 weeks post additional boost in all groups ($p<0.001$, GMT range/A244gD-=23340-54245; MNgD-=37050-60887; 92TH023=5320-13405; CaseA2=1106-3901) but significantly declined 24 weeks post additional boost ($p<0.001$, GMT range/A244gD-=4271-5991; MNgD-=4631-8903; 92TH023=189-459; CaseA2=76-159). Only IgG responses to CaseA2 2 weeks post additional boost were significantly higher ($p<0.005$) than those 2 weeks post 1st and 2nd boosts in all groups. Though IgG GMT to all proteins declined 24 weeks post additional boost, they were higher than those 24 weeks post 1st and 2nd boost, except IgG to A244gD- (Gr1) and 92TH023 (Gr1 and Gr2; fold changes range/A244gD-=0-75; MNgD-=0-79; 92TH023=0-6; CaseA2=1-2). IgA to gp120 (all groups) and 92TH023 (Gr1, Gr3 and PLB) significantly increased ($p<0.05$) 2 weeks post additional boost but declined to initial levels (GMT=50) 24 weeks post additional boost. We did not detect an additional boosting effect of IgA to CaseA2 in any group.
Conclusion: An additional boost of AIDSVAX B/E increased plasma HIV-specific IgG antibodies. IgG to gp70V1V2 CaseA2 which inversely correlated with HIV infection risk in RV144, increased preferentially over IgA, a direct correlate of HIV infection risk. These findings support the hypothesis that administration of late recombinant protein boosts may be a strategy to enhance and extend preventive vaccine efficacy observed in RV144.

307 INCREASE IN B CELL RESPONSES UPON LATE BOOST STRATEGIES OF ALVAC-HIV/AIDSVAX B/E

Alexandra Schuetz[1], Siriwat Akapirat[2], Weerawan Chuenarom[2], Punnee Pitisutthithum[3], Sorachai Nitayaphan[2], Suwat Chariyalertsak[4], Jaranit Kaewkungwal[3], Sanjay Phogat[5], Faruk Sinangil[6], Merlin L. Robb[7], Nelson L. Michael[7], Jerome H. Kim[8], Mark de Souza[9], Robert J. O'Connell[1], Sandhya Vasan[1]
[1]US Military HIV Research Program in Thailand, Bangkok, Thailand, [2]Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, [3]Mahidol University, Bangkok, Thailand, [4]Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand, [5]Sanofi Pasteur, Swiftwater, PA, USA, [6]Global Solutions for Infectious Diseases, San Francisco, CA, USA, [7]US Military HIV Research Program, Silver Spring, MD, USA, [8]International Vaccine Institute, Seoul, South Korea, [9]SEARCH, Bangkok, Thailand

Background: Memory B cells, along with terminally differentiated plasmablasts (PB), are responsible for long-term persistence of humoral immunity elicited by most vaccines. In RV144, high V1V2-specific IgG antibodies were identified as an inverse correlate for risk, highlighting the potential importance of B cells.
Methods: In RV306 HIV-uninfected volunteers received the ALVAC-HIV/AIDSVAX B/E prime-boost regimen used in RV144 followed by different one-year late boosts with ALVAC-HIV/AIDSVAX B/E. B cell ELISpots detecting gp120 A244Δ11gDneg-specific IgG-producing PB and long-lived memory B cells using peripheral mononuclear cells (PBMC) were performed pre-immunization (wk0), post ALVAC-HIV/AIDSVAX B/E prime-boost regime (wk26) and post different late boosts at wk50, wk62 or wk74, and at wk96. A244Δ11gDneg-specific plasma antibodies were assessed by ELISA.
Results: No B cell responses were detected at wk0 or in placebo recipients at any time-point. At wk26 23/58 (40%) and 52/58 (90%) showed PB and memory responses, respectively. With no late boost 3/9 (33%) maintained PB and 7/9 (78%) memory responses. With ALVAC-HIV/AIDSVAX B/E late boost at wk50 12/14 (86%) showed PB and 14/14 (100%) memory responses. Following a late boost at wk62 and wk74 11/11 (100%) showed PB and memory responses,

respectively. There was a significant increase in the magnitude of PB responses between wk26 (12 SFC/10^6 PBMC) and after the late boosts at wk50 (67 SFC/10^6 PBMC, p<0.001), wk62 (75 SFC/10^6 PBMC, p<0.0001) and wk74 (73 SFC/10^6 PBMC, p<0.0001), but not when no boost was administered (12 SFC/10^6 PBMC, p=NS). A similar trend was observed for memory responses (Table 1). Late boost at wk74 increased the magnitude of memory responses significantly compared to the late boost at wk50 (3433 vs. 2457 SFC/10^6 PBMC, p=0.01). Memory B cell responses at the late boost correlated strongly with IgG geometric mean titers (GMT) at wk96 (r=0.61, p<0.0001). At wk96 the magnitude of PB and memory responses decreased for all late boost groups to frequencies similar to wk26, however still correlated with GMT at wk96 (PB: r=0.32, p=0.01, memory B cells: r=0.66, p=0.01).

Conclusion: Late boosts of the ALVAC-HIV/AIDSVAX B/E prime-boost increased the number and frequency of gp120-specific PB and memory B cell responders compared to when no boost was administered, with memory responses being predictive of IgG levels at wk96. New strategies to increase antigen-specific B cell responses could contribute to increased antibody durability.

Table 1: Magnitude of plasmablast and memory B cell responses for the different late boost groups.

	Plasmablast Response [SFC/10⁶ PBMC]			Memory B Cell Response [SFC/10⁶ PBMC]		
	wk26	late boost	wk96	wk26	late boost	wk96
wk50 no boost	12	12	3*	870	437	70**
wk50 boost		67***	17		2457****	605
wk62 boost		75****	10		3653****	1074
wk74 boost		73***	18		3433****	1093

All data are median and all comparisons were made to the respective wk26 time-point; **p<0.01, ***p<0.001 and ****p<0.0001.

308 EPITOPES ASSOCIATED WITH HIV-1 DYNAMICS AFTER DC-BASED THERAPEUTIC VACCINATION

Mathieu Surenaud[1], Laura Richert[2], Monica Montes[3], Sandy Zurawski[3], Karolina Palucka[4], Jacques Banchereau[4], Rodolphe Thiébaut[2], **Jean-Daniel Lelievre**[1], Christine Lacabaratz[1], Yves Levy[1]

[1]INSERM, Créteil, France, [2]INSERM, Bordeaux, France, [3]Baylor Institute for Immunology Research, Dallas, TX, USA, [4]Vaccine Research Institute, Créteil, France

Background: Improvement of therapeutic vaccine strategies in the perspective of HIV cure is warranted. The DALIA-1 phase I trial evaluated a new DC-based therapeutic vaccine that consisted in ex-vivo generated IFN-α DC loaded with LIPO-5 (HIV-1 Nef 66-97, Nef 116-145, Gag 17-35, Gag 253-284 and Pol 325-355 lipopeptides). Nineteen patients on c-ART (antiretroviral treatment) received four injections followed by a 24-week c-ART interruption (ATI). Four weeks after the last injection, an increase in breadth of immune responses was detected by IFN-γ ELISpot and Luminex assays (Y. Levy et al, EJI 2014). An inverse correlation was found between the frequency of polyfunctional CD4+ T cells detected by intracellular staining (ICS) assays after vaccination and the maximum viral load (VL) post-ATI. Here, we performed epitope mapping to dissect anti-HIV-1 responses and correlations between vaccine-induced responses and maximum VL post-ATI.

Methods: PBMC from 16 participants were incubated with 36 (15-mer) and 56 (9-mer) overlapping peptides encompassing the LIPO-5 sequences. Cytokine responses were detected using 48h Luminex and 7 day ICS assays. Comparison of responses with predicted peptide/MHC class I and class II binding affinities (NetMHCpan 3.0 and NetMHCpanII 3.1 servers) was performed.

Results: IL-13 and IL-2 (15-mer Luminex) T-cell responses detected after four vaccinations and before ATI were inversely correlated with maximum VL post-ATI (Spearman r=-0.66; P=0.007 and r=-0.58; P=0.02, respectively for breadth; r=-0.71; P=0.003 and r=-0.66; P=0.007, respectively for magnitude). Sum of IL-13 and IL-2 responses directed to six 15-mer peptides (from Gag, Pol and Nef regions of LIPO-5) was strongly associated with lower maximum VL post-ATI (Spearman r=-0.71; P=0.003). Using ICS, IL-13 and IL-2 were detected in both CD4+ and CD8+ T cells after 9-mer and 15-mer peptide stimulations. Luminex and ICS functional assays allowed us to identify vaccine-elicited CD4+ T cell responses that were not predicted a priori by peptide binding prediction bio-informatic tools.

Conclusion: We showed that ex vivo DC vaccination, as a vehicle of HIV lipopeptide delivery, was broadly immunogenic and elicited responses against a set of epitopes from Gag, Pol and Nef. IL-2 and IL-13 functional responses were associated with a better control of VL post-ATI. Moreover, new HIV-1 CD4+ T-cell immunogenic epitopes, not predicted by peptide/MHC binding algorithms, were identified.

309 SIV REBOUND KINETICS FOLLOWING TLR7-AGONIST & THERAPEUTIC VACCINE ADMINISTRATION

Jeffrey Gerold[1], So-Yon Lim[2], Christa E. Osuna[2], Dan Barouch[2], James Whitney[2], Alison L. Hill[1]

[1]Harvard University, Cambridge, MA, USA, [2]Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: Immunotherapy is a promising approach to prevent or control HIV rebound following cessation of antiretroviral therapy (ART). We previously tested a toll-like receptor 7 (TLR7) agonist, alone and combined with Ad26/MVA therapeutic vaccination, on rebound in SIV-infected rhesus macaques. A subset of animals in each study achieved remission, but the mechanism of action of these treatments and the source of differences in outcomes between individuals remains unknown.

Methods: We conducted an in-depth characterization of viral load kinetics following ART interruption in each study using a novel viral dynamics model that includes reactivation of latent infection and adaptive immune responses. We developed a Bayesian inference algorithm to estimate model parameters for individual animals from viral load kinetics and determine which parameters are impacted by which therapy.

Results: Our model describes the kinetics of rebound well in all animals in both studies. In the TLR7-only study, in which animals started ART during chronic infection, we found that although mean rebound time was the same in treated vs control groups, the kinetics were different. TLR7 treatment reduced inferred reservoir exit rate (log_{10} -9.87 vs -5.65 cells/ml/day, p=0.01), but also increased viral growth rate (1.8 versus 0.77 per day, p=0.03). We used the model to estimate the number of latent cells contributing to viral blips, and found that between 0.1% and 1.2% of SIV DNA was reactivated, perhaps representing a large fraction of the replication-competent reservoir. These findings are supported by the absence of rebound despite CD8 depletion and lack of detectable replication-competent reservoir in 2/11 treated animals. In the combined TLR7-agonist and vaccine study, in which animals started ART during acute infection, we found that TLR7 alone did not significantly change any viral dynamic parameters. The combined TLR7/vaccine reduced both the initial viral growth rate (0.56 vs 0.85 per day, p=0.02) and increased the inferred immune proliferate rate (log_{10} -0.17 vss -3.99 per day, p=0.0006).

Conclusion: Analysis of viral rebound kinetics using mathematical models suggests that TLR7-agonist alone administered during chronic infection can lead to some reductions in the functional latent reservoir in most animals and complete clearance in other animals, while the post-treatment control obtained with TLR7+therapeutic vaccination is mainly due to immunologic stimulation, not reservoir reduction.

310 IPROTECT1: A VAC-3S VACCINE PHASE II STUDY IN HIV-INFECTED PATIENTS

Christine Katlama[1], Gilles Pialoux[2], Laurent Cotte[3], Pierre-Marie Girard[4], Anne Simon[1], Jacques Reynes[5], Jürgen K. Rockstroh[6], Jose M. Gatell[7], Alain Devidas[8], Yazdan Yazdanpanah[9], Odile Launay[10], Laurence Weiss[11], Gerd Fätkenheuer[12], Béhazine Combadière[13], Vincent Vieillard[13]

[1]Pitié-Salpêtrière Hospital, Paris, France, [2]Tenon Hospital, Paris, France, [3]CHU de Lyon, Lyon, France, [4]Saint-Antoine Hospital, Paris, France, [5]CHU de Montpellier, Montpellier, France, [6]Bonn University Hospital, Bonn, Germany, [7]Hospital Clinic of Barcelona, Barcelona, Spain, [8]Centre Hospitalier Sud Francilien, Corbeil-Essonne, France, [9]Bichat–Claude Bernard Hospital, Paris, France, [10]Cochin Hospital, Paris, France, [11]Georges Pompidou European Hospital, Paris, France, [12]University of Cologne, Cologne, Germany, [13]INSERM, Paris, France

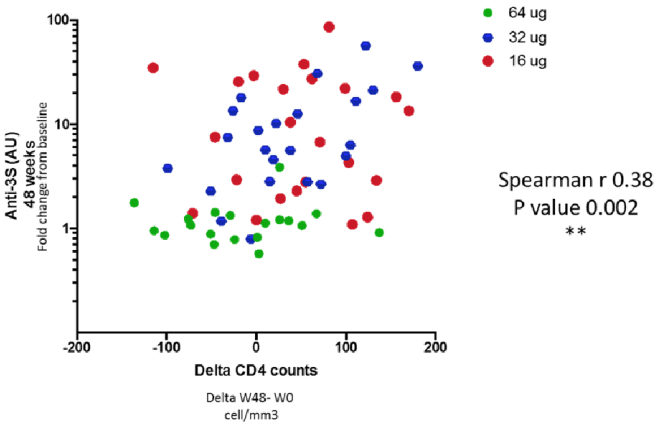
Background: 3S is a highly conserved motif of HIV-gp41 protein. High level of anti-3S antibodies (Abs) has been associated with lower HIV disease progression. Preclinical studies in SHIV-infected macaques demonstrated that anti-3S Abs are associated with protection of CD4 loss during infection. VAC-3S is a therapeutic vaccine composed of 3S motifs-coupled with CRM197 carrier in aluminum salt adjuvant. Previous Phase 1 study demonstrated the safety of VAC-3S.

Methods: IPROTECT1 was a randomized, double-blind, placebo-controlled Phase 2 Study. Eighty-six patients (85 completed) with HIV RNA < 50 cp/mL on ART, with CD4 between 200 and 500 c/mm^3 were randomized to receive VAC-3S 16 µg (group A n=24), 32 µg (group B n=25), 64 µg (group C n=23) or placebo (n=14). All individual received 6 injections (W0, W4, W8, W12, W36, W48) except for arm C (3 injections at W0, W4, W8). The primary endpoint was the proportion of vaccine responders defined as anti-3S Abs > 35 AU one month

after the third injection. Secondary endpoints included changes in CD4 count, CD4/CD8 ratio and inflammation markers. A post-hoc analysis, categorized patients in 3 groups according to anti-3S Ab response: non-responders (NR: < 4-fold increase), low-responders (LR: between 4 and 10-fold increase), and high-responders (HR: ≥10 fold-increase).

Results: At baseline (mean values), patients were mostly males (79.1%), age: 47 yrs, ART duration: 13.65 yrs, CD4 cells: 365.2, CD4/CD8: 0.7075. The proportion of responders versus placebo was 45.8% (p=0.0026), 62.5% (p=0.0002) and 47.8% (p=0.0020) in the 16, 32 and 64 µg groups, respectively. No statistical differences were observed in secondary endpoints. In post-hoc analysis, 20 patients were HR, 16 LR and 50 NR. CD4 nadir, age, HIV duration did not impact anti-3S response except for CD4/CD8 ratio (p=0.0069). At week 48, a significant increase in CD4 count (+ 60 CD4/mm^3; p=0.0029) was observed in patients with anti-3S Ab >100 AU, compared to baseline. Anti-3S responses were significantly correlated with CD4 increase in all vaccinated patients (p=0.002). One viral rebound was observed after ART discontinuation. VAC-3S was well tolerated with no SAEs and no systemic AEs leading to premature discontinuation; 69% of patients experienced mild local reactions.

Conclusion: VAC-3S was safe and induced a significant Ab response, higher in patients with higher CD4/CD8 ratio at baseline. An increase in CD4 count was observed in patients with higher Ab rate.



311 PHASE I CLINICAL TRIAL OF AN MRNA-BASED THERAPEUTIC VACCINE AGAINST HIV-1 INFECTION

Lorna Leal[1], Alberto C. Guardo[2], Sara Moron-Lopez[3], Maria Salgado[3], Beatriz Mothe[3], Carlo Heirman[4], Kris Thielemans[4], Pieter Pannus[5], Christian Brander[3], Rob Gruters[6], Arno Andeweg[6], Javier Martinez-Picado[3], Montserrat Plana[2], Felipe Garcia[1]

[1]Hospital Clinic of Barcelona, Barcelona, Spain, [2]IDIBAPS, Barcelona, Spain, [3]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [4]Vrije Universiteit Brussel, Brussels, Belgium, [5]Institute of Tropical Medicine, Antwerp, Belgium, [6]Erasmus University Medical Center, Rotterdam, Netherlands

Background: The efficacy of therapeutic vaccines has been modest. The combination of new vectors targeting dendritic cells (DC) pathways and new antigenic sequences to redirect responses toward target unmutated epitopes could be necessary to achieve the remission of HIV-1 infection. We performed the first-in-human clinical trial with naked mRNA (iHIVARNA) encoding DC activation signals (TriMix:CD40L+CD70+caTLRA4) combined with HIV antigenic sequences (HTI sequence:comprising 16 joined fragments from Gag, Pol, Vif and Nef) rationally selected to redirect the responses to the most vulnerable viral targets.

Methods: A dose scalating phase I clinical trial was performed in 21 chronic HIV-1 infected patients who received 3 intranodal doses of mRNA at weeks 0, 2 and 4 as follow: TriMix 100mg (n=3), TriMix 300mg (n=3), TriMix 300mg+HTI 300mg (n=3), TriMix 300 mg+HTI 600mg (n=6), TriMix 300 mg+HTI 900mg (n=6). Primary end-point was safety and secondary-exploratory end-points were immunogenicity (ELISPOT), changes in reservoir (caHIV-DNA and caHIV-RNA), ultrasensitive plasma RNA (usVL) and transcriptome (limma).

Results: Overall, the vaccine was safe and well tolerated. No serious adverse events (AEs) were observed. There were 31 grade 1/2 and 1 grade 3 AEs, from which half of grade 1/2 and the grade 3 were definitely not related to the vaccination. Patients who received the highest dose showed a moderate increase in T cell responses spanning HTI sequence (IN) at w8 whereas no changes were observed in responses against the rest of the HIV-1 proteome (OUT). In addition, the proportion of responders receiving any dose of iHIVARNA (n= 15) increased from 31% at w0 to 80% post-vaccination. This increase was not observed in patients receiving TriMix alone (n=6, from 50% to 67%). Vaccination did no impact on caHIV-DNA levels in any of the studied arms. However, caHIV-RNA expression and usVL were transiently increased in patients receiving the higher doses of iHIVARNA at w5 and 6. We did not observe differentially expressed genes in any of the groups-wise comparisons, although gene set analysis indicates slight effects on pathways such as RNA metabolism and host response to viruses.

Conclusion: This phase I exploratory dose-escalating trial showed that iHIVARNA was safe and well tolerated, was able to induce moderate HIV-specific immune responses and transiently increased caHIV-RNA expression. These data support further exploration of iHIVARNA in the ongoing phase II study.

312 HIV ANTIBODY GLYCOFORMS MODULATE IMMUNE COMPLEX-DRIVEN INNATE AND ADAPTIVE IMMUNITY

Giuseppe Lofano[1], Wen-Han Yu[1], Margaret Ackerman[2], Todd J. Suscovich[1], Galit Alter[1]

[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Dartmouth College, Hanover, NH, USA

Background: HIV broadly neutralizing antibodies (bNAbs) confer protection following passive immunization, but the immunological mechanisms that drive their development in a fraction of HIV infected individuals are poorly understood. Structural features of bNAbs indicate that they originate from extensive B cell germinal center reactions, which rely on immune complex (IC)-mediated delivery of antigen to follicular dendritic cells (FDCs). However, little is known about the role of immune complexes in tuning the evolution of bNAbs.

Methods: Here we characterized the HIV-specific antibody responses in a group of Neutralizers that neutralized 80% of 11 tier 2 viruses, and a matched group of Non-Neutralizers that exhibited no detectable neutralizing activity. Firstly, we applied a system serology Fc-profiling platform to determine Fc structural features that are associated with the development of Fab neutralizing activity. Then, we developed a new series of Fc-engineered immune complexes-based adjuvants and characterized their mechanisms of action in mouse vaccination studies.

Results: We show that HIV-specific antibodies from Neutralizers mediate better antigen phagocytosis and complement deposition, bind better Fc-receptors and complement proteins, and are associated with increased functionality in mouse vaccination studies (Fig.1A). We than hypothesized that such functional differences were determined by structural modifications of the HIV-specific antibodies. Biophysical characterization of the antibody Fc of HIV-specific antibodies revealed that sialylated IgG1 antibodies were associated with the development of bNAbs (Fig.1B). Given the importance of antigen-antibody immune complexes in driving antibody Fab maturation, we rationally designed immune complex-based vaccines with IgG1 antibody glycoforms to use in mouse vaccination studies. Finally we show that sialylated IgG1 antibodies, in immune complexes with HIV gp120, work as adjuvants to promote enhanced antigen uptake from innate immune cells, expanded germinal centers and increase HIV-specific humoral responses as compared to non-sialylated IgG1 antibodies (Fig.1C-D).

Conclusion: This work supports a potentially critical adjuvanting role for specific glycosylated IC forms in promoting more effective B cell selection that may contribute to the rational design of neutralizing antibody-inducing vaccines against HIV.

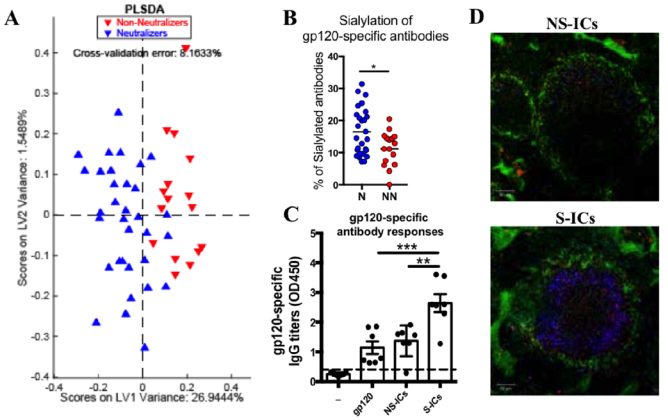


Fig.1: Sialylated antibody-immune complexes promote innate and adaptive immunity. **(A)** PLSDA analysis of the top best biophysical features that contribute to bNAbs development among 50 features measured by the systems serology approach in HIV infected individuals. **(B)** Univariate analysis of the percentages of sialylated gp120-specific antibodies detected in sera of Neutralizers (N) or Non-Neutralizers (NN). **(C)** Balb/c mice (n=6–8) were immunized twice, 3 weeks apart, with alum-adjuvanted gp120, or NonSialylated-ICs (NS-ICs) or Sialyltated-ICs (S-ICs) and 10 days later we measured the titers of gp120-specific IgG antibodies **(C)** by ELISA. **(D)** Spleen sections from mice immunized with NN-ICs or S-ICs 3 hours post vaccination were stained for confocal microscopy analysis to detect Macrophages (anti-CD169, green), germinal center areas (anti-GL7, red) and the fluorescently labeled-gp120 (blue). *p<0.05, **p<0.01, ***p<0.001.

313 RIFAXIMIN USE DOES NOT ALTER SCD14 LEVELS IN HIV-INFECTED PERSONS ON SUPPRESSIVE ART

Anuradha Ganesan[1], Deborah McMahon[2], Netanya S. Utay[3], Jennifer Bell[4], Heather Burris[1], Timothy Whitman[5], Jing Qin[6], Jeffrey Laczek[5], Patrick Young[5], Brian K. Agan[1], Sheila Kumar[7], Dean Follmann[6], Stephen Wank[7], Frank Maldarelli[8]
[1]Uniformed Services University of the Health Sciences, Bethesda, MD, USA, [2]University of Pittsburgh, Pittsburgh, PA, USA, [3]University of Texas at Houston, Houston, TX, USA, [4]Leidos Biomedical Research, Inc, Frederick, MD, USA, [5]Walter Reed National Military Medical Center, Bethesda, MD, USA, [6]NIAID, Bethesda, MD, USA, [7]NIH, Bethesda, MD, USA, [8]NCI, Rockville, MD, USA

Background: Immune activation (IA) plays a central role in the pathogenesis of HIV infection. A potential driver of IA is the translocation of gut microbial products. Elevated levels of soluble CD14 (sCD14) are associated with all-cause mortality in HIV-infected persons. One source of elevated sCD14 is lipopolysaccharide (LPS) exposure from gut bacteria. Rifaximin (RFX) is an oral, non-absorbable systemic antibiotic that reduces serum LPS levels. Previously, RFX had a modest effect on cellular IA markers in HIV infected immune non-responders (Tenorio, 2015). We sought to study the effects of RFX on sCD14 levels in chronically suppressed HIV-infected persons.
Methods: In this double blind, multicenter, randomized crossover clinical trial HIV infected persons on suppressive ART (< 50 cps/mL, ≥3 years), were randomized to receive either RFX 550 mg or placebo twice daily for 28 days. After a 4-6 week wash-out participants switched treatment arms completing an additional 28 days of study treatment. The study had 95% power to detect a 0.20 pg/mL difference in sCD14 levels. CD38 and HLA-DR expression on CD4+ and CD8+ T cells was used to measure IA. To assess treatment effects, we calculated the difference in changes, for all parameters, for the participants. We tested the hypothesis that the median differences of these changes were zero using a paired Wilcoxon test.
Results: Of 42 randomized participants, 37 had evaluable results (median age 47y, 92% male, 32% African-American, median baseline CD4 count 646 cells/uL; 2 participants were non-responders). The median baseline sCD14 level was 1.45 mcg/ml (range 0.86-3.0). The median change in plasma sCD14 levels during the RFX and placebo phases of the study were 0.07 (IQR -0.10, 0.22) mcg/mL and 0.00 (-0.19, 0.15) mcg/mL respectively, with no significant change in plasma sCD14 levels (p=0.51). We found no change in the frequency of CD4+ or CD8+ cells expressing HLA-DR, CD38, or both with the use of RFX. An additional statistical test to assess drug carryover revealed no differential effect by period, (p=0.661).
Conclusion: Short term RFX in HIV infected persons taking ART with a median CD4 count >500 cells/uL did not reduce sCD14 levels or result in changes in cellular IA; reductions in IA noted previously in immune non-responders were not present in this broader cohort of HIV infected individuals. Earlier intervention or longer duration of RFX therapy may be necessary to affect IA.

314 EFFECT OF SWITCHING TO RALTEGRAVIR AND/OR ADDING LOSARTAN ON HIV IMMUNE ACTIVATION

Berta Torres[1], Alberto C. Guardo[2], Amanda Fabra[2], Lorna Leal[1], Cristina Rovira[2], Carmen Hurtado[2], Manel E. Bargalló[2], Constanza Lucero[1], Irene Fernandez[1], Flor Etcheverry[1], Jose M. Gatell[1], Montserrat Plana[2], Felipe Garcia[1]
[1]Hospital Clinic of Barcelona, Barcelona, Spain, [2]IDIBAPS, Barcelona, Spain

Background: Inflammation and immune activation markers associated with end-organ diseases like atherosclerosis are higher in treatment-suppressed HIV patients than in non-HIV population. No therapies have been developed to effectively target these mediators. A decrease of immune activation markers after raltegravir intensification and anti-inflammatory properties of the angiotensin receptor antagonist losartan have been reported. The objective of this clinical trial was to investigate the effect of switching to raltegravir and/or adding losartan on the inflammatory/immune-activation mediators in treated HIV patients
Methods: 48 chronic HIV patients successfully treated with 2 NRTI and 1 NNRTI or PI during at least 48w were randomized to: continue the same ART (n=12), switch NNRTI/PI to raltegravir (n=12), add losartan (n=12) or switch NNRTI/PI to raltegravir and add losartan (n=12) for 48w. Markers of T CD4 and CD8 lymphocytes activation (HLADR+38+) and senescence (CD28-CD57+), monocyte activation (CD14+, CD16+) and inflammation (hsCRP, TNF-alpha, D-dimer and IL-6) were determined at baseline and at w48 and compared between groups.
Results: Median age was 41 years. The median (IQR) time since diagnosis was 8 (5-11) years and patients were on successful ART for a median (IQR) 5 (3-10) years. Median (IQR) nadir, baseline CD4 count and CD4/CD8 ratio was 307 (221-390), 723 (571-927) c/mm^3 and 0,93 (0,6-1,2), respectively. Patients who switched to raltegravir showed a higher decrease in all activated [CD4+38+HLADR+ -1,3 vs -0,6 (p=0.033); CD8+38+HLADR+ -1.6 vs 1.3 (p=0.02)] and senescent [CD4+28-57+ -0.3 vs 0.26 (p=0.04); CD8+28-57+ -6.1 vs 3.8 (p=0.002)] T lymphocyte populations than those who did not change ART. CD4/CD8 ratio increased a median of 0.35 in patients in the raltegravir group vs 0.03 in patients not taking raltegravir (p=0.002). No changes were observed in patients allocated to losartan. Differences between groups in monocyte subpopulations or inflammation markers were not observed.
Conclusion: Switching a NNRT/PI containing regimen to raltegravir significantly improved immune system as measured by a decrease in activated and senescent T lymphocyte subpopulations and an increase in CD4/CD8 ratio in successfully treated HIV patients. Conversely, adding losartan did not have any impact on inflammation or T cell/monocyte activation or senescence.

315 TLR9 AGONIST ENHANCES B CELL DIFFERENTIATION AND ANTIBODY PRODUCTION IN HIV+ ADULTS

Mariane H. Schleimann[1], Line K. Vibholm[1], Maria-Louise R. Kobberø[1], Manuel Schmidt[2], Burghardt Wittig[3], Tine Damsgaard[1], Peter Ahlburg[1], Michel Hellfritzsch[1], Rikke Olesen[1], Lars Østergaard[1], Paul W. Denton[1], Martin Tolstrup[1], Ole S. Søgaard[1]
[1]Aarhus University Hospital, Aarhus, Denmark, [2]Mologen AG, Berlin, Germany, [3]Freie Universität Berlin, Berlin, Germany

Background: HIV-infected individuals greatly suffer from B cell dysfunction, partly due to increased fibrosis and destruction of lymph node architecture. As we test curative strategies for HIV it is apparent that an improvement of the immune system is a necessity. To boost immunity, we treated HIV+ individuals with the TLR9 agonist lefitolimod (MGN1703). Here we report the effects on B cell differentiation as well as total plasma IgG levels as it has been shown that TLR9 agonists stimulation of B cells lead to enhanced humoral immunity.
Methods: We performed a single-arm phase 1b/2a clinical trial, where 13 HIV+ adults on ART received lefitolimod (60 mg s.c.) twice weekly for 24 weeks (NCT02443935). We analyzed B cell differentiation status on freshly isolated PBMCs (baseline, on weeks (wk)12 and 24) and on freshly isolated mononuclear cells from lymph nodes (baseline, wk24) via flow cytometry. We also analyzed total plasma IgG and IgG subtypes using a standard clinical assay. On-drug time-points were compared to baseline using Wilcoxon signed-rank test.
Results: B cell differentiation and maturation can be identified through multiple phenotypic stages. We examined key B cell subsets and found a

substantial increase in the proportions of peripheral blood plasmablasts (wk12 p=0.033), which is the precursor of the antibody-secreting plasma cell. In the lymph nodes, we found an increase in proportions of follicular B cells (p=0.016) and the germinal center B cells (p=0.078), the main B cell subsets that reside in primary and secondary B cell follicles. Consistent with these changes toward a more differentiated B cell phenotype we found increased levels of total IgG (p=0.019) as well as subclasses IgG1 (p=0.042), IgG2 (p=0.021), and IgG3 (p=0.002), after 12 wk treatment. Of note, the IgG3 subclass is superior in its binding affinity for Fc-receptors and is known to be particularly effective in the induction of effector functions.

Conclusion: Lefitolimod markedly enhanced B cell differentiation in circulating B cells. The increase in plasmablasts is indicative of an enhanced differentiation of activated antibody-secreting plasma cells, which is supported by observed increase in IgG plasma levels. In lymph nodes the increase in follicular and germinal center B cells point towards a restoration of lymph node architecture. Overall, these data suggest improved lymph node function and humoral immune response in HIV+ individuals on ART, when treated with lefitolimod.

316 A BISPECIFIC APPROACH FOR TARGETING NEGATIVE CHECKPOINT RECEPTORS IN HIV-1 LATENCY

Debbie S. Ruelas[1], Yanyan Zheng[1], Laura Garvin-Queen[1], Fahimeh Raoufi[1], Laurence Fayadat-Dilman[1], Yuan Li[2], Julie Strizki[2], Richard Barnard[2], Steven G. Deeks[3], Mohammad Tabrizifard[1], **Daniel Gorman**[1]

[1]Merck & Co, Inc, Palo Alto, CA, USA, [2]Merck & Co, Inc, West Point, PA, USA, [3]University of California San Francisco, San Francisco, CA, USA

Background: HIV infection is associated with persistent upregulation of PD-1, LAG-3, TIGIT and perhaps other checkpoint molecules, particularly on HIV-specific T cells. We hypothesize that simultaneous engagement of multiple targets via bispecific antibodies (BsAbs) will enhance anti-HIV efficacy compared to single or combination approaches.

Methods: Two BsAbs targeting the negative checkpoint receptors PD-1 & LAG-3 and PD-1 & TIGIT, as well as the corresponding monospecific antibodies, were developed. The secretion of 10 pro-inflammatory cytokines by PBMCs from HIV-infected subjects following stimulation with gag peptides in the presence of BsAbs or monospecific antibodies was quantified. Checkpoint receptor expression by HIV-specific CD8 T cells from infected individuals was evaluated. Assays to measure the ability of BsAbs to bind receptors in cis or trans were developed. Imaging flow cytometry combined with FRET was used to compare BsAb and monospecific antibody internalization.

Results: We studied PMBCs from 26 HIV-infected individuals (18 treated and 8 untreated). As expected, HIV antigens stimulated the secretion of cytokines (IFNγ, IL-2, and TNFα); this effect was enhanced following BsAb co-treatment in a subset of individuals, with the impact more pronounced in untreated donors. About 1 in 3 of all subjects screened demonstrated increased IFNγ production in response to ex vivo BsAb treatment versus isotype control. IFNγ ex vivo responses were generally higher following BsAb-treatment as compared to monospecific antibody-treatment. As compared to total CD8 T cells, LAG-3 and TIGIT receptors were higher on PD-1-positive HIV-specific CD8 T cells from HIV-infected individuals. BsAbs demonstrated binding in both cis- and trans-orientation and were capable of internalization.

Conclusion: Previous studies in cancer and other fields have demonstrated a benefit of targeting multiple antigens simultaneously using BsAbs. Our experiments will inform the use of BsAbs versus a combination of bivalent antibodies for an immune checkpoint-targeting approach to treat HIV infection. In addition, the findings that BsAbs are capable of both cis-binding, trans-binding, and internalization are essential to understanding the therapeutic potential of BsAbs. Together this work provides a greater overall understanding of BsAb function and efficacy for immune checkpoint-targeting approaches in HIV infection.

317 HIV INFECTION OF TARGET CELLS IN PEDIATRIC TONSIL IS INHIBITED BY AN HSP90 INHIBITOR

Ria Goswami[1], Holly A. Heimsath[1], Riley J. Mangan[1], Joshua A. Eudailey[1], Guido Ferrari[2], Timothy Haystead[2], Barton F. Haynes[1], Sallie Permar[1]

[1]Duke Human Vaccine Institute, Durham, NC, USA, [2]Duke University, Durham, NC, USA

Background: HIV-1 transmission via breastfeeding, accounting for ~half of the 150,000 pediatric infections annually, often goes unrecognized for many months leading to high viral loads. Therefore, immediate cART cannot be expected to achieve rapid viral suppression in these infants, potentiating the need for an additional antiviral strategy. HIV utilizes cellular heat shock protein 90 (Hsp90) for completion of its life cycle and bystander T cell activation. Therefore, we hypothesize that targeting Hsp90 along with cART will achieve rapid virologic control and limit establishment of viral reservoir in infants. In the current study, we aimed to investigate the role of an Hsp90 inhibitor Hs10, in inhibiting replication of HIV-1 in human tonsils, representing an in vitro model of an important viral reservoir of breast milk transmission.

Methods: Mononuclear cells, isolated from tonsil tissues of children <10 years of age, were infected with GFP-expressing HIV-1. The frequency and activation of T cell subtypes infected in presence or absence of Hs10 was evaluated using flow cytometry.

Results: Tonsillar mononuclear cells were infected by HIV-NLGI (mean: 4.02±1.80%, n=3) and HIV-JRFL (mean: 0.57±0.26%, n=3).The highest frequency of infected cells was represented by the central memory populations. Yet, this population was only 4.59±2.98% of the total infected cells, indicating that different subsets of tonsillar CD4+ cells can be targeted by HIV-1. A dose-response curve for Hs10 demonstrated that 100nM concentration was most effective in inhibiting the frequency of HIV infected of tonsillar cells in vitro (mean inhibition: 65.8±15.91%, n=5), without promoting cell death (mean live cells: 88.58±11.70%, n=5). Addition of Hs10 also resulted in a reduction in early activation of CD4+ T cells (CD25+ CD4+: mean reduction: 68.3±5.4%, n=5). Interestingly, even when the compound was added 24h pi, the proportion of infected T cells was reduced by 68.4% (n=5), demonstrating that this compound can target established infections in lymphoid tissues.

Conclusion: Our study demonstrates that inhibition of Hsp90 blocks HIV infection by reducing the number of target cells blocking bystander T cell activation. This study is anticipated to provide compelling data towards the efficacy of combining Hsp90 inhibitors and cART to achieve rapid virologic control, and limit establishment of HIV reservoirs in pediatric populations, which would open the possibility of HIV remission or functional cure in HIV-infected breastfed infants.

318 ALTERED AND INCOMPLETE IMMUNE RECONSTITUTION IN HIV+ STEM CELL TRANSPLANT RECIPIENTS

Daniel D. Murray[1], John Zaunders[1], Carole Ford[2], Kersten Koelsch[1], Samuel T. Milliken[2], Orla Morrissey[3], Sharon Avery[4], Joseph Sasadeusz[5], Matthew Law[1], Anthony Kelleher[1], Sharon R. Lewin[6], David A. Cooper[1], John Moore[2], Mark Polizzotto[1]

[1]Kirby Institute, Sydney, NSW, Australia, [2]St. Vincent's Hospital, Sydney, NSW, Australia, [3]Monash University, Melbourne, VIC, Australia, [4]Alfred Hospital, Melbourne, VIC, Australia, [5]Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia, [6]University of Melbourne, Melbourne, VIC, Australia

Background: HIV+ individuals are at increased risk of developing the malignancies that require allogeneic stem cell transplants (ASCT). While there is increasing evidence of the safety of ASCT in HIV+ individuals on antiretroviral therapy (ART), there has been little evaluation of the kinetics of immune reconstitution.

Methods: We prospectively evaluated HIV and CMV viral loads, and immune reconstitution measured by CD4 and CD8 peripheral T cell counts in six HIV+ individuals on ART undergoing ASCT for haematological malignancies. T cell subsets were compared with HIV-negative ASCT controls (n=17). Four HIV ASCT subjects also consented to fine-needle biopsy (FNB) of inguinal lymph-nodes pre and up to 4 years post-ASCT, and these findings were compared to non-ASCT HIV+ (treated n=11, untreated n=10) and HIV-negative (n=10) controls. Frozen PBMC were available for two subjects and we performed additional detailed flow cytometric characterisation to determine CD4 and CD8 subsets.

Results: Characteristics for HIV-ASCT subjects can be found in Table 1. There were no significant differences in CD4 T cell counts between HIV ASCT subjects (median, IQR=367, 188 cells/μl) and controls (484, 444 cells/ μl) at time-points ~6-12 months post-ASCT. In contrast, CD8 T cells trended higher in HIV-ASCT subjects (1693, 1556 cells/ μl) vs controls (748, 922 cells/ μl; p=NS). In two subjects, both with elevated CD8 counts, further characterisation showed that one individual had elevated activated, non-gut homing, terminally differentiated CD8 T cells, while the other predominantly had activated, gut homing CD8 T cells. Comparisons of FNB T cells showed significantly lower CD4 T cells in HIV-ASCT (median, IQR = 3.1x104, 1.5x105 cells), compared to both HIV+ non-ASCT subjects, on ART (2.3x105, 1.9x105 cells) and untreated (5.9x105, 1.1x106 cells) and HIV-negative non-ASCT controls (8.9x105, 9.8 x105 cells).

Conclusion: HIV-ASCT individuals showed comparable peripheral blood recovery of CD4 T-cells, but increased numbers of CD8 T-cells post-ASCT – with detailed flow cytometry showing that the subsets that make up these elevated CD8 T cells appear to vary between subjects. The FNB data suggests that, compared with non-ASCT controls, nodal CD4 T cell recovery is impaired, even several years post-ASCT. While subject numbers are limited, the differences seen here suggest that co-infections and HIV associated factors, such as pre-existing immune impairment, may impact immune reconstitution.

Table 1. HIV-ASCT Characteristics

	HIV-ASCT (n=6)
Age (Median, Range)	50, 42-60
Gender:	
Male	5/6
Female	1/6
Underlying Malignancy:	
Acute Myeloid Leukemia	4/6
Plasmablastic Non-Hodgkins Lymphoma	1/6
Multiple Myeloma	1/6
Conditioning:	
Myeloablative (Cyclophosphamide + total body irradiation)	1/6
Reduced Intensity (Fludarabine + Cyclophosphamide)	1/6
Reduced Intensity (Fludarabine + Melphalan)	4/6
Suppressed HIV at time of transplant	6/6
HIV reactivation post-ASCT	0/6
CMV reactivation post-ASCT	2/6

319LB A4B7-BLOCKADE COMBINED WITH VRC01 MODULATES IMMUNE RESPONSES TO SHIV-AD8 INFECTION

Giulia Calenda[1], Ines Frank[1], Geraldine Arrode-Bruses[1], Amarendra Pegu[2], Wang Keyun[2], James Arthos[3], Claudia Cicala[3], Brooke Grasperge[4], James Blanchard[4], Olga Mizenina[1], Agegnehu Gettie[5], Anthony S. Fauci[3], John R. Mascola[2], **Elena Martinelli**[1]

[1]Population Council, New York, NY, USA, [2]Vaccine Research Center, NIAID, Bethesda, MD, USA, [3]NIAID, Bethesda, MD, USA, [4]Tulane National Primate Research Center, Covington, LA, USA, [5]Aaron Diamond AIDS Research Center, New York, NY, USA

Background: Passive transfer of VRC01, the first in a family of a new generation of broadly anti-HIV neutralizing antibodies (bNAb), protects macaques from SHIV acquisition. However, protection against repeated challenges rapidly decreases with decreased antibody availability. Infusion of a simianized anti-α4β7 mAb (Rh-α4β7) just prior to, and during repeated vaginal exposures to SIVmac251 protected macaques from vaginal SIV acquisition.

Methods: To determine if addition of Rh-α4β7 would increase the protective activity of VRC01, 3 groups of animals were treated with 1) VRC01-alone or 2) a combination of VRC01 + Rh-α4β7 or 3) control antibodies prior to the initiation of weekly vaginal exposures to SHIV-AD8. Inoculations with Rh-α4β7 continued every 3 weeks through the acute and early-chronic phase of infection.

Results: Rh-α4β7 did not increase the protective effect of VRC01 against SHIV-AD8 acquisition. However, VRC01-Rh-α4β7-treated animals had a viral set-point 1 Log_{10} lower, on average, than animals receiving VRC01 alone. Moreover, the inclusion of Rh-α4β7 provided complete protection of blood CD4 T cell counts. While rectal SIV-DNA loads were slightly higher in VRC01-pre-treated animals from both VRC01-groups around 4 weeks post-infection, they significantly decreased over time in Rh-α4β7-treated animals compared to the controls. No significant differences were noted in SIV DNA and RNA loads in other tissues at necropsy. Interestingly, VRC01-Rh-α4β7-treated macaques had fewer IL-17 producing cells in blood and rectal tissue during the acute phase of infection than the controls. Moreover, blood T cells from the VRC01-Rh-α4β7 group released more IFNγ in response to peptides derived from the 2nd variable loop (V2-loop) of the SHIV-AD8 envelope compared to the other 2 groups. In contrast, T cell responses to a pool of envelope consensus B peptides were decreased and there were no differences in the response to gag peptides. At necropsy (~20 weeks post-infection), VRC01-Rh-α4β7-treated macaques had significantly more IFNγ-producing T cells in the gut. Differences in T cell subsets in inguinal lymph nodes were present in both treatment groups compared to the controls.

Conclusion: The combination of VRC01 and Rh-α4β7 decreased chronic viral load and altered immune responses against SHIV-AD8. Further exploration of the effect of combining other bNAbs with Rh-α4β7 on SIV/HIV infection is warranted and may lead to novel preventive and therapeutic strategies.

320 TRANSCRIPTIONAL BLOCKS UNDERLYING HIV LATENCY DIFFER BETWEEN GUT AND BLOOD IN VIVO

Sushama Telwatte[1], Sulggi Lee[1], Ma Somsouk[1], Hiroyu Hatano[1], Christopher Baker[1], Peggy Kim[2], Tsui-Hua Chen[1], Jeffery Milush[1], Peter W. Hunt[1], Steven G. Deeks[1], Joseph K. Wong[2], Steven A. Yukl[2]

[1]University of California San Francisco, San Francisco, CA, USA, [2]San Francisco VA Medical Center, San Francisco, CA, USA

Background: The gut is a critical site for HIV replication and persistence. Tissue-specific environments likely impact the size and activity of the reservoir. We hypothesized that the mechanisms and degrees of HIV transcriptional blocks underlying HIV latency differ between the gut and blood.

Methods: We investigated the mechanisms that inhibit HIV transcription in vivo using a validated panel of RT-ddPCR assays to quantify HIV transcripts suggestive of transcriptional interference (U3-U5; "read-through"), initiation (TAR), elongation (R-U5-tRNA; "long LTR"), distal transcription (nef), completion (U3-polyA; "polyA"), and multiple splicing (tat-rev). Total RNA and DNA were extracted from matched FACS-sorted CD4+T cells from blood and rectum (n=7) and from matched PBMCs and rectal biopsies (n=9); all samples were obtained from individuals on effective ART. Levels of each transcript were quantified and expressed as absolute copies/10^6 cells (normalized to a reference gene), ratios of each transcript to total (TAR) and processive (long) transcripts, and average transcription levels per provirus (HIV RNA/DNA).

Results: Rectal biopsies showed low levels of read-through transcripts (median=23 copies/10^6 cells) and a gradient of total (679)>elongated (75)>nef (16)>polyA (11)>multiply-spliced HIV RNAs (<1) [$p<0.05$ for all comparisons], demonstrating blocks to HIV transcriptional elongation, completion and splicing. Levels of total (TAR) transcripts per CD4+T cell and per provirus were significantly lower in the rectum compared to blood (median 2.7 vs. 31.8, $p=0.016$; and 3.5 vs. 15.4, $p=0.008$; respectively), indicative of lower HIV transcription initiation in the rectum. The ratio of total to elongated transcripts in CD4+T cells was 6-fold lower in rectum than blood ($p=0.016$), suggesting less of a block to HIV transcriptional elongation in the rectum. There was also a trend toward a lower ratio of read-through/elongated transcripts in rectal CD4+T cells ($p=0.078$), suggesting less transcriptional interference.

Conclusion: The blood and gut differ in relative contributions of mechanisms governing HIV transcription/latency, with a greater block to HIV transcriptional initiation in the gut (not due to transcriptional interference) but less block to elongation. These mechanistic differences may reflect tissue-specific variation in host gene expression, viral sequences, and/or extracellular milieu and are important to consider in designing therapies that aim to eliminate latent cells in all tissue compartments.

321 PATTERN RECOGNITION RECEPTOR AGONISTS INDUCE HIV IN ART SUPPRESSED HIV+ DONOR CELLS

Jasmine Kaur, Angela Tsai, George Kukolj, Tomas Cihlar, Jeffrey Murry

Gilead Sciences, Inc, Foster City, CA, USA

Background: CD4+ T cells latently infected with HIV are difficult to eliminate due to minimal expression of HIV antigens. Reservoir clearance may require activation of latent HIV. Agonists of pattern recognition receptors (PRRs) stimulate innate immunity and can induce T cell activation. Several studies indicate that innate immunity activators can induce latent HIV in various in vitro models, but to date there has not been a systematic study of their activity in cells isolated directly from ART-suppressed HIV infected individuals.

Methods: Peripheral blood mononuclear cells (PBMCs) or CD4+ T cells were isolated from ART-suppressed HIV-infected donors and treated with a panel of agonists known to stimulate specific PRRs. Pairwise combinations of active agonists were also evaluated. Cytokine production was assessed 24 hours after treatment initiation. HIV RNA in culture supernatants was assessed by

quantitative PCR following a 4-day treatment with PRRs. Statistical significance was assessed using the Wilcoxon matched pair signed rank test.
Results: Agonists of TLR3 (Poly I:C HMW), TLR2/1 (Pam3CSK4), TLR7 (vesatolimod), TLR8 (GSI-288) and NOD2 (romurtide) induced HIV RNA expression of 3.1 (N=15, $p < 0.01$), 2.4 (N=22, $p < 0.001$), 2.2 (N=24, $p < 0.01$), 2.0 (N=26, $p \leq 0.05$), and 1.9 (N=15, $p < 0.01$) fold, respectively, relative to PBMCs treated with the vehicle control. Among the active agonists, only compounds targeting TLR2/1 were directly active in isolated CD4+ T cells (2.2-fold increase, $N = 6$, $p < 0.01$). TLR3 and TLR7 agonists had the greatest activity in combination, inducing 5.5-fold activation of HIV relative to vehicle treated control ($N = 11$, $p < 0.001$). All agonists tested, regardless of their ability to activate expression induced IL-6 at the concentrations used to assess latency reversal.
Conclusion: Agonists of multiple PRRs induced modest, but consistent activation of HIV expression in cells from ART-suppressed HIV infected individuals with TLR3 and TLR2/1 agonists being most active. Notably, these compounds were at least as effective as the TLR7 agonist vesatolimod, which can activate the reservoir in vivo in SIV-infected rhesus macaques.

322 TRANSCRIPTIONAL REPROGRAMMING IN CCR5+ MEMORY CD4+ T CELLS PROMOTES HIV-1 LATENCY

Liang Shan[1], Kai Deng[2], Adam Capoferri[3], Robert Siliciano[2]
[1]Washington University St Louis, St Louis, MO, USA, [2]Johns Hopkins University, Baltimore, MD, USA, [3]Johns Hopkins Hospital, Baltimore, MD, USA

Background: Despite extremely effective combination antiretroviral therapy (cART), HIV-1 persists in a small pool of latently infected, resting memory CD4+ T cells. Without elimination of this latent reservoir, patients cannot be cured and must receive lifelong antiretroviral treatment. Current approaches to purging the latent reservoir involve pharmacologic reactivation of HIV-1 transcription by agents that reverse viral latency. To date, no broadly applicable strategy has been developed to effectively clear latent HIV-1 in patients. Although mechanisms for repression of HIV-1 gene expression at the transcriptional and translational levels have been well characterized, it remains unclear how HIV-1 enters a state of latency in vivo.
Methods: Peripheral blood for the isolation of primary CD4+ T cells was obtained from HIV-1-infected patients. Genomic DNA was extracted from resting CD4+ T cells from each patient for deep sequencing of HIV-1 env or quantitative measurement of HIV-1 DNA. To measure frequency of latent HIV-1 in various subsets of CD4+ T cells, naive, CCR5+ and CCR5- memory CD4+ T cells (CD4RO+) were purified by FACS and then used for limiting dilution virus outgrowth assay.
Results: We performed viral outgrowth assays and deep sequencing to analyze the HIV-1 envelope (env) sequences of the replication-competent viruses from resting CD4+ T cells of cART-treated patients. A dominant presence of replication-competent CCR5-tropic virus was found in most of the patients. We hypothesized that CCR5+ resting memory CD4+ T cells that maintained CCR5 expression throughout the T cell activation and relaxation process should be the most susceptible host cells for HIV-1 latent infection.The frequency of HIV-1 DNA was 10 to 100 fold higher in CCR5+ resting memory CD4+ T cells than other memory or naïve cells. We performed viral outgrowth assay to measure frequency of latent HIV-1. 6 out of 7 patients had a higher frequency of latently infected cells in CCR5+ resting memory CD4+ T cells than in CCR5- resting memory CD4+ T cells (4.8 fold increase, 95% confidence interval 1.752 to 13).
Conclusion: In this study, using in vitro cell-based model and patient CD4+ T cells, we demonstrated that the establishment of latent infection y by R5-tropic virus occurs selectively in CCR5-expressing effector CD4+ T cells.

323 LTR METHYLATION AND RESIDUAL VIREMIA IN INDIVIDUALS ON SUPPRESSIVE ART

César N. Cortés-Rubio, Santiago Avila-Rios, Gonzalo Salgado-Montes de Oca, Margarita Matías-Florentino, Christopher E. Ormsby, Ana P. Carranco-Arenas, Gustavo Reyes-Terán
National Institute of Respiratory Diseases, Mexico City, Mexico

Background: There are contrasting results regarding the role of methylation of the HIV LTR promoter region on provirus expression in individuals on suppressive antiretroviral treatment (ART). We longitudinally studied changes in the LTR sequence and methylation status and their possible association with residual viremia in virologically suppressed persons.
Methods: Blood samples from 12 HIV infected individuals on suppressive ART were obtained in three-month intervals for 1 year. Residual plasma viral load (pVL) was assessed with a limit of detection of 1 copy/mL. A fragment of the LTR U3-R region was amplified from total CD4+ T cells in both bisulfite-treated and untreated samples and deep sequenced on a MiSeq instrument. The degree of CpG methylation was assessed as a methylation index defined as a weighed fraction of variants showing methylation in each of the 9 HXB2 canonical CpG sites.
Results: Viral LTR contained 4-11 CpG sites. Over time, we observed both loss and gain of LTR CpG sites in predominant variants as well as different numbers of transcription factor binding sites that could potentially be regulated by CpG methylation. In general, LTR methylation was common and was observed in all patients at least at one time point. Nevertheless, LTR methylation showed a dynamic behavior through time. Variation in the degree of methylation between different time points coincided with alternation in predominance of heavily methylated vs. unmethylated variants. In general, variants lacking methylated sites, showed loss of one or more CpG sites. Variants showing 8 methylated CpG sites (CpG2 site was usually mutated) were common (observed in 12/12 patients in at least one time point). We observed a negative correlation between the CpG methylation index and residual pVL in only one patient ($r=-0.9596$, $p=0.04$).
Conclusion: We show strong evidence that LTR methylation can vary significantly along time in proviruses from circulating CD4+ T cells, possibly explaining differences between previous cross-sectional studies. We also observed that the association between LTR methylation and residual pVL is weak, but can exist in some virally suppressed patients. Further studies in specific cell subpopulations and in tissues are necessary to assess the role of viral LTR methylation as a latency mechanism.

324 WITHDRAWN

325 EXOSOMAL TAT REACTIVATES LATENT HIV-1

Xiaoli Tang, Huafei Lu, Stacey Chapman, Bharat Ramratnam
Brown University, Providence, RI, USA

Background: Highly active antiretroviral therapy (HAART) can suppress but not eradicate HIV-1. Clinical grade Latency Reversal Agents (LRAs) can reactivate latent HIV-1 in vitro but have not reproducibly reduced HIV-1 burden in vivo
Methods: Here, we describe the latency reversing potency of HIV-1 Tat formulated as an exosomal preparation. The backbone of Tat was altered to include both an N-terminus membrane signal and a C-terminus nuclear localization signal. To facilitate CD4+ cellular delivery, we further modified the construct by addition of a CD4+ receptor targeting moiety (Interleukin -16 C-terminal 20 amino acid domain) fused to the N-terminus of lysosome-associated membrane protein 2 variant b (Lamp2b). The resulting construct (pExo-Tat) was engineered into the backbone of both lentivirus and adeno-associated virus allowing the generation of cell lines that permanently produced exosomes harboring Tat (Exo-Tat).
Results: Exo-Tat was 3-fold more potent than LRAs (HDACi, Disulfiram) in activating virus using cell line models of HIV-1 latency or promoter activity. We next isolated rCD4+ T lymphocytes from 14 HIV-1 infected individuals on suppressive HAART (7-20 years). Exo Tat was incubated with rCD4+ T cells and viral reactivation was assessed by quantifying cell associated HIV RNA or p24 antigen levels in fresh uninfected cells co-cultured with supernatants of Exo-Tat treated patient rCD4+T. Exo-Tat activated HIV as measured by intracellular HIV-1 RNA (14/14) and serial p24 levels in culture media (3/3). We next compared the latency reversing potency of Exo-Tat with that of LRAs panobinostat and disulfiram. While these two LRAs did not consistently reactivate latent HIV-1 from rCD4+ T cells, both synergistically enhanced the potency of Exo-Tat by up to 4-fold. Exo-Tat had no effect on rCD4+T cell apoptosis, immune activation status or cytokine expression as measured by flow cytometry and ELISA.
Conclusion: Our findings identify exosomal Tat as a new class of biologic product with potential utility in the combinatorial targeting of latent HIV-1.

326 SINGLE-CELL TRANSCRIPTOMICS TO EVALUATE HIV LATENCY ESTABLISHMENT IN CD4 T CELLS

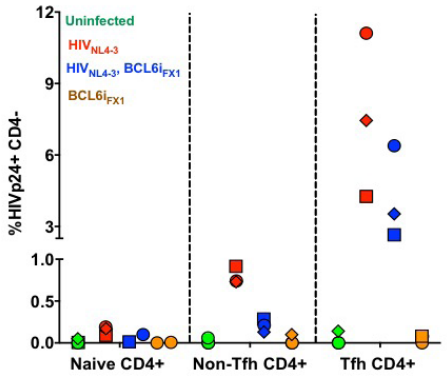
Lesley R. de Armas, Kyle Russell, Sion Williams, Robert K. Suter, Stefano Rinaldi, Li Pan, Suresh Pallikkuth, Rajendra Pahwa, Ramzi T. Younis, Savita Pahwa
University of Miami, Miami, FL, USA

Background: HIV eradication is hindered by the existence of latent HIV reservoirs in CD4 T cells. T follicular helper (Tfh) cells are a subset of CD4 T cells present in lymph nodes (LN) which harbor high frequencies of HIV-infected cells. Here, we used a primary cell model of HIV latency and the dual reporter virus, HIV DuoFluo (provided by E. Verdin, UCSF) to investigate latency establishment in CD4 and Tfh cells.
Methods: Tonsils from HIV-neg donors (n=8) were obtained as a source of LN CD4 T cells. Purified CD4 were activated with anti-CD3/CD28 beads for 3d prior to infection with HIV DuoFluo, containing GFP under HIV-LTR promoter and mK02 under EF1α promoter. Live, uninfected (U, GFP-mK02-), latent (L, GFP-mK02+), and productive (P, GFP+mK02+/-) infected cells were analyzed 3d later for surface expression of CD4, CXCR5, and PD1 and were sorted in bulk for gene expression (GE) analysis of 96 genes involved in T cell function and metabolism by Fluidigm Biomark assay. Single-cell sorting of U, L, and P cells (62 cells per group) was performed using cells from one tonsil donor for 3' whole transcriptome amplification using BD Precise platform. Limma and FDR correction were applied to determine significant differences in GE.
Results: Tfh (PD1+CXCR5+) were more permissive to latent infection compared to Non-Tfh (PD1-CXCR5-) cells by comparing ratios of L: P (Mean: 0.4 vs. 1.0, respectively, p=0.02 student's t test). Biomark analysis of Tfh cells showed differential GE of 36 genes between P and U and 8 unique genes between P and L cells (ANOVA, p<0.05). 0 genes were exclusively differentially expressed (DEGs) between L and U, though IL21 was downregulated in P and L Tfh compared to U which may affect overall function of Tfh. P had reduced expression of genes involved in transcriptional regulation and metabolism compared to U, and L had higher expression of TNF superfamily members and restriction factor, APOBEC3G compared to P. In single cell analysis, U and L overlapped with 0 DEGs while P showed 202 DEGs compared to U and 155 compared to L (121 overlapped between the 2 comparisons). FCGR2A, the proposed marker of latent cells in blood was not detectable in sorted single cells suggesting differences between blood and LN markers of HIV latency.
Conclusion: Our methods using an established HIV latency model and bulk and single cell transcriptomic analysis in LN cells shed light on biology of latency in a crucial anatomical site for HIV persistence and are valuable tools for investigating cure strategies.

327 BCL6 INHIBITION REPRESSES THF/NON-TFH HIV INFECTION AND T-CELL/MYELOID ACTIVATION

Yanhui Cai[1], Mohamed Abdel-Mohsen[1], Costin Tomescu[1], Matthew Fair[1], Livio Azzoni[1], Emmanouil Papasavvas[1], Fengtian Xue[2], Jie Sun[3], Neil D. Romberg[4], Carole Le Coz[4], Luis Montaner[1]
[1]Wistar Institute, Philadelphia, PA, USA, [2]University of Maryland, Baltimore, MD, USA, [3]Indiana University, Indianapolis, IN, USA, [4]Children's Hospital of Philadelphia, Philadelphia, PA, USA

Background: Germinal center CD4+ follicular helper T cells (Tfh) are highly susceptible to HIV infection and constitute a viral reservoir during antiretroviral therapy (ART). B cell lymphoma 6 (BCL6) is a master transcription factor for Tfh cells that if blocked can inhibit ex vivo HIV infection. BCL6-specific inhibition also reduces the frequency of lymphoid Tfh cells, germinal center formation, and pulmonary inflammatory sequelae in mice. Here we tested a novel BCL6 inhibitor to assess its antiviral effect in Tfh and non-Tfh CD4+ T cells and monocyte-derived macrophages (MDM) and its ability to modulate immune activation ex vivo.
Methods: We used the inhibitor FX1 to block BCL6 activity in human CD4+ T cells, MDM and PBMC ex vivo. HIV infection was performed by spinoculation with or without FX1. HIV infection was measured by flow cytometry analysis, p24 ELISA assay and qPCR assay. HIV reactivation was assessed by stimulating PBMC from ART-suppressed individuals with phorbol-12-myristate-13-acetate plus ionomycin (PMA/IO) following by quantification of supernatant p24 via ultrasensitive p24 assay. Intracellular cytokine production was analyzed by flow cytometry after LPS stimulation for TLR4-mediated immune activation, and after GS9620 stimulation for TLR7-mediated immune activation. Statistical analysis was performed using Wilcoxon test.
Results: In CD4+ T cells, FX1 treatment resulted in lower expression of HIV receptors (CD4, CXCR4 and CCR5, n=6, p<0.05) and down-regulation activation markers (HLA-DR, n=9, p<0.01). In PBMC, FX1 treatment reduced monocyte cytokine production in response to LPS (TNF-a, n=8, p<0.01; IL6, n=8, p<0.05), as well as pDC responses to GS9620 by lower TNF-a expression (n=7, p<0.05). FX1 treatment reduced ex vivo HIV infection of CD4+ T cells (n=6, p<0.05), tonsillar Tfh (n=3) / non-Tfh CD4+ T cells (n=5), and MDM (n=4), as well as multi-spliced HIV RNA production (n=6, p<0.05). As expected, FX1 treatment repressed HIV reactivation by PMA/IO (n=2), as evidenced by lower p24 production.
Conclusion: Our data indicate that BCL6 inhibition may reduce HIV replication beyond ART by: 1) limiting TLR-4- and TLR-7- mediated inflammatory responses, 2) inhibiting HIV replication in lymphoid CD4+ Tfh cells, and 3) restricting de novo viral infection in CD4+ T cells and macrophages. Our data suggest that BCL6-specific inhibition should be explored in vivo as a foundation for a reduction in HIV persistence in ART-suppressed subjects.



328 IDENTIFICATION OF SMALL MOLECULES THAT INHIBIT REACTIVATION OF LATENT HIV-1

Benni S. Vargas, Feng Han, Nicholas S. Giacobbi, Phalguni Gupta, Nicolas Sluis-Cremer
University of Pittsburgh, Pittsburgh, PA, USA

Background: A major barrier to curing HIV-1 infection is the persistence of a quiescent but replication-competent latent viral reservoir in resting CD4+ T cells. Theoretically, if one could manipulate the epigenetic state of the HIV-1 provirus, or interfere with the epigenetic control mechanisms involved in viral transcriptional activation, one could silence the latent proviruses for an extended time-period, or possibly for a lifetime, thus enabling a functional cure. In this regard, the primary goal of this study was to identify small molecules that can effectively block the reactivation of latent HIV-1, independent of the stimulus used to reverse latency.

Methods: We screened a unique collection of 418 kinase inhibitors (Selleckchem) that target a wide range of cellular signaling pathways using the 24ST1NLESG cell line of HIV-1 latency. The screen was carried out with the kinase inhibitors alone (2μM), or in combination with 3 latency reversing agents: 1μM prostratin, 10nM panobinostat or 1μM JQ-1. Follow-up studies included screening the kinase library for cellular toxicity and detailed dose-response analyses.

Results: We identified 21 kinase inhibitors, mostly targeted toward PKC, MEK or ERK, that blocked the activity of prostratin only. Twenty-three kinase inhibitors, targeting mTOR, PI3K or GSK-3, inhibited panobinostat activity only. We identified 4 inhibitors which blocked the activity of JQ-1 only. We found an additional 30 compounds that inhibited the activity of all 3 latency reversing agents. Of these, Danusertib, an Aurora kinase inhibitor; and PF-3758309, a PAK4 inhibitor, were found to be the most potent. The concentration of Danusertib required to inhibit 50% (i.e., IC50) of HIV-1 latency reversal in the 24ST1NLESG cell line by prostratin, panobinostat, JQ-1 and TNF-α was determined to be 40±16, 110±43, 147±21 and 192±23 nM, respectively. The concentration of Danusertib that resulted in 50% cytotoxicity (i.e., CC50) was 29.7±3.4 μM (therapeutic index > 150). The IC50 values determined for PF-3758309 for inhibition of prostratin, panobinostat, JQ-1 and TNF-α activity were 0.07±0.04, 0.4±0.03, 1.2±0.3 and 0.8±0.09 nM, respectively. The CC50 for PF-3758309 was 4.3±1.2 μM (therapeutic index > 3,300). Ongoing studies are evaluating the activity of the inhibitors in cells from HIV-infected individuals.

Conclusion: We have identified 2 kinase inhibitors, Danusertib and PF-3758309, which potently block the reactivation of latent HIV-1, independent of the stimulus used to reverse latency.

329 CONTRIBUTION OF LNCRNAS IN ESTABLISHMENT OF HIV LATENCY IN CENTRAL MEMORY CD4 T CELLS

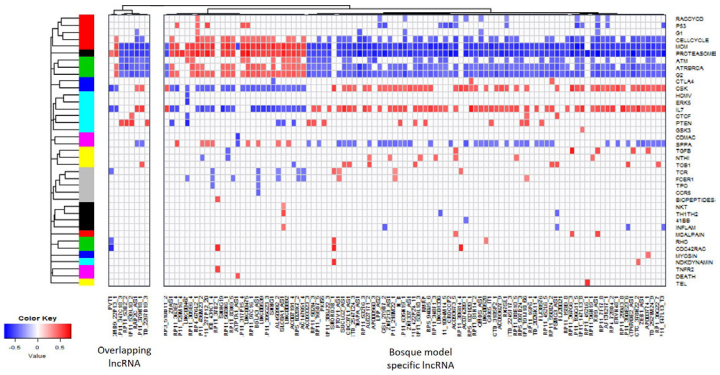
Wim Trypsteen[1], Cory White[2], Alberto Bosque[3], Pieter Mestdagh[1], Steve Lefever[1], Celsa A. Spina[4], Linos Vandekerckhove[1], Nadejda Beliakova-Bethell[4]
[1]Ghent University, Ghent, Belgium, [2]University of Southampton, Southampton, UK, [3]The George Washington University, Washington, DC, USA, [4]University of California San Diego, La Jolla, CA, USA

Background: HIV cure research has been hampered by the existence of a latent viral reservoir that persists in infected individuals receiving antiretroviral therapy. To date, most of the cure research has focused on protein-coding genes but recently the interest in the study of long non-coding RNA (lncRNA) has risen, as these molecules could provide insight in new therapeutic strategies and further complete insight in the HIV life cycle.

Methods: Transcriptome profiling was performed (total RNA-Seq) in two primary HIV latency models of central memory CD4 T cells (TCM) to investigate changes in lncRNA expression. Subsequently, differentially expressed mRNAs and lncRNAs were identified in both models and a guilt-by-association analysis was implemented to infer biological roles for the lncRNAs in HIV latency.

Results: In the primary HIV latency models, we respectively identified 826 & 471 mRNAs (87.8% & 76.2%) and 115 & 147 lncRNAs (12.2% & 23.8%) that were significantly differentially expressed (FDR<0.05) between uninfected and latently infected TCM cells. Between models, 10 lncRNAs were overlapping (oa. NEAT1 and PVT1) and many of these lncRNAs were associated with pathways involved in cell cycle regulation and pathways with a link to HIV latency: IL-7, PTEN, CSK and CCR5. In addition, a cluster of 17 lncRNAs was associated with the p53 pathway and corroborate earlier findings in this TCM model that illustrated p53-dependent latency establishment. One of these upregulated p53-linked lncRNAs, 7SLRNA, has a characterized inhibitory role in the p53 pathway and would suit as a possible new therapeutic target.

Conclusion: Altogether, this study demonstrates that several lncRNAs play a role in HIV latency and can be linked to biological pathways with importance in HIV latency establishment and maintenance. Some of these lncRNAs, i.e. NEAT1, PVT1 or 7SLRNA, represent possible targets for reversing HIV latency and contribute to a HIV cure.



330 TRANSLATION EFFICIENCY LIMITS HIV-1 LATENCY REVERSAL

Phillip Tomezsko[1], Daniel R. Kuritzkes[2], Silvi Rouskin[3], Athe Tsibris[2]
[1]Harvard University, Cambridge, MA, USA, [2]Brigham and Women's Hospital, Boston, MA, USA, [3]MIT, Cambridge, MA, USA

Background: The synthesis of virus proteins is an absolute requirement for any strategy that leverages humoral or cell-mediated immunity to eradicate HIV. The purpose of this study was to determine if the HIV-1 RNA produced after latency reversal leads to efficiently translated mRNA.

Methods: To comprehensively assess LRA-induced HIV-1 translation across the genome, we performed parallel mRNA-seq and ribosome profiling in the ACH-2 and J89 cell lines. We assessed HIV-1 transcription and translation after a 24-hour incubation with PMA/ionomycin (PMAi) or the histone deacetylase inhibitor romidepsin (RMD), relative to an untreated control condition. We developed an analysis pipeline that used Salmon and DESeq2 to quantify cellular and viral transcripts. Transcription and translation were reported in the unit transcripts per million (TPM), a unit of measure that normalizes by gene length and sequence depth. Translational efficiency (TE) was defined as the ratio of ribosome footprint to mRNA TPM for a given HIV-1 gene.

Results: Treatment with PMAi and RMD increased virus transcription above basal levels. Averaged across all HIV-1 genes in replicate experiments, approximately 46- and 40-fold more HIV-1 mRNA TPM were observed in PMAi- or RMD-treated ACH-2, respectively, and 238- and 242-fold more HIV-1 mRNA TPM in PMAi- or RMD-treated J89, respectively, relative to untreated cells. For translation, HIV-1 ribosome footprint TPM increased 65- and 11-fold with PMAi and RMD treatment in ACH-2 and 271- and 116-fold in J89, respectively. Using HIV-1 gag, tat, and env as representative examples of unspliced, singly spliced, and multiply spliced mRNA, the TE in PMA/iono-treated ACH-2 was 1.36, 4.83, and 0.2, respectively, whereas TE after RMD was 0.15, 1.21, and 0.04. In PMA/iono-treated J89 TE was 1.3, 22.6, and 0.9, respectively; TE after RMD was 0.8, 4.8, and 0.3. The TE ratios (PMA/iono:RMD) for gag, tat, and env were 9.4, 4.0, and 4.9 in ACH-2 and 1.8, 4.7, and 2.6 in J89.

Conclusion: In both ACH-2 and J89 cells, comparable proportions of HIV-1 mRNA were produced with PMAi or RMD treatment but the translation efficiency was lower with RMD. These data support the premise that a post-transcriptional block may limit the latency reversal potential of HDACi. Evaluation of candidate LRA compounds/combinations should include a rigorous assessment of HIV-1 translation.

331 LRA TREATMENT ALTERS ANTIGEN PROCESSING AND PEPTIDE PRESENTATION IN CD4 T CELLS

Julie Boucau, Alvaro Sanchez Bernabeu, Sylvie Le Gall
Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

Background: HIV persists as a latent infection in memory CD4 T cells. Current approaches for eradication rely on a shock and kill strategy where pharmaceutical agents reactivate the latent reservoir leading to cytopathic

effects or immune clearance. Immune recognition requires the presentation of HIV peptides by MHC at the cell surface following LRA-induced HIV protein expression and processing. Some of the LRA that showed promising in vitro activity but limited efficacy in clinical trials such as HDAC inhibitors and PKC agonists have not been evaluated for their effects on HIV antigen processing and presentation by MHC.

Methods: We assessed the hydrolytic activities of cytosolic peptidases in live primary CD4 T cells treated with HDACi or PKCa using a fluorometric assay. The effects on antigen processing were studied by an in vitro degradation experiment of synthetic HIV peptides in cytosolic extracts of mock- or LRA-treated CD4 T cells. Finally, we analyzed the effects of LRA treatment of PBMCs on the MHC-peptidome by direct acid elution from the cell surface and mass spectrometry analysis.

Results: Treatment with HDACi significantly decreased the hydrolytic activities of the proteasome and cytosolic aminopeptidases in primary CD4 T cells by up to 0.8-fold, whereas treatment with PKCa increased these activities by up to 4.9-fold. Consequently, the degradation of HIV synthetic peptides in cytosolic extracts from LRA-treated primary CD4 T cells yielded altered degradation patterns with 4-8 sites significantly changed in a 35-mer and 2-4 in a 24-mer depending on the LRA. Additionally, there were changes in the generation of known epitopes as well as other potential HLA-binding peptides. Treatment with LRA partly changed the MHC-peptidome of PBMCs, showing common peptides as well as different numbers and location of peptides derived from some common source proteins.

Conclusion: The observed changes in the hydrolytic activities of cytosolic peptidases in primary CD4 T cells upon LRA-treatment result in altered peptide degradation and a modified MHC-peptidome. The effects are both drug- and sequence-dependent. These results suggest that productively infected and LRA-reactivated CD4 T cells might present different HIV epitopes to the immune system, thus requiring different CD8 T cells responses for effective clearance of reservoirs.

332 SPONTANEOUS REACTIVATION OF LATENT HIV-1 PROMOTERS IS LINKED TO THE CELL CYCLE

Yik Lim Kok[1], Stefan Schmutz[2], Anne Inderbitzin[1], Kathrin Neumann[1], Audrey Kelley[1], Lisa Jörimann[1], Mohaned Shilaih[1], Valentina Vongrad[1], Roger Kouyos[1], Huldrych F. Günthard[1], Christian Berens[3], Karin Metzner[1]
[1]University Hospital Zurich, Zurich, Switzerland, [2]University of Zurich, Zurich, Switzerland, [3]Friedrich Loeffler Institute, Jena, Germany

Background: Long-lived latently HIV-1-infected cells represent a major barrier to eradication of the virus. Studies examining these cells are hindered by their low frequencies in HIV-1-infected individuals. We, therefore, developed a dual-fluorescence HIV-1-based vector containing a pair of genetic insulators flanking a constitutive fluorescent reporter gene cassette to study HIV-1 latency.

Methods: SUP-T1 cells were transduced with our VSV-G-pseudotyped genetic insulators-containing vector. The protective effects of the genetic insulators were demonstrated through long-term (up to 394 days) stable fluorescence profiles in cell populations representing both active and latent HIV-1 infections. The capability of our genetic insulators-containing vector to reproduce HIV-1 integration site patterns was confirmed by the analysis of various features in 1,941 vector integration sites derived from two independent transductions. With our verified HIV-1 infection model, monoclonal cells representing latent infections were sorted and the reactivation potentials of latent HIV-1 promoters at various integration sites were examined. Spontaneous reactivation of HIV-1 promoters in these cells were observed and factors contributing to this phenomenon were investigated by means of transcriptomic and cell cycle analyses.

Results: The reactivation potentials of latent HIV-1 promoters are influenced by both vector integration sites and integrity of the vector genomes. In latent cell clones exhibiting a small subpopulation of cells with spontaneously reactivated HIV-1 promoters, higher expression levels of genes involved in cell cycle progression are observed in these cell subpopulations compared to the majority of cells with HIV-1 promoters that remained latent. Consistently, larger fractions of spontaneously reactivated cells are in the S and G2 phases of the cell cycle. Furthermore, genistein and nocodazole treatment of these cell clones, which halt cell cycling in the G2 phase, resulted in a 1.4–2.9-fold increase in spontaneous reactivation.

Conclusion: Our stable HIV-1 infection and latency model reveals that the spontaneous reactivation of latent HIV-1 promoters is linked to the cell cycle.

333 CYTOSINE METHYLATION OF THE HIV LTR WHEN STARTING ART IN ACUTE VS CHRONIC INFECTION

Sarah LaMere[1], Sara Gianella[1], Antoine Chaillon[1], Christina Huynh[1], Susan J. Little[2], Davey M. Smith[2]
[1]University of California San Diego, La Jolla, CA, USA, [2]University of California San Diego, San Diego, CA, USA

Background: Targeting epigenetic mechanisms of HIV latency could be important for eradication. Cytosine methylation of mammalian promoters is one mechanism that represses transcription, and previous studies showed that it accumulates in a CpG island of the 5′ LTR in HIV latency models. Studies from clinical samples are rare and have produced conflicting results.

Methods: We compared the % cytosine methylation in 13 HIV-infected persons: 6 who started ART during early HIV infection within 5 months from the estimated date of infection and were sampled within 2 years, and 7 from a cohort who began ART during chronic infection. Both cohorts were composed of caucasian MSM men with ages ranging from 21-50Y, all with undetectable viral loads. DNA from PBMCs was extracted and bisulfite converted, and the proximal LTR was amplified and sequenced. The entire LTR from unconverted DNA was also sequenced and subjected to base composition analysis (BCA). BCA was also performed on sequences from the LANL database from acute (Fieberg stage 2) and chronic (Fieberg stage 5-6) infection. One-tailed Mann-Whitney p-values were used for all statistical tests.

Results: The % methylated non-CpG cytosines exceeded the % methylated CpG for most (10/13) individuals. Most non-CpG cytosines existed in CTG motifs. There was a significantly higher % CpG methylation in individuals treated early compared to those treated during chronic infection ($p=0.036$). There was no difference in non-CpG cytosine methylation between the two groups ($p=0.38$). Base composition analysis showed that the chronic group had a higher observed to expected ratio (O/E) of CpG residues in the LTR than the acute group ($p=0.067$), while the O/E ratio of CTG trinucleotides was not different ($p=0.42$). Sequence analysis of the LTR from acute vs chronically infected untreated individuals from the LANL database yielded similar results, with the chronic group having a higher O/E of CpG than the acute group ($p=0.0073$).

Conclusion: CpG % methylation was lower in the chronic group, and this could be due to an increased CpG frequency in the LTR of chronically infected individuals. Non-CpG methylation was recently reported in mammalian genes, but this is the first report of its presence in HIV provirus. In this context it is seen most often in CTG trinucleotides, which exhibit no difference between acute and chronic groups. Non-CpG methylation is a novel and potentially important mechanism in the brain and should be explored further in latent reservoir tissues.

334 IMPACT OF TREATMENT INTERRUPTION ON HIV RESERVOIRS AND IMMUNOLOGIC PARAMETERS

Katherine Clarridge[1], Jana Blazkova[1], Kevin Einkauf[2], Marissa Hand[1], Mary Petrone[1], Eric Refsland[1], Jesse Justement[1], Victoria Shi[1], Erin Huiting[1], Catherine Seamon[1], Susan Moir[1], Michael Sneller[1], Mathias Lichterfeld[2], Tae-Wook Chun[1]
[1]NIAID, Bethesda, MD, USA, [2]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

Background: Suppression of human immunodeficiency virus (HIV) and improvements in health outcomes have been achieved in infected individuals receiving antiretroviral therapy (ART). Nonetheless, the vast majority will experience plasma viral rebound upon cessation of therapy, underscoring the need for developing additional therapeutic strategies that allow durable virologic remission following the interruption of ART. Analytical treatment interruption (ATI) is an essential component of future clinical trial design to determine the efficacy of immune-based therapies in suppressing and/or eradicating HIV. Here, we investigated the effect of short-term ATI on the HIV reservoir and immunologic parameters in HIV-infected individuals.

Methods: In depth immunologic and virologic analyses were conducted using clinical specimens obtained from ten HIV-infected individuals prior to ART discontinuation, during ATI, and following reinitiation of ART. The effect of ATI on the HIV reservoir was determined by measuring the level of HIV proviral DNA, cell-associated HIV RNA, and replication-competent HIV in CD4+ T cells. Characterization of intact and defective near full-length HIV proviral DNA was performed using single-genome, next-generation sequencing. Examination of immunologic parameters included longitudinal analyses of CD4+ and CD8+ T cells as well as cytokine and inflammation markers in plasma. Expression of activation and exhaustion markers was analyzed using flow cytometry.

Results: The median duration of the ATI phase was 57 days. All study participants experienced plasma viral rebound and resumed ART. HIV burden increased significantly in the CD4+ T cells during plasma viral rebound. However, the size of the HIV reservoirs, including the frequency of CD4+ T cells carrying replication-competent virus, returned to pre-ATI levels 6 to12 months after the study subjects resumed ART. Of note, the proportions of near full-length, genome-intact, and structurally defective HIV proviral DNA sequences were similar prior to ATI and following reinitiation of ART. Furthermore, no significant differences in immunologic or activation and exhaustion parameters were found between pre-ATI and post-ATI time points.
Conclusion: Our data indicate that short-term ATI is not associated with permanent expansion of the persistent HIV reservoirs nor irreversible immune system abnormalities. These findings support the inclusion of ATI in future clinical trials when evaluating strategies for achieving ART-free remission.

335 SHORT-TERM ART INTERRUPTION HAS LITTLE EFFECT ON LEVELS OF INTEGRATED PROVIRAL DNA

Zachary Strongin[1], Radwa Sharaf[1], Jake VanBelzen[2], Jeffrey Jacobson[3], Elizabeth Connick[4], Paul Volberding[5], Daniel Skiest[6], Rajesh T. Gandhi[7], Daniel R. Kuritzkes[1], Una O'Doherty[2], Jonathan Z. Li[1]
[1]Brigham and Women's Hospital, Boston, MA, USA, [2]University of Pennsylvania, Philadelphia, PA, USA, [3]Temple University, Philadelphia, PA, USA, [4]University of Arizona, Tucson, AZ, USA, [5]University of California San Francisco, San Francisco, CA, USA, [6]Baystate Health, Springfield, MA, USA, [7]Massachusetts General Hospital, Boston, MA, USA

Background: HIV analytic treatment interruption (ATI) represents the ultimate test to assess strategies aimed at achieving sustained ART-free remission, but questions remain about the effects of ATI on the viral reservoir. We validated a size-selection-based assay for quantifying integrated proviral HIV DNA as a measure of HIV reservoir size and assessed the impact of ATI on reservoir size after ART resumption.
Methods: Cryopreserved PBMCs were obtained for 12 participants from previously completed ACTG ATI trials with available samples pre-ATI (T1) and ≥24 weeks after ART resumption (T3). Four participants also had samples available during the ATI (T2). Genomic DNA was separated from episomal DNA by size-selection using the BluePippin pulsed-field gel electrophoresis system and proviral DNA levels quantified by qPCR. Assay validation was first performed by spiking non-integrated HIV DNA into genomic DNA extracted from HIV-uninfected individuals to confirm successful elimination of the episomal HIV fragments. In addition, HIV-infected cell lines and participant samples were used to compare results to the standard Alu-*gag* assay.
Results: The size-selection-based proviral DNA assay eliminated 99% of non-integrated HIV DNA species and correlated strongly with the established Alu-*gag* assay (Spearman r=0.94, P=0.02). The median ATI duration was 12 weeks (range 6-67 weeks). For the majority of individuals, integrated DNA levels increased during ATI (median +94 HIV DNA copies/10^6 PBMCs) and subsequently declined after ≥24 weeks of ART (median -109 HIV DNA copies/10^6 PBMCs). There was no significant difference in levels of HIV integrated DNA between the pre- and post-ATI time points. The median ratio of post:pre-ATI (T3:T1) HIV DNA levels was 0.95 (Q1, Q3: 0.8, 1.6). In those with higher HIV DNA levels post-ATI, the increase in proviral DNA levels was generally small, with a median change of 10.9 HIV DNA copies/10^6 PBMCs (Q1, Q3: 6.9, 19.9 HIV DNA copies/10^6 PBMCs). There was no significant correlation between duration of ATI and the ratio of post:pre-ATI reservoir size.
Conclusion: We validated a size-selection-based proviral DNA assay that is less sample- and labor-intensive than the currently used assays. Levels of integrated HIV DNA showed minimal change after short-term ATI followed by ART resumption, suggesting that short-term ATI can be conducted without a significant impact on levels of integrated proviral DNA.

336 HIV REBOUND DRIVEN BY RARE SUPERSPREADING CD4+ T CELL LINEAGES

Jason M. Hataye[1], Joseph P. Casazza[1], David R. Ambrozak[1], Katharine Best[2], C J. Liang[3], Sam Darko[1], Amy R. Henry[1], Farida Laboune[1], Taina T. Immonen[4], Frank Maldarelli[4], Takuya Yamamoto[5], Daniel Douek[1], Brandon Keele[4], Alan S. Perelson[2], Richard A. Koup[1]
[1]NIAID, Bethesda, MD, USA, [2]Los Alamos National Laboratory, Los Alamos, NM, USA, [3]NIAID, Rockville, MD, USA, [4]Frederick National Laboratory for Cancer Research, Frederick, MD, USA, [5]National Institutes of Biomedical Innovation, Health and Nutrition, Osaka, Japan

Background: The average number of new infections generated per individual, the basic reproductive number R0, has been estimated for within-host HIV productively infected cells, but cell variation in infectious potential remains unknown. Further, R0 was derived from the most rapid phase of exponential growth, whereas little is known of how such growth arises from a founder cell. Here we define the antecedent population dynamics of viral recrudescence from ex-vivo CD4+ T cells undergoing HIV latency disruption.
Methods: Resting CD4+ T cells from 7 donors on antiretroviral therapy (ART) were stimulated and cultured in the presence of ART to quantify initial virus release by gag qRT-PCR in the absence of new infections, or in viral outgrowth cultures to determine the probability that an initial release resulted in productive infection. Single genome and deep sequencing of virus revealed clonality. The experimental results were fit to computational models to test key assumptions. Stochastic simulation allowed estimation of individual reproductive numbers for single latently infected CD4+ T cells.
Results: R0 for latently infected CD4+ T cells was estimated at 4, lower than previously found for productively infected cells. The distribution giving rise to this mean was highly skewed; ~95% of single latent cells resulted in no new infections, while ~3% spawned a 'superspreader' lineage resulting in tens to hundreds of first round infections that were primarily responsible for establishment. Superspreading was an emergent system property resulting from at least three dynamic aspects of early virus release and growth: 1. The majority of initial latently infected CD4+ T cells and their progeny died before virus was released. 2. While the average total release from one productively infected cell was 1000 HIV RNA copies, variability in cell survival and proliferation had the potential to amplify and further disperse the total release due to one founder latent cell. 3. Establishment of productive infection was most likely when the initial release resulting from one or more latent cells exceeded a critical growth threshold of 5000 HIV RNA copies.
Conclusion: Each dynamic aspect defined here is a potential viral vulnerability that could be targeted to prevent rebound. Further, the extreme variability noted among latent cell infection potentials must be accounted for to realistically predict in-vivo time to rebound following ART interruption, and thus the clinical efficacy of cure intervention candidates.

337 HIV-1 VIRAL REBOUND AND SAFETY OUTCOMES OF POSTPARTUM TREATMENT INTERRUPTION IN WOMEN

Catherine N. Le[1], Paula Britto[2], Sean Brummel[2], Risa M. Hoffman[1], Patricia M. Flynn[3], Taha E. Taha[4], Anne Coletti[5], Mary Glenn Fowler[6], Karin L. Klingman[7], James A. McIntyre[8], Jonathan Z. Li[9], Judith S. Currier[1]
[1]University of California Los Angeles, Los Angeles, CA, USA, [2]Harvard University, Cambridge, MA, USA, [3]St. Jude Children's Research Hospital, Memphis, TN, USA, [4]The Johns Hopkins University, Baltimore, MD, USA, [5]FHI 360, Durham, NC, USA, [6]Johns Hopkins Hospital, Baltimore, MD, USA, [7]DAIDS, NIAID, Bethesda, MD, USA, [8]Chris Hani Baragwanath Hospital, Johannesburg, South Africa, [9]Brigham and Women's Hospital, Boston, MA, USA

Background: Structured, temporary treatment interruptions are useful in studies investigating aspects of HIV cure by further characterizing the size and dynamics of the latent viral reservoir. However, the associated short-term safety is not well-established, particularly in women.
Methods: Participants from the 1077HS and 1077BF/FF components of the PROMISE trial were included in this analysis. Asymptomatic HIV-positive women with baseline CD4 T-cell counts ≥ 350 cells/mm^3 were randomized up to 42 days after delivery to continue or discontinue ART. All had HIV-1 RNA ≤ 400 copies/ml within 30 days of randomization. The preferred ART regimen was emtricitabine/tenofovir disoproxil fumarate plus lopinavir/ritonavir. We evaluated time-to-detectable viral load, grade 2 or higher sign/symptom and laboratory safety events, HIV/AIDS-related events, and WHO stage 2 and 3 clinical events in the first 30 weeks of treatment interruption. HIV-1 RNA was measured at 4 weeks for 1077HS and 6 weeks for 1077BF/FF, followed by 12 week intervals. Time to virologic rebound was estimated as the time of randomization to first positive HIV-1 RNA above the limit of detection. Survival probability estimates were calculated using interval censored methods. Safety events were summarized counting the highest grade for each participant.
Results: 1076 eligible women discontinued ART in the 1077HS and BF/FF trials. Median age was 28 years, CD4 count 766 cells/mm^3 (IQR 618, 957 cells/mm^3). Median duration on ART before discontinuation was 17 weeks. Median time to virologic rebound by interval censoring method was 2 weeks (95%CI 1.6, 2.46). The proportion who remained suppressed off ART at 8, 12 and 24 weeks was

11% (95% CI 4.9%, 24.9%), 7% (95% CI 5.3%, 8.4%) and 6% (95%CI 4.1%, 7.6%) respectively. Of the 993 women who had virologic rebound within 30 weeks and were off ART, 10% experienced grade 2 or higher sign/symptom or laboratory events (3% grade 3 and <1% grade 4). 12 women (1%) experienced any clinical event: 3 bacterial infections, 4 herpes zoster infections, 3 moderate weight loss, 1 fungal nail infection and 1 seborrheic dermatitis.
Conclusion: In this large cohort of young, postpartum women with high CD4 cell counts, 6% of participants remained virally suppressed at 24 weeks. Serious adverse events during the first 30 weeks off ART were rare. These data suggest that short treatment interruptions in HIV-cure related studies can be done safely in young women with nadir CD4 counts above 350 cells/mm^3.

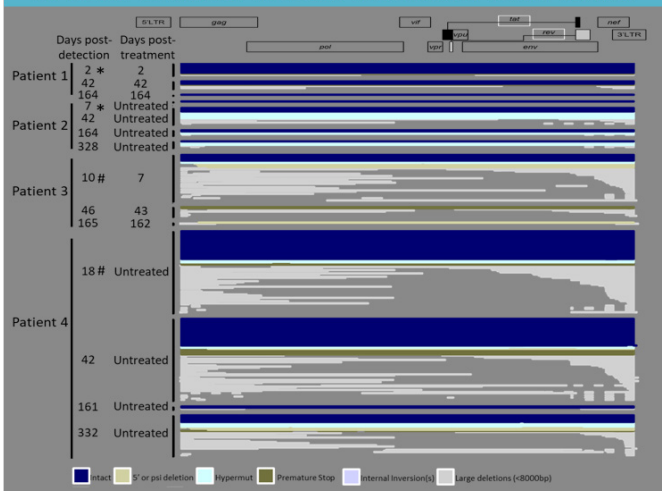
338 A5340: BRIEF ATI DOES NOT ALTER THE SIZE OR COMPOSITION OF THE LATENT HIV-1 RESERVOIR

Katharine J. Bar[1], D. B. Salantes[1], Yu Zheng[2], Felicity Mampe[1], Subul A. Beg[3], Jun Lai[3], Randall Tressler[4], Richard A. Koup[5], James A. Hoxie[1], Mohamed Abdel-Mohsen[6], Edgar T. Overton[7], Robert Siliciano[3], Janet Siliciano[3], Pablo Tebas[1]
[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Harvard University, Cambridge, MA, USA, [3]Johns Hopkins Hospital, Baltimore, MD, USA, [4]NIH, Bethesda, MD, USA, [5]Vaccine Research Center, NIAID, Bethesda, MD, USA, [6]Wistar Institute, Philadelphia, PA, USA, [7]University of Alabama at Birmingham, Birmingham, AL, USA
Background: The effect of an analytical treatment interruption (ATI) on the latent reservoir remains unknown. We evaluated the impact of transient viremia on the latent reservoir in participants who underwent an ATI in A5340, a clinical trial investigating the effect of VRC01 during ATI. We also assessed the relatedness of viruses sampled pre-ATI and at rebound.
Methods: We quantified total HIV-1 DNA and cell-associated RNA in CD4+T cells and replication competent virus by quantitative virus outgrowth assay (QVOA) in resting memory CD4+T cells from leukopharesis samples collected pre-ATI and 6 months post-ART resuppression in 9 participants. Single genome sequencing-derived gp160 *env* sequences from plasma virus obtained pre-ART, at first detectable rebound, and from pre- and post-ATI QVOA cultures were analyzed phylogenetically. Select *envs* were cloned and tested for VRC01 neutralization sensitivity.
Results: Participants median ART duration prior to ATI was 4.7 years (range 3.6 to 14.5). The median duration of viremia during ATI was 5 weeks (range 4 to 6) and participants were suppressed on ART for a median of 34 weeks (range 23 to 44) prior to post-ATI sampling. Total DNA, cell-associated RNA, and infectious units per million cells by QVOA were not statistically different pre- and post-ATI ($P>0.3$, Wilcoxon signed rank test), with median $\log_{10}$ change of 0.3 copies, 0.08 copies, and -0.05 infectious units per million cells, respectively. In each participant, pre- and post-ATI QVOA sequences fell within the pre-ART plasma phylogeny, but did not specifically align within rebound lineages. Expanded clones comprised 30% to 95% of participants' reservoirs, with similar frequencies pre- and post-ATI. Thus, sequences showed no evidence for enrichment of rebound viruses post-trial and pre-trial QVOA viruses failed to predict the identity of rebound virus. Pre-ART, rebound and QVOA Envs for each participant had similar IC50s to VRC01.
Conclusion: Quantitative and phylogenetic analyses suggest a brief ATI does not expand the latent reservoir. While clonal QVOA populations comprised a substantial fraction of replication competent peripheral latent virus, they did not rebound *in vivo* upon ATI despite similar VRC01 sensitivities. Results provide reassurance for participants of clinical trials employing ATI and highlight the challenge of accurately characterizing the full range of the replication competent latent reservoir that reactivates *in vivo*.

339 HIV RESERVOIR ESTABLISHMENT DURING HYPERACUTE CLADE C INFECTION

Guinevere Q. Lee[1], Kavidha Reddy[2], Kevin Einkauf[1], Kamini Gounder[2], Krista Dong[1], Bruce D. Walker[1], Xu G. Yu[1], Thumbi Ndungú[2], Mathias Lichterfeld[3]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Africa Health Research Institute, Mtubatuba, South Africa, [3]Brigham and Women's Hospital, Boston, MA, USA
Background: Little is known about the establishment of HIV reservoir at the earliest stages of infection. Here, we analyzed clade C HIV-1 reservoir seeding in women identified with hyperacute infections in Durban, South Africa through twice-weekly screening of high-risk individuals.
Methods: PBMC were available from two patients detected at Fiebig II: (1) peak viremia 2.6x10^6 HIV-1 RNA copies/mL, treated same day, (2) peak 7.7x10^5, remained untreated, and two patients detected at Fiebig V: (3) peak 130, on-treatment for 7 days, (4) peak 5.7x10^7, remained untreated. Longitudinal samples were available at 1, 6, and 12-month post-detection. Total PBMC DNA was extracted, diluted for single-template full-HIV-genome PCR, and Illumina deep-sequenced. "Intact" proviral genomes were defined as the absence of deleterious mutations (out-of-frame indels, premature stop codons, large deletions).
Results: Immediately post-detection at study baseline, HIV reservoir sizes in patients at Fiebig II was lower than those at Fiebig V (0.8, 2.2 versus 3.4, 31.1 genome-intact HIV per million PBMC), and relative contribution of intact genomes to the total pool of HIV DNA were higher in Fiebig II than V (82%, 100% versus 14%, 35%, Figure1). Also at baseline, no APOBEC3G/3F-hypermutated HIV DNA was detected at Fiebig II, in contrast to 5% and 4% at V. In all four patients, HIV reservoir sizes decreased over a year by ~1-10 fold. Among all 87 genome-intact proviruses detected in all patients over one year, 87-100% of genetic variations were single-base substitutions distributed evenly across the viral genome, suggesting that single-base substitution errors during reverse transcription was the predominant driver leading to early reservoir diversity. This diversity increased over time in untreated patients (median pairwise single-base differences within-sample increased from 0 to 18 and 4 to 39) but decreased in treated patients (from 3 to undetectable, and from 3 to 6 to 0). Of interest, a genome-intact provirus that had a single-base substitution that translated into Y143H, an integrase inhibitor resistance associated mutation, was detected 1-month post-detection from patient 1, whose regimen contained raltegravir since day-zero, indicating early-seeding of a drug-resistant variant.
Conclusion: Early HIV reservoirs in PBMC were small and had high levels of sequence homogeneity. Single-base substitutions were the major source of genetic diversity, and early treatment limited diversification.

Figure 1. Cross-sectional display of all HIV proviral genomes detected during early HIV reservoir seeding in four hyperacutely-infected women (*Fiebig II, #Fiebig V).



340 MOLECULAR PROFILE OF HIV-1 RESERVOIRS IN EARLY-TREATED INFANTS FROM BOTSWANA

Pilar Garcia Broncano[1], Kevin Einkauf[1], Ce Gao[1], Guinevere Q. Lee[1], Kenneth Maswabi[2], Gbolahan Ajibola[2], Sikhulile Moyo[2], Terence Mohammed[2], Thabani Ncube[2], Joseph Makhema[2], Kathleen M. Powis[3], Xu G. Yu[1], Daniel R. Kuritzkes[4], Roger L. Shapiro[5], Mathias Lichterfeld[4]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Brigham and Women's Hospital, Boston, MA, USA, [5]Harvard University, Boston, MA, USA
Background: Latently HIV-1 infected CD4 T cells represent an extremely small, yet highly durable viral reservoir in infected adults, but the molecular structure and composition of proviral reservoirs in infants with neonatal HIV-1 infection remain unclear. Immediate initiation of antiretroviral therapy (ART) in HIV-infected infants enrolled in the Early Infant Treatment Study (EIT) in Botswana provides an opportunity to evaluate the evolution of HIV-1 reservoirs in the developing neonatal immune system.

Methods: Serial PBMC samples were collected from five infants with neonatal HIV-1 infection who started ART within 72 hours after birth (n=4) or within 31 days after birth (n=1), and were followed for 84-96 weeks (w). Genomic DNA was subjected to near full-length amplification of single-genome templates of HIV-1. Resulting products were individually sequenced with Illumina MiSeq.
Results: Intact full-genome proviral sequences represented an average of 41% of all detected sequences at baseline after delivery, compared to 21% of detected sequences after 84/96w of ART. This corresponded to an average frequency of 76 and 3 intact sequences per million PBMCs at baseline and after 84/96w of treatment, respectively, and is consistent with a half-life of 18 weeks for intact proviral sequences during the first two years of life. Viral sequence defects most frequently detected included large deletions, premature stop codons, and hypermutations. Clonally-expanded proviral sequences, defined as identical viral sequences detected more than once within the same patient, were detected at baseline, 4w, 72w and 84/96w for intact sequences, and at all time points except baseline for defective sequences. At 84/96w, 20% of all intact and 21% of all defective sequences belonged to clusters of clonally-expanded sequences. Two distinct clusters of intact proviral sequences with profound phylogenetic distance, consistent with dual transmission from a likely superinfected mother, were detected in one of the study infants at baseline and 4w; notably, only one of these proviral sequence clusters remained detectable at subsequent time points.
Conclusion: ART initiated very early during neonatal HIV-1 infection leads to profound decline of intact proviral sequences in infected infants, and results in remarkably low frequencies of intact proviruses after 84/96w of treatment. Clonal expansion of viral sequences is most visible during the second year of therapy.

Distribution of intact and defective HIV sequences in early-treated HIV-1 infected infants from Botswana

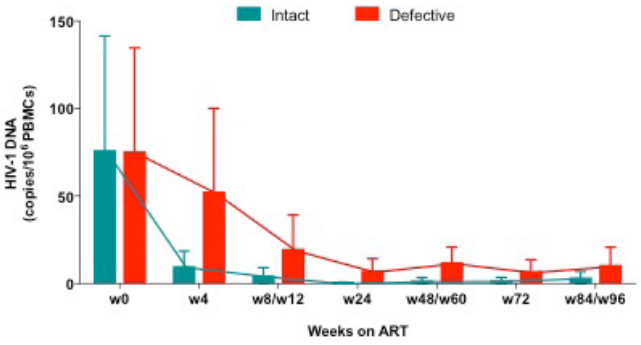


Figure: Evolution of HIV reservoir at 84-96 weeks in early-treated HIV-1 infected infants of Early Infant Treatment Study from Botswana, as average of intact and defective HIV sequences detected per million of peripheral blood mononuclear cells (PBMCs). Values are expressed as means and standard error (SEM).

341 HIV RNA PERSISTS LONG-TERM IN LYMPH NODES OF INDIVIDUALS INITIATED ON ART IN FIEBIG I

Omolara Baiyegunhi[1], Funsho Ogunshola[1], Nasreen Ismail[1], Krista Dong[2], Bruce D. Walker[2], Thumbi Ndungú[1], Zaza Ndhlovu[2]
[1]University of KwaZulu-Natal, Durban, South Africa, [2]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

Background: One of the major barriers to achieving HIV remission through combination antiretroviral therapy (cART) is the persistence of virus in reservoirs and tissue sanctuaries. B cell follicles and germinal centres (GCs) within lymph nodes (LNs) are immune privileged sites with the potential to support low level virus replication. However, the persistence of replicating virus within this tissue compartment during cART is controversial. Furthermore, the phenotype and localization of cell subsets that support virus replication in LNs in the presence of cART is unknown. Here, we used excised LNs and paired peripheral blood samples from 17 HIV infected subjects who initiated cART in Fiebig stage I from the well-characterized FRESH cohort to investigate the persistence of virus replication and to identify cell subsets that harbor residual virus during cART. Eight chronic untreated and eight HIV negative individuals were also included in the study as controls.
Methods: The phenotype and localization of GC cell subsets were defined using flow cytometry and immunohistochemistry (IHC) respectively. RNAscope; an in-situ RNA hybridization assay was used in combination with IHC to visualize the cellular localization of HIV RNA in LN sections. HIV RNA was further quantified ex-vivo in GC Tfh subsets using digital droplet PCR (ddPCR).
Results: From IHC results, there was a positive correlation between the magnitude of GCs and HIV plasma viral load (r=0.6, p=0.07) in untreated individuals. Interestingly, the excessive GC T follicular helper (GCTfh) cells' expansion observed in chronic HIV was significantly attenuated by early treatment (p=0.01). HIV Gag p24 antigen was detected almost exclusively in the GCs even after one year of cART mediated viral suppression. Specifically, follicular dendritic cells and GC Tfh cells harbored most of the detectable Gag p24. Furthermore, RNAscope for Gag-Pol multiplexed with BCL-6 confirmed GC localization of HIV RNA during early cART.
Conclusion: Taken together, our results demonstrate the persistence of low level viral replication in the lymph nodes of early treated HIV infected individuals. This study highlights the need for future interventions directed at eliminating residual virus replication in tissue sanctuaries during cART.

342 THE HIV RESERVOIR DURING EARLY ANTIRETROVIRAL THERAPY AND MARAVIROC INTENSIFICATION

Antoine Chaillon, Sara Gianella, Steven Lada, Maile Karris, Douglas D. Richman, Sanjay R. Mehta, Susan J. Little, Joel O. Wertheim, Davey M. Smith
University of California San Diego, La Jolla, CA, USA

Background: Residual viremia is common during antiretroviral therapy (ART), and could be caused by ongoing low-level virus replication or by release of viral particles from infected cells. Intensification of ART should impact ongoing viral propagation but not virion release. Here, we sought to identify HIV evolution in the context of a randomized controlled trial (RCT) of ART intensification with maraviroc (MVC) in individuals who initiated ART shortly after infection.
Methods: Eighteen acutely infected men were enrolled in a RCT, and followed for a median of 107 weeks. Participants started ART with (n=9) or without (n=9) intensification with MVC within 90 days of infection. Levels of HIV DNA and cell free RNA were quantified by droplet digital PCR. Deep sequencing of C2-V3 env, gag and pol (454-Roche) was performed on longitudinally collected plasma and PBMC samples while on ART. Sequence data were analyzed for evidence of evolution by: 1) molecular diversity analysis, 2) non-parametric test for panmixia and 3) tip-date randomization technique within Bayesian framework (Figure). To validate the proposed approach, we performed the analyses mentioned above in a group of 9 ART naïve HIV infected individuals with serially collected blood plasma samples.
Results: There was a longitudinal decay of HIV DNA after initiation of ART with no difference between MVC intensification groups (-0.08±0.01 $\log_{10}$ copies/week in MVC+ vs -0.09±0.01 $\log_{10}$ copies/week in MVC-, p=0.62). All participants had low-level residual viremia (median: 2.8 RNA copies/mL). Across participants a median of 56 (IQR:36-74), 29 (IQR:25-35) and 40 (IQR:31-54) haplotypes were generated for env, gag and pol regions, respectively. Sequence analysis and Bayesian simulations revealed no clear evidence of viral evolution during ART and no difference in viral diversity or population structure from individuals with or without MVC intensification. We confirmed in a positive control dataset the ability to reveal the temporal structure of the data using a similar framework.
Conclusion: Further efforts focusing on elucidating the mechanism(s) of viral persistence in various compartments using recent sequencing technologies are still needed and potential low-level viral replication should always be considered in cure strategies.

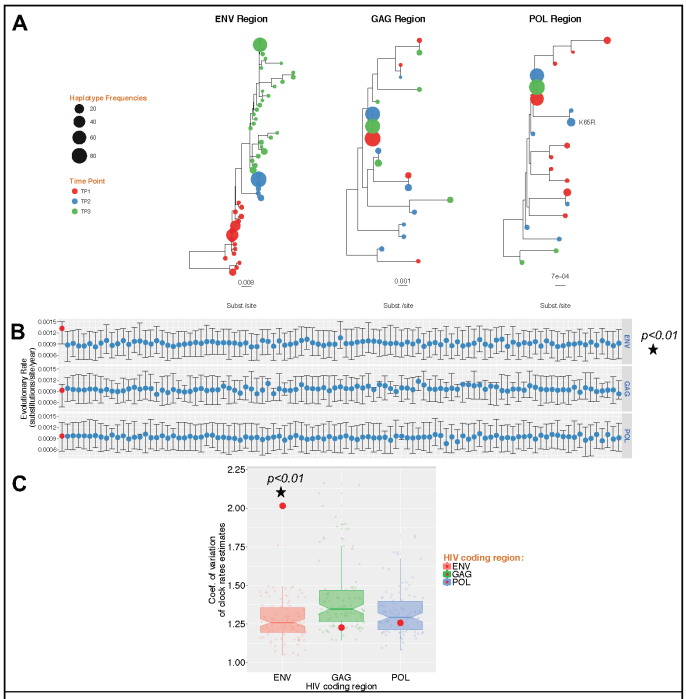


Figure. Phylogenetic and Bayesian Framework to Identify HIV Evolution. The proposed figure illustrates the C2-V3, gag and pol approximate maximum likekihood phylogeny (**Panel A**), the posterior mean and 95% HPDs of the substitution rates for HIV *env*, *gag* and *pol* regions (**Panel B**) and the coefficient of variation of the substitution rates for HIV *env*, *gag* and *pol* regions of actual dataset versus randomly permuted replicates (**Panel C**) for one participant with evidence of viral evolution within env region. **Panel B.** Posterior mean and 95% highest posterior density (HPD) intervals of the substitution rates estimated from the actual data sets (far left value red dots) and the 100 permuted replicates for HIV *env*, *gag* and *pol* regions (blue dots). **Panel C.** The *p*-value represents the number of times the coefficient of variation (determined as $\frac{Mean\ Evolutionary\ Rate}{Variance}$ where variance = *(95%HPD upper – 95%HPD lower)* of the true dataset was smaller than the coefficient of variation in the permuted replicates.

343 HIV SEROLOGY FOLLOWING TREATMENT INTERRUPTION IN VERY EARLY TREATED PEOPLE

Rapee Trichavaroj[1], Supanit Pattanachaiwit[2], Sasiwimol Ubolyam[3], Panadda Sawangsinth[4], Jintana Intasan[4], Eugène Kroon[4], Donn Colby[4], Robert J. O'Connell[1], Sandhya Vasan[1], Praphan Phanuphak[2], Nittaya Phanuphak[2], Jintanat Ananworanich[5], Mark de Souza[4], Siriwat Akapirat[1]
[1]Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, [2]Thai Red Cross AIDS Research Center, Bangkok, Thailand, [3]HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [4]SEARCH, Bangkok, Thailand, [5]Walter Reed Army Institute of Research, Silver Spring, MD, USA

Background: Antiretroviral therapy (ART) initiated during acute HIV infection (AHI) may result in HIV seronegativity. Little is known about the serologic profile following ART treatment interruption (ATI) in such individuals. Knowledge gained could inform recommendations for HIV diagnostic testing following pre- and post-exposure prophylaxis.
Methods: Participants initiating ART and virally suppressed during Fiebig (F)-I or F-III stage of AHI were enrolled in two ATI studies and resumed ART with VL > 1000 copies/ml (median duration of ATI was 4.5 weeks). HIV serostatus was determined pre- (median [range]:122.6 wks [5.0-285.1]) and post-ATI; median:5.3 wks [0.4-53.9]), using Avioq HIV Microelisa (AVQ, 2ndG IA), Genscreen HIV-1/2 (GSC, 3rdG IA), Architect HIV Ag/Ab Combo (ARC, 4thG IA), Determine HIV-1/2 (DET, RDT), SD Bioline HIV-1/2 3.0 (BIO, RDT) and Serodia HIV (SRD, RDT), all of which are widely used in Thailand: ARC 35%, DET 62%, BIO 32% and SRD 14% of laboratories (N=264) surveyed.
Results: Participants (N=8) initiating ART during F-I AHI were frequently HIV seronegative pre-ATI by AVQ (88%), followed by ARC, BIO, DET (75%), and GSC and SRD (38%). The frequency of seropositivity following ATI varied for participants (75%-88%) depending on the test (Table 1). One participant was HIV seronegative throughout the study by ARC only while another showed non-reactivity to all tests throughout the study. Eighty % of participants initiating ART during F-III AHI (N=5) were HIV seronegative pre-ATI by BIO and 40% by ARC, AVQ and DET. All participants were seropositive pre-ATI by GSC and SRD. All participants were seropositive post ATI for all tests. Pre-ATI HIV seronegative frequencies ranged from 23%-69% for kits using viral lysate (AVQ, SRD), and 23-77% for kit using Env and Gag (GSC, BIO) as AG. Increased HIV seronegative frequencies (62%) pre-ATI was observed with test kits employing HIV Env (gp41) as the detecting AG (ARC, DET). Similar HIV seropositive frequencies following ATI were detected with all tests (85%-92%).
Conclusion: HIV serology may remain negative following early ART initiation, particularly in Fiebig I, with frequencies differing by tests. However, the majority of participants who underwent short ATI became HIV seropositive on almost all tests.

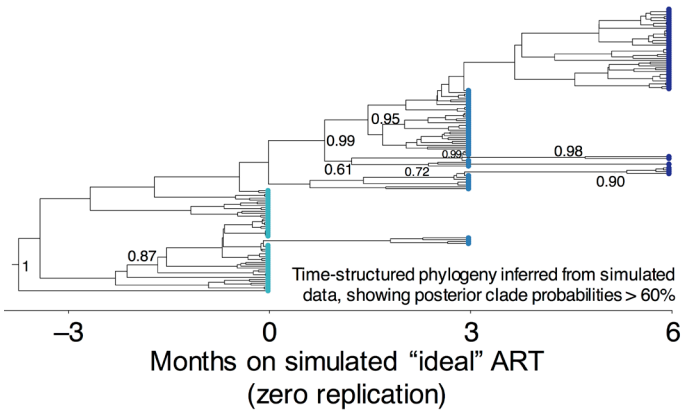
Table 1: Frequency of Seropositivity

	Fiebig I -% Reactive		Fiebig III -%Reactive	
Test	**Pre-ATI**	**Post-ATI**	**Pre-ATI**	**Post-ATI**
ARC	25	75	60	100
GSC	62	88	100	100
AVQ	12	75	60	100
DET	25	88	60	100
BIO	25	75	20	100
SRD	62	88	100	100

344 REEVALUATING SIGNALS OF VIRAL REPLICATION & EVOLUTION IN LYMPHOID TISSUE DURING ART

Daniel S. Rosenbloom[1], Alison L. Hill[2], Sarah B. Laskey[3], Robert Siliciano[3]
[1]Columbia University Medical Center, New York, NY, USA, [2]Harvard University, Cambridge, MA, USA, [3]Johns Hopkins University, Baltimore, MD, USA

Background: Mechanisms for long-term HIV persistence despite antiretroviral therapy (ART) continue to be debated. Many studies have offered evidence that ART halts self-sustaining viral replication in most patients and that long-lived resting memory CD4+ T-cells support a stable latent reservoir (LR) of integrated virus. However, Lorenzo-Redondo et al. [Nature, 2016] deep-sequenced lymph node and blood samples from three participants during the first six months of ART, finding viral genetic signals of persistent replication and evolution. We show that these signals are expected outcomes of the known multi-phasic decay of infected cells during ART and do not provide evidence of ongoing replication.
Methods: We designed a simulation of HIV infection before and after ART, including changes in viral population size, multiple infected cell types with different lifespans, and mutation/selection within and outside sequenced regions. To test the hypothesis that the observed genetic signals could arise without replication, ART was assumed to block all new infection. To estimate infected cell lifespans, we fit a multi-phase decay model to longitudinal LR measurements from early-treated individuals. Roughly 12,000 simulations were run with a range of plausible parameter values; those with realistic levels of genetic diversity and divergence were included in analyses. To reduce reliance on assumed parameter values, we repeated our analysis using actual sequence data from acute infection to seed a hypothetical LR.
Results: At zero, three, and six months following ART initiation, short-lived viral populations comprise >99%, 96%, and 76% of infected resting cells, masking the persistent reservoir. Applying the same population genetic and phylogenetic methods previously used to support claims of ongoing replication in lymphoid tissue, we found that up to 57% of simulations generated a false signal of ongoing replication in all tests. Time-structured phylogenies can also yield a misleading appearance of evolution (Figure). Analysis of acute infection data suggests that individuals with major sequence changes before treatment (CTL escape) produce a false signal of ongoing replication 92% of the time.
Conclusion: Investigation of ongoing replication during ART must wait >1 year following the start of ART; earlier analysis is unreliable. Where possible, population genetic studies of viral evolution should be conducted with reference to specific models of viral dynamics and literature on growth/decay of subpopulations.



345 MONITORING THE IMPACT OF ART MODIFICATION WITH LONGITUDINAL FDG-PET IN SIV-MODEL

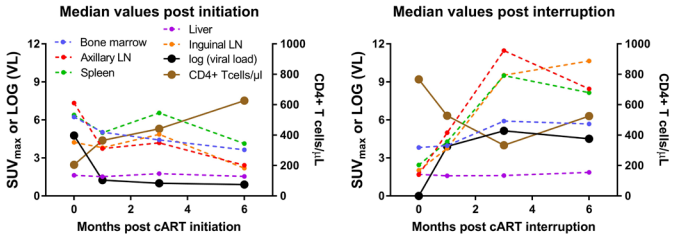
Sanhita Sinharay[1], Sharat Srinivasula[2], William T. Schreiber-Stainthorp[1], Swati Shah[1], Paula DeGrange[3], Andrew Bonvillain[3], Jing Wang[2], Lori E. Dodd[3], H. Clifford Lane[3], Dima A. Hammoud[1], Michele Di Mascio[3]
[1]NIH, Bethesda, MD, USA, [2]Leidos Biomedical Research, Inc, Frederick, MD, USA, [3]NIAID, Bethesda, MD, USA

Background: The aim of this study was to assess immune activation in various organs by longitudinally measuring changes in glucose metabolism associated with initiation and interruption of combination antiretroviral therapy (cART) in SIV-infected macaques. We also assessed the associations of various markers of disease activity with tissue metabolic activity.

Methods: Whole body 18F-Fluorodeoxyglucose (FDG) PET-imaging was obtained on seven SIV-infected macaques at various time points before and after initiation (n=5)/interruption (n=5) of cART, up to 9 months after treatment modification. SUVmax values were measured in the spleen, axillary and inguinal lymph nodes (axLNs, ingLNs), liver and bone marrow (BM). Univariate and multivariate mixed-effect linear regression models estimated the associations of FDG uptake with peripheral blood CD4 cell counts, plasma viral load (VL) and serum cytokine levels (IL-1ra, IL2, IL-8, IL-15 and MCP-1). We used the Spearman rank statistic to correlate BM SUVmax to SUVmax values of the rest of the organs, using the bootstrap to account for repeated measures.

Results: FDG uptake showed concomitant changes with peripheral markers of disease after initiation/interruption (Fig. 1). In the univariate analyses, except for the liver, a significant inverse association of FDG uptake in each organ was found with CD4 counts ($P<0.05$) and direct association with plasma VL ($P\leq0.001$). In the multivariate analyses, only plasma VL remained statistically significantly associated with the FDG-uptake in the lymphoid organs ($P<0.01$ for axLNs, ingLNs and spleen) and the BM ($P<0.05$). Spearman rank correlations between BM SUVmax and SUVmax of the lymphoid organs (spleen, AxLNs and IngLNs) were significant ($P<0.001$).There were no statistically significant correlations detected between FDG uptake and serum cytokines.

Conclusion: Changes in immune activation as measured by glucose metabolism (FDG PET) following initiation/interruption of cART were observed in the spleen and clusters of lymph nodes, as previously reported by other groups. A new finding in this study however is that a similar pattern is also observed in the BM, a primary lymphoid organ. The plasma VL appears to be the primary factor affecting FDG uptake in these lymphoid organs, suggesting an inflammatory/hematopoietic reaction to peripheral viral rebound or control.



346 SPREAD OF HIV-DNA IN CD4+ T-CELL SUBSETS DEPENDS ON ART INITIATION TIMING

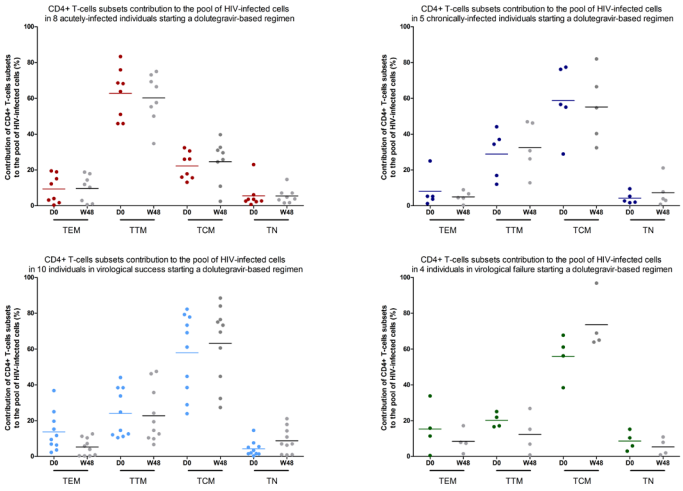
Pierre Gantner[1], Cindy Barnig[1], Marialuisa Partisani[1], Geneviève Beck-Wirth[2], Jean-Pierre Faller[3], Martin Martinot[4], Mahsa Mohseni-Zadeh[4], Christine Cheneau[1], Marie-Laure Batard[1], Patricia Fischer[1], Béatrice Uring-Lambert[1], Siamak Bahram[1], David Rey[1], Samira Fafi-Kremer[1]
[1]Hôpitaux Universitaires de Strasbourg, Strasbourg, France, [2]Groupe Hospital Regional–Mulhouse Sud Alsace, Mulhouse, France, [3]Hôpital Nord Franche Comté, Belfort, France, [4]Hôpital Louis Pasteur, Colmar, France

Background: Life-long resting CD4+ T-cells are the major long-lasting reservoir in HIV-infected individuals. The aim of our study is to analyze the dynamics of archived HIV-DNA in CD4+ T-cells subsets in individuals starting successful dolutegravir-based regimen over 48 weeks.

Methods: Participants from the prospective longitudinal DRONE study (NCT02557997) including: treatment-naïve individuals who initiated treatment with a dolutegravir-based regimen during acute (AI) or chronic (CI) infection, and treatment-experienced individuals who started a dolutegravir-based regimen while in virological success (VS) or in the aftermath of virological failure (VF), were enrolled in this substudy. Peripheral blood mononuclear cells (PBMCs) from baseline and week 48 of successful treatment were sorted in effector memory (TEM), transitional memory (TTM), central memory (TCM) and naïve (TN) CD4+ T-cells for total HIV-DNA measurements. Bayesian methods were used to estimate the posterior probability (Pr) that HIV-DNA decreased for more than 0.25 log copies/10^6 cells at week 48.

Results: Twenty-seven participants (8, 5, 10, 4 individuals in the AI, CI, VS and VF group, respectively) were included. Patients were primarily male (88%) with a median age of 38 years (range, 20-54). At baseline, the highest contributions to the HIV-infected pool of CD4+ T-cells were observed in TTM cells in the AI group (62.8%), but in TCM cells for the CI, VS and VF groups (58.8%, 57.9%, 55.8%), respectively (Figure). After one year of dolutegravir-based regimen, TTM cells for the AI group (60.2%) and TCM cells for the CI, VS and VF groups (55.2%, 63.2% and 73.6%, respectively) still represented the main HIV reservoir. In these respective cells, a HIV-DNA decline was observed after 48 weeks of treatment in the AI group (4.00 to 3.26 log copies/10^6 TTM cells, Pr>99%), in the CI group (4.07 to 3.57 log copies/10^6 TCM cells, Pr=92%) and in the VF group (4.13 to 3.84 log copies/10^6 TCM cells, Pr=59%) but not in the VS group (4.19 to 4.12 log copies/10^6 TCM cells, Pr=8%).

Conclusion: HIV-DNA was mainly confined to TTM or TCM cells, when antiretroviral treatment was introduced in acute or chronic HIV infection, respectively. Forty-eight weeks of a dolutegravir-based regimen lowered the HIV-DNA load in these reservoir cells when treatment was introduced in acute infection, chronic infection or in case of virological failure but not as a switching therapy.

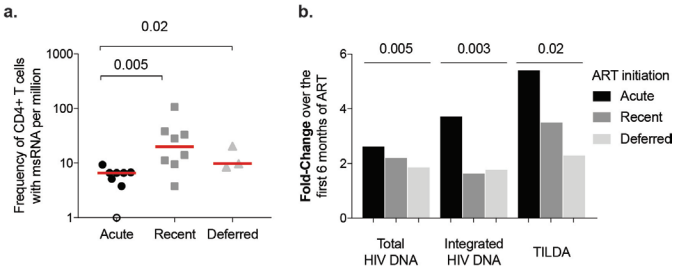


347 RAPID DECAY OF HIV PERSISTENCE MARKERS IN ACUTELY ART-TREATED INDIVIDUALS IN PERU

Marta Massanella[1], Rachel A. Bender Ignacio[2], Javier R. Lama[3], Amelie Pagliuzza[1], Ricardo Alfaro[3], Jessica Rios[3], Carmela Ganoza[3], Delia Pinto-Santini[2], Trupti I. Gilada[2], Ann Duerr[2], Nicolas Chomont[1]
[1]Centre de Research du Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]Asociacion Civil Impacta Salud y Educacion, Lima, Peru

Background: Early ART initiation confers several benefits on HIV-related morbidity and clinical outcomes and can lead to natural control of HIV replication upon ART interruption in a subset of individuals. We evaluated how timing of ART initiation impacts the size of the HIV reservoir during early infection in a subset of the Sabes study, a randomized clinical trial in Peru.
Methods: HIV-infected MSM and transgender women who were diagnosed while sero-negative (acute, n=12), or were sero-positive and <90 days from last negative RNA test (recent, n=16), were randomized to receive ART immediately (acute immediate [AI], n=8 and recent immediate [RI], n=11) or after 24 weeks deferral (D, n=9). We quantified total and integrated HIV DNA in CD4 T cells by real-time PCR, and used TILDA (Tat/rev Induced Limiting Dilution Assay) to measure the frequency of CD4 T cells producing multiply spliced RNA (msRNA) as a proxy for virus production, with and without stimulation.
Results: As expected, viral loads measured before ART initiation (week 0: Acute & Recent, week 24: D) were significantly higher in the acute group compared to either recent or D groups (6.78, 5.71 and 5.05 $\log_{10}$ copies/ml, respectively, p<0.01 both comparisons). Total and integrated HIV DNA did not differ in the 3 groups prior to ART, although TILDA frequencies with and without stimulation were higher in the acute and recent groups than the D group (p<0.05 all comparisons). After 6 months of ART, levels of integrated HIV DNA were significantly lower in the AI group than in the RI group (p=0.03); the inducible reservoir measured by TILDA was smaller in the AI group than in the RI or D groups (p=0.005 and 0.02, respectively, Figure 1a). During the first 6 months of ART, all three measurements of HIV persistence decreased more in the AI group than in those treated later (Figure 1b, all p<0.02). The TILDA/integrated HIV DNA ratio at study entry and 24 weeks later were highly correlated (R=0.87, p<0.001), suggesting that the relative proportion of inducible and defective proviruses was maintained over 6 months.
Conclusion: ART initiation during acute infection limits the size of the inducible reservoir, but the apparent benefit does not extend to persons who initiated ART after seroconversion. Markers of HIV persistence had a steeper decay in acutely treated individuals than in the two groups treated slightly later. Initiating ART during acute infection may facilitate HIV remission in concert with additional eradication strategies.

Figure 1: Change in markers of HIV persistence markers during the first 6 months of ART. 1a: Frequency of HIV msRNA+ T cells (TILDA) (at week 24 in AI, RI and week 48 in D) 1b: Fold-change in HIV persistence markers.



348 IL-21 PLUS IFNA LIMITS VIRAL PERSISTENCE AND REBOUND IN SIV-INFECTED RHESUS MACAQUES

Maria Pino[1], Luca Micci[1], Justin L. Harper[1], Colin T. King[1], Guido Silvestri[1], Jeffrey D. Lifson[2], Mirko Paiardini[1]
[1]Yerkes National Primate Research Center, Atlanta, GA, USA, [2]Leidos Biomedical Research, Inc, Frederick, MD, USA

Background: Although ART suppresses HIV replication, residual inflammation persists, and contributes to non-AIDS-related morbidity in infected subjects. Inflammation can also promote HIV persistence during ART. We showed that administration of IL-21 reduces chronic inflammation in ART-treated, SIV-infected rhesus macaques (RMs). In this study, we sought to combine the anti-inflammatory functions of IL-21 with the antiviral properties of IFNα to reinvigorate antiviral responses. We hypothesize that increased antiviral responses in a context of lower inflammation would impact on viral persistence on ART and viral rebound following ART treatment interruption (ATI).
Methods: 21 RMs infected with SIVmac239 started TDF/FTC/DTG treatment at day 35 post-infection; ART was continued for 12 months. 14 RMs received Macaquized (M)-IL-21-IgFc (100 µg/kg, SC, weekly for 4 weeks) at initiation and mid-way thru ART. This group also received M-IFNα-IgFc (500,000 IU, SC, weekly for 5 weeks) prior to ATI. The remaining seven RMs served as ART-only controls. Five controls and eight treated RMs underwent ATI. Upon ART-discontinuation, the eight IL-21/IFNα-treated RMs received PEGylated-IFNα-2a, 7 µg/kg, SC, weekly for 7 weeks.
Results: ART suppressed plasma viremia (pVL) (<30 RNA copies/mL) in all RMs. During ART, IL-21 reduced levels of activated (HLA-DR+CD38+) and proliferating (Ki-67+) T cells in PB, RB, and LN as compared to ART-only controls (P<0.01). Levels of inflammation remained lower during and after addition of IFNα (P<0.01). Gut SIV-DNA levels (P<0.05) and the frequency of LN CD4+ T cells harboring replication-competent SIV (P<0.01) were reduced in IL-21/IFNα treated RMs as compared to controls. Upon ART-interruption, IL-21/IFNα-treated RMs exhibited delayed viral rebound with a median of 21 days as compared to 9 days in controls (P=0.0009). Moreover, IL-21/IFNα-treated RMs maintained reduced viremia in comparison to controls up to 45 days after ATI (1.3 log lower; P=0.0004). The increased viral control was temporally limited, with IFNα interruption leading to pVL in treated RMs at levels no longer different from controls.
Conclusion: These data support the safety of a combined IL-21 and IFNα treatment for HIV infection. While IL-21 effectively reduces inflammation, addition of IFNα prior and after ART-discontinuation resulted in a more effective control of viral rebound. The synergy of such therapeutics may promote reinvigoration of host responses toward reduction of latent HIV reservoirs.

349 CD4 DEPLETION IN SIV-INFECTED MACAQUES ON EARLY ART HAS NO IMPACT ON VIRAL REBOUND

Adrienne E. Swanstrom, Taina T. Immonen, Claire Deleage, Kelli Oswald, William J. Bosche, Douglas K. Schneider, Sirish Khanal, James A. Thomas, Cathi Pyle, Charles M. Trubey, Jacob D. Estes, Jeffrey D. Lifson, Brandon Keele, **Gregory Q. Del Prete**
Frederick National Laboratory for Cancer Research, Frederick, MD, USA

Background: To date, no approaches have been identified that reduce the replication-competent viral reservoir that persists during suppressive combination antiretroviral therapy (cART) by a degree large enough to consistently delay off-cART viral rebound. Early initiation of cART limits the size of the persistent viral reservoir that is established, making for a more tractable target for subsequent interventions. To evaluate the impact of substantial ablation of the viral reservoir in the setting of limited initial reservoir establishment, we administered a CD4-depleting antibody to SIV infected rhesus macaques that had initiated early cART.
Methods: Ten rhesus macaques started daily cART (TDF/FTC/DTG) 4 days post-infection (IV) with molecularly-barcoded SIVmac239M. Beginning at 30 weeks post-cART initiation, 5 animals received 5-6 biweekly doses of rhesusized CD4-depleting antibody; 5 animals served as controls. CD4+ cell depletion and cell-associated viral DNA (vDNA) levels were monitored in blood and lymph nodes (LN). Following the last dose of anti-CD4 antibody, animals remained on cART for 1 year. cART was then discontinued, with monitoring for viral rebound, rebounding viral variants in plasma, and estimation of viral reactivation rates.
Results: By ~7 weeks post-cART initiation, plasma viral loads in all animals were stably suppressed to <15 viral RNA copies/ml. Consistent with limited reservoir establishment, cell-associated vDNA measurements were low in PBMC (median 1.7 vDNA copies/10^6 cells) and LN (median 2.1 vDNA copies/10^6 cells) pre-anti-CD4 administration, with no significant differences between experimental groups. Following anti-CD4 administration, CD4 T cell counts in blood declined by 96.3-99.9% and in LN by 78-91%. By one year after the last anti-CD4 treatment, CD4 counts returned in depleted animals to levels 23-65% lower than pre-depletion. Upon cART cessation, there was no significant difference between depleted and control groups, respectively, in time to first positive plasma viral load (median 27 days vs 17 days), unique rebounding variants (median 2 vs 4), or calculated reactivation rates (mean once per 6 days vs once per 3 days).

Conclusion: Despite limited reservoir establishment with early cART, profound depletion of CD4+ T cells, including those potentially harboring virus, had no measurable impact on off-cART viral rebound. These findings underscore the potency that will be required of reservoir reducing strategies to meaningfully reduce total body reservoir size.

350 SIV PERSISTS IN LYMPHOID TISSUES DESPITE ALEMTUZUMAB-INDUCED CD4+ T CELL DEPLETION

Afam Okoye[1], Colleen Xu[1], Mukta Vaidya[1], Derick M. Duell[1], William B. Brantley[1], Alejandra Marenco[1], Yoshinori Fukazawa[1], Haesun M. Park[1], Thomas A. Rasmussen[2], Jeffrey D. Lifson[3], Michael K. Axthelm[1], Steven G. Deeks[4], Louis J. Picker[1], Sharon R. Lewin[5]

[1]Oregon Health and Sciences University, Portland, OR, USA, [2]Aarhus University Hospital, Aarhus, Denmark, [3]Leidos Biomedical Research, Inc, Frederick, MD, USA, [4]University of California San Francisco, San Francisco, CA, USA, [5]Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia

Background: Alemtuzumab (ATM) is a lymphocyte-depleting humanized anti-CD52 monoclonal antibody used for the treatment of multiple malignancies and licensed for relapsing-remitting multiple sclerosis. Here, we evaluated whether ATM can deplete long-lived latently infected CD4+ memory T cells in SIV-infected rhesus macaques (RM) on suppressive combination antiretroviral therapy (cART). We hypothesized that ATM-induced depletion and reconstitution in the presence of cART may significantly reduce SIV persistence.

Methods: RM were initially screened for CD52 expression on erythrocytes using an agglutination assay to minimize any risk of hemolysis. Nine RM were intravenously inoculated with SIVmac239 and after 12 days received cART (tenofovir/emtricitabine/dolutegravir). Once sustained virus suppression (<15 RNA copies/ml) was achieved, 6 RM received intravenous doses of ATM at 5mg/Kg on days 0, 7, 14 and 29. Three RM did not receive ATM (controls). Lymph node (LN) and gastrointestinal tract (GIT) tissue was collected at 10 and 20 weeks. SIV DNA and RNA were quantified by qPCR/qRT-PCR and markers of immune activation by flow cytometry.

Results: ATM induced a rapid and profound depletion in circulating lymphocyte populations, including T cells, NK cells, B cells and monocytes, including a significant depletion in CD4+ memory and naive T cells in the blood (>95%) and some depletion in LN (~50%). CD4+ T regulatory cells were also significantly depleted (>90%). T cell reconstitution was associated with a massive burst in memory T cell proliferation as measured by Ki67, which peaked around 3-4 weeks post-ATM and followed by a gradual recovery of all T cell subsets in blood. After 7 months, naïve, central, and effector memory CD4+ T cell subsets were 51%, 60% and 100% of pre-ATM levels, respectively. Post-ATM, but while still on cART, plasma SIV RNA remained detectable but below 15 copies/ml with only 1 of 6 RM showing blips above 100 SIV RNA copies/ml. At 10 weeks post-ATM, total SIV DNA in peripheral blood mononuclear cells (PBMC) decreased from a mean of 2.4 to 1.4 log copies per 10e6 cells (p=0.03); however, SIV DNA in peripheral LN and GIT remained unchanged.

Conclusion: Although ATM can significantly reduce SIV DNA levels in the PBMC of SIV-infected RM on cART, low level viremia persists. The minimal effect on SIV DNA in LN and GIT suggests either limited depletion in those tissues or a rapid reconstitution at those sites post-ATM, perhaps by expanded clones.

351 ΔCCR5 ANTI-HIV CAR T CELLS ENGRAFT AND PERSIST IN SHIV-INFECTED PIGTAIL MACAQUES

Thor A. Wagner[1], Christopher Peterson[2], Brenda Seymour[3], Taylor Mesojednik[3], Jeb English[3], Bryan Sands[1], Courtnee Clough[1], Karsten Eichholz[2], Larry Corey[2], Hans-Peter Kiem[2], David J. Rawlings[1]

[1]University of Washington, Seattle, WA, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]Seattle Children's Research Institute, Seattle, WA, USA

Background: Persistence of HIV-infected cells with replication competent provirus is the primary barrier to HIV cure. To eradicate HIV-infected cells, we developed chimeric antigen receptors (CAR) that utilize single chain variable fragments (scFv) from broadly neutralizing monoclonal antibodies, and protected the CAR+ cells from HIV infection by disrupting CCR5. To test this approach in vivo, we treated SHIV-infected pigtail macaques with autologous CCR5-disrupted(ΔCCR5), VRC07-523-based CAR+ T cells.

Methods: Six pigtail macaques were leukapheresed prior to infection with the CCR5-tropic SHIV-1157ipdN4. 12 weeks after SHIV infection and one week after immunoconditioning with cyclophosphamide, ΔCCR5 CAR+ T cells were infused in the absence of antiretroviral therapy. Four animals received VRC07-523-derived CAR+ ΔCCR5 T cells and two animals received GFP+ cells as a control. Engineered T cells were tracked in the peripheral blood and various tissues using flow cytometry, and confirmed by PCR amplification and sequencing of the CAR and the CCR5 locus. One CAR treated animal underwent necropsy after two weeks, the rest underwent necropsy six weeks after CAR T cell treatment.

Results: A median of 88% (range 74-90%) of the engineered T cells expressed either the CAR or GFP transgene. 71% (range 44-78%) of CCR5 alleles were disrupted in the CAR T cell product, as measured by an endonuclease re-cleavage assay. Cells were expanded ex vivo 20.5 fold (range 11-30). Animals were treated with 67 million (range 28-90 million) CAR+ or control cells per kg. Compared to the GFP control animal, all four CAR treated animals had detectable populations of CAR+ T cells in the bone marrow, PBMC, spleen, and lung at necropsy, as measured by flow cytometry and PCR-based assays.

Conclusion: This is one of the first attempts to study HIV-specific, infection resistant CAR T cell therapy in nonhuman primates. We successfully engineered nonhuman primate T cells with high-levels of CAR expression and CCR5 disruption. CAR+ T-cells persisted in vivo at levels consistent with cell proliferation. We are working to evaluate the antiviral effect of the CAR T cells and to determine if the CAR T cells that persist are functional. Based on initial data, methods to improve the persistence and distribution of infection-resistant CAR T cells may be important.

352 FULLY MHC-MATCHED ALLOGENEIC HSCT IN SIV-INFECTED, ART-SUPPRESSED MACAQUES

Helen Wu, Benjamin Burwitz, Shaheed Abdulhaqq, Christine Shriver-Munsch, Tonya Swanson, Alfred Legasse, Katherine Hammond, Jason Reed, Mina Northrup, Stephanie Junell, Gabrielle Meyers, Richard Maziarz, Jeffrey Stanton, Jonah Sacha

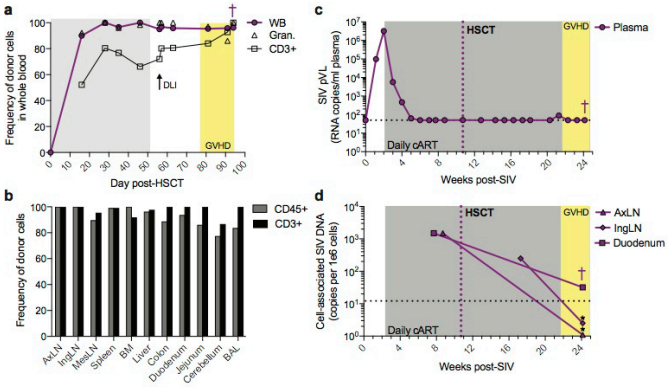
Oregon Health and Sciences University, Portland, OR, USA

Background: Timothy Brown remains in cART-free HIV remission following allogeneic hematopoietic stem cell transplant (HSCT), but attempts to recapitulate his cure have been unsuccessful. We recently established a nonhuman primate model of fully MHC-matched allogeneic HSCT to investigate the mechanism of cure in Timothy Brown. In this model, a reduced intensity conditioning (RIC) regimen consisting of chemotherapy, CD3 depletion, and total body irradiation (TBI) prior to HSCT results in durable, full multi-lineage donor chimerism in SIV-naïve HSCT recipients. Here, we sought to investigate (1) if similar results could be achieved without TBI, and (2) the impact of allogeneic HSCT on SIV reservoir size in cART-suppressed, SIV-infected recipients.

Methods: Allogeneic HSCT was performed with fully MHC-matched Mauritian cynomolgus macaque (MCM) donor-recipient pairs, including two fully cART-suppressed, SIV-infected recipients. Mobilized peripheral stem cells collected from donors by leukapheresis were transplanted into recipients following RIC with or without TBI. Donor engraftment was monitored by Illumina sequencing of single nucleotide polymorphisms. Immune subset reconstitution was assessed longitudinally by flow cytometric phenotyping and complete blood counts.

Results: We performed two HSCTs without TBI, both resulting in low T cell donor chimerism (<15%). The first, SIV-naïve recipient experienced incomplete T cell rebound resulting in polyoma virus reactivation and euthanasia. The second, cART-suppressed, SIV-infected recipient stabilized post-HSCT, and experienced a reduction in lymph node-associated SIV DNA despite incomplete T cell donor chimerism. Adding back TBI for HSCT of a second cART-suppressed, SIV-infected recipient resulted in high levels of donor chimerism in whole blood (>95%) and T cells (~80%) within 30 days of HSCT (see figure). Subsequent donor lymphocyte infusion increased blood and tissue T cell donor chimerism levels to nearly 100%, but led to development of clinical graft-versus-host disease (GVHD) and euthanasia. At necropsy, SIV DNA was below the limit of detection in lymph nodes, constituting a ~3 log reduction from pre-HSCT levels.

Conclusion: These data demonstrate that TBI is critical to achieving high levels of T cell donor chimerism post-HSCT in MCM, and that while HSCT immune conditioning decreases the viral reservoir size, GVHD is associated with enhanced reservoir clearance. This model facilitates future studies of HSCT-mediated HIV cure.



(a) Longitudinal donor chimerism levels in whole blood, blood granulocytes, and blood T cells. Light gray box indicates period of immunosuppressive treatment. Yellow box indicates period of clinical GVHD. DLI = donor lymphocyte infusion. Cross indicates timepoint of necropsy. **(b)** Donor chimerism levels in CD45+ and CD3+ tissue cells at necropsy. **(c, d)** SIV plasma viral loads (c) and cell-associated viral loads (d). Dark gray box indicates period of antiretroviral treatment. Vertical dotted purple line indicates timepoint of HSCT. Horizontal dotted black line indicates limit of detection for the assay. Asterisks indicate only one of two replicates came up positive.

353LB IL-15 TREATMENT INCREASES CYTOTOXIC LYMPHOCYTES IN LN FOLLICLES AND REDUCES SHIV RNA

George Pavlakis[1], Dionysios C. Watson[1], Eirini Moysi[1], Antonio Valentin[1], Cristina Bergamaschi[1], Santhi Devsundaram[1], Sotirios Fortis[1], Claire Deleage[2], Jacob D. Estes[2], Elena Chertova[2], Jeffrey D. Lifson[2], Constantinos Petrovas[3], Barbara K. Felber[1]

[1]NIH, Frederick, MD, USA, [2]Leidos Biomedical Research, Inc, Frederick, MD, USA, [3]NIAID, Gaithersburg, MD, USA

Background: Heterodimeric interleukin-15 (hetIL-15) is a native stable form of the cytokine that activates and expands cytotoxic T and NK cells. Based on its properties and extensive preclinical data, hetIL-15 is currently evaluated in humans for the treatment of cancer. We study the effects of hetIL-15 in infected macaques to evaluate its use in HIV infection and especially in the reduction of SIV/SHIV reservoir towards a functional cure.

Methods: Rhesus macaques, either chronically infected by SHIV or uninfected received injections of hetIL-15 over 2 weeks using increasing doses of cytokine (step-dosing). At the end of the treatment, the animals were sacrificed and the hetIL-15 effects on different lymphocyte populations isolated from tissues collected at necropsy were monitored by multi-parametric flow cytometry and quantitative multiplexed confocal microscopy (histo-cytometry). Cell-associated viral RNA and plasma viral load was measured by quantitative PCR.

Results: This protocol was safe in rhesus macaques and resulted in systemic expansion of CD8+ T lymphocytes and NK cells with higher granzyme B content. These expanded cell populations were found in both effector sites, such as liver, vagina and rectum, and secondary lymphoid tissues. Importantly, a significant increase in cytotoxic effector memory CD8+ T cells was found in lymph nodes (LN) from all hetIL-15-treated macaques. CM9 tetramer staining demonstrated that the increase of CD8+ effector T cells in lymphoid organs included actively proliferating SIV-specific T cells with higher granzyme content. Imaging analysis by histo-cytometry revealed that these effector CD8+ T cells infiltrated the B cell follicles where chronically infected follicular helper CD4+ T cells are located. Following hetIL-15 treatment, cell-associated RNA was decreased in LN and plasma viral load was also decreased. Treatment of macaques under Antiretroviral Therapy (ART) with this regimen was also safe and induced cytotoxic CD8+ accumulation in LN follicles.

Conclusion: Step-dose administration of hetIL-15 is a well-tolerated regimen that results in systemic activation and expansion of cytotoxic leukocytes that infiltrate areas where chronic HIV-infected cells reside. These results suggest that hetIL-15 could be useful in disrupting sanctuary sites within the B cell follicles and reducing long-term viral reservoirs in HIV-1 infected individuals, thus contributing to a functional cure of the infection.

354 GAMMA/DELTA CELLS TARGET THE HIV RESERVOIR: IMMUNOTHERAPEUTIC POTENTIAL FOR HIV CURE

Chloe Whitworth, Carolina Garrido, Katherine Sholtis, Matthew Clohosey, Nancie Archin, David M. Margolis, **Natalia Soriano-Sarabia**

University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: Gamma/delta T cells constitute an attractive alternative/complementary effector population as they exert potent cytotoxic and antiviral functions. Cancer immunotherapy using gamma/delta T cells and pamidronate (PAM) has been extensively developed. Our objective is to analyze the immunotherapeutic potential of gamma/delta T cells to clear reactivated HIV.

Methods: Cells from HIV-infected donors on suppressive ART were studied in autologous cellular systems using isolated cells. Vdelta2 cells were expanded with PAM and IL-2 for 14 days. Activation, exhaustion and cytotoxic markers of expanded Vdelta2 cells was analyzed by flow cytometry. Cytotoxic assays were assessed measuring CD107a expression by flow cytometry. For inhibition assays, infected CD4 cells were co-cultured with Vdelta2 cells. Latency clearance assays were performed to analyze the capacity of gamma/delta T cells to clear viral production after autologous resting CD4 cells had been reactivated using vorinostat.

Results: Vdelta2 cells from HIV-infected individuals expanded up to 120-fold after 14 days in culture. 65% of expanded Vdelta2 cells display markers of a central memory phenotype, 23% were transitional memory and 8% were effector memory. 37% of the expanded Vdelta2 cells expressed CD8, 50% displayed a cytotoxic phenotype (Vdelta2+CD56+) and 30% displayed an ADCC-like phenotype characterized by the expression of CD16. Cytotoxic assays showed significantly higher expression of CD107a when expanded Vdelta2 cells were cultured with HIV-superinfected CD4 cells compared to non-superinfected CD4 cells. Viral inhibition assays showed that expanded Vdelta2 cells are potent inhibitors of HIV p24 antigen production showing a mean of 85% reduction, compared to viral production by CD4 cells alone. Finally, latency clearance assays demonstrated lower recovery of replication-competent HIV after reactivation of autologous resting CD4 cells when gamma/delta T cells were present in the coculture system.

Conclusion: Our results support that gammadelta cells immunological functions are maintained in HIV-infected individuals and that their antiviral activity can be expanded ex vivo to target the HIV reservoir in fully suppressed individuals upon latency disruption. This is the first proof-of-concept showing that gammadelta cells remain able to target and clear autologous HIV reservoir and suggest that gammadelta cells are strong candidates to current immunotherapeutic interventions aimed for HIV reservoir eradication strategies.

355 BLOCKADE OF IFNAR RESCUES ANTI-HIV-1 CD8 T CELL FUNCTIONS TO REDUCE HIV-1 RESERVOIR

Liang Cheng[1], Jianping Ma[1], Guangming Li[1], Zhiyuan Hu[1], Liguo Zhang[2], Lishan Su[1]

[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]Chinese Academy of Sciences, Beijing, China

Background: Type I interferons (IFN-I) are critical for controlling virus infections, but their persistent expression also contributes to impaired host immunity and virus persistence. Although IFN-I inhibit HIV-1 replication in vitro and in vivo, persistent IFN-I induction is correlated with immune dysfunction and disease progression in HIV-1 infected patients and in SIV infected monkeys. Moreover, despite efficient suppression of HIV-1 replication with combined antiretroviral therapy (cART), low levels of IFN-I signaling persist in some individuals, which may impede immune recovery and foster viral persistence.

Methods: We developed a monoclonal antibody to human IFN-α/β receptor (α-IFNAR) which can block IFN-I signaling in vivo. Humanized mice with persistent HIV-1 infection were treated with cART and IFNAR blockade Ab or isotype control (and human CD8 depleting mAb). At termination, T cell phenotype (expression of activation marker CD38 and HLA-DR, exhaustion marker PD-1, TIM3) was detected by FACS. T cell function was detected by ex vivo HIV-1 Gag peptide pool stimulation followed with IL-2/IFN-γ/TNF-α intracellular staining. Transcriptome analyses by RNA-seq were performed with purified human CD8 T cells to identify pathways and genes contributing to IFN-I-induced T cell dysfunction. To measure HIV-1 reservoir, we detect cell-associated HIV-1 DNA and RNA by PCR, and replication-competent HIV-1 by the quantitative virus outgrowth assay(QVOA). In addition, we measured virus rebound after cART discontinuation.

Results: In HIV-infected humanized mice with cART, IFNAR blockade reduces the level of T cell activation (expression of CD38 and HLA-DR), reverses T cell exhaustion (expression of PD-1 and TIM-3). Transcriptome analysis by RNA-seq with purified CD8 T cells also indicated that IFNAR blockade reduced the expression of ISGs and genes involved in immune activation, exhaustion and cell

death. We also found that IFNAR blockade rescued anti–HIV-1 T cells response. Most strikingly, we found that IFNAR blockade in the presence of cART reduced the size of HIV-1reservoirs in lymphoid tissues and delayed HIV-1 rebound after cART cessation in the HIV-1–infected hu-mice. Finally, we found that CD8 T cells rescued by IFNAR blockade were essential for HIV-1 reservoir reduction.
Conclusion: We conclude that low levels of IFN-I signaling contribute to HIV-1–specific CD8 T cell dysfunction and foster HIV-1 persistence in cART treated hosts.

356 A PHASE 1 STUDY OF ALT-803 (IL-15 SUPERAGONIST) TO CLEAR LATENT HIV RESERVOIRS

Zachary Davis[1], Ann Thorkelson[1], Jodi Anderson[1], Hing C. Wong[2], Jonathan Karn[3], Curtis Dobrowlski[3], Jeffrey S. Miller[1], Sarah Cooley[1], Daniel Douek[4], Timothy Schacker[1]
[1]University of Minnesota, Minneapolis, MN, USA, [2]Altor Bioscience, Miramar, FL, USA, [3]Case Western Reserve University, Cleveland, OH, USA, [4]NIH, Bethesda, MD, USA
Background: A primary barrier to HIV cure is the large latent reservoir in tissues. Efforts to clear these cells are hampered by defects in both adaptive and cellular immune responses. IL-15, a cytokine that stimulates NK and T cells has potential to reverse these defects and to clear virus infected cells.
Methods: We are conducting a Phase 1 dose escalation trial of ALT-803 in HIV+ adults. ALT-803 is an IL-15 superagonist/IL-15 receptor α complex (IL-15N72D/IL-15Rα-Fc) and is in clinical trials for hematologic and solid organ malignancies. Clinical trials in cancer patients have shown that subcutaneous (SQ) administration (compared to intravenous (IV)) is well tolerated and gives favorable pharmacokinetics at doses between 10-20 mcg/kg weekly. HIV+ people on ART with plasma viral load < 20 copies/ml and CD4 T cells > 500 cells/µl receive an IV or SQ injection of ALT-803 weekly for 3 weeks. Blood is obtained for assessments of cell activation and proliferation, and changes to the virus reservoir. Three people are planned to receive the drug at each dose level. The dose escalation scheme is 0.3 mcg/kg IV then 1, 3, and 6 mcg/kg SQ.
Results: A total of 7 individuals have been dosed to date. The mean age was 42 and mean CD4 T cell count was 865 cell/µl. The mean time from diagnosis was 9.7 years and the mean time on ART was 5.3 years. The first 2 participants received 0.3 mcg/kg IV and the remaining 5 received 1.0 mcg/kg SQ. SQ dosing was associated with an injection site rash and adenopathy. Eight of the first 13 doses were associated with transient low-level plasma viremia. We measured a 7.6-fold increase in NK cell activation, a 23-fold increase in CD4 activation and a 10-fold increase in CD8 T cell activation in LN 48 hours after dosing. We used the EDITS assay (Envelope Detection by Induced Transcription-based Sequencing, developed by Dr. Karn, CWRU) to measure inducible cell-associated HIV RNA. Prior to Con A stimulation we measured a significant increase in HIV transcription after the first 2 ALT-803 doses but after dose 3 there were fewer transcription events. With ConA stimulation there was a trend towards decreasing transcription events (Figure).
Conclusion: At these relatively low doses of ALT-803, the drug is safe and well-tolerated. The drug is biologically active and causes activation and proliferation of CD4, CD8 T cells and NK cells and induces transcription of HIV. These studies suggest ALT-803 reactivates virus from latency and activates NK and T cells.

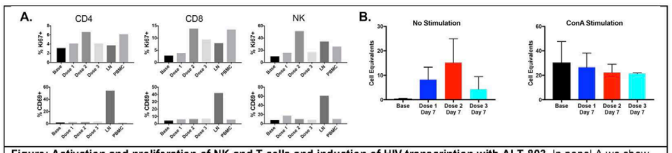


Figure: Activation and proliferation of NK and T cells and induction of HIV transcription with ALT-803. In panel A we show the activation (CD69) and proliferation (Ki67) of CD4, CD8, and NK cells from a single subject after each dose. Base = PBMC from prior to the first dose. Dose 1-3 = PBMC from 24 hours after the administration of ALT-803. LN and PBMC = LN mononuclear cells and PBMC obtained 48 hours after the 3rd dose. In Panel B we show results from the EDITS assay on the same subjects using PBMC obtained 7 days after the indicated dose (just prior to the next dose). Cell equivalents = number of cells with latent provirus induced to transcribe HIV.

357 EFFECT OF 24 WEEKS TLR9 AGONIST THERAPY ON CTL RESPONSES AND VIRAL REBOUND DURING ATI

Line K. Vibholm[1], Giacomo Frattari[1], Mariane H. Schleimann[1], Rikke Olesen[1], Mathias Lichterfeld[2], Anni Winckelmann[1], Christina V. Konrad[1], Vibeke Klastrup[1], Thomas A. Rasmussen[1], Manuel Schmidt[3], Burghardt Wittig[4], Lars Østergaard[1], Paul W. Denton[1], Martin Tolstrup[1], Ole S. Søgaard[1]
[1]Aarhus University Hospital, Aarhus, Denmark, [2]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [3]Mologen AG, Berlin, Germany, [4]Freie Universität Berlin, Berlin, Germany
Background: Combination antiretroviral therapy (cART) disrupts the fatal course of infection but does not eradicate the HIV reservoir. Previously we have shown that 4 weeks treatment with the TLR9 agonist lefitolimod (MGN1703, Mologen AG) adjunctive to cART functions as both a latency reversing agent and as activator of cytotoxic NK cells. In this 2nd part of the trial, we assessed safety and evaluated if extended administration of lefitolimod could enhance the HIV-specific T cell responses, decrease the latent reservoir and prolong time to rebound.
Methods: This was a phase Ib/IIa, open label, investigator-initiated clinical trial (NCT02443935). We included 13 HIV-infected individuals on cART. Lefitolimod (60 mg s.c.) was administered twice weekly for 24 weeks while participants remained on cART. Safety was assessed at each visit. After the 24-week dosing period, most participants initiated an analytical treatment interruption (ATI) until viral rebound occurred (two consecutive plasma HIV RNA >5000 c/mL). Blood samples were collected at baseline, after 12 and 24 weeks and at time of rebound. HIV-specific immunity was assessed by CD8+ T cell intracellular cytokine stain (ICS) for IFN-γ, TNF-α and IL-2. Total HIV DNA was measured by ddPCR. Plasma HIV RNA was measured by Cobas Taqman assay.
Results: Lefitolimod was safe and well tolerated. ICS revealed a significant (p=0.0068) cohort-wide increase in IFN-γ response in HIV-specific CD8+ T Effector Memory (TEM) and Terminally Differentiated (TTD) cells from baseline to after 24 weeks treatment. On a cohort level, HIV DNA did not change significantly during the treatment period. During the ATI, one individual who initiated cART during chronic infection (pre-cART HIV RNA >100,000 c/mL and nadir CD4 of 29 cells/µL) demonstrated plasma HIV RNA levels below limits of detection (20 c/mL) for >21 weeks. Notably, this person had the highest percentage of polyfunctional HIV-specific CD8+ TEM (IFN-γ+, TNF-α+ and IL-2+) which further increased 3-fold from baseline to end of treatment, indicating that polyfunctional HIV-specific CD8+ T cells might have contributed to the observed virological control. Time to rebound for the remaining 8 individuals participating in the ATI was comparable to historical data.
Conclusion: In conclusion, 24 week adjunctive TLR9 agonist therapy was safe, enhanced HIV-specific T cell responses and might increase time to rebound in some individuals with strong polyfunctional HIV-specific CD8+ TEM responses.

358 IFN-A INDUCES NK-DEPENDENT HIV DNA DECLINE IN ART-TREATED HIV/HCV COINFECTED PATIENTS

Stephane Hua[1], Selena Vigano[1], Samantha Tse[1], Zhengyu Ouyang[1], Sean Harrington[1], Jordi Negron[1], Pilar Garcia-Broncano[1], Giulia Marchetti[2], Miguel Genebat[3], Manuel Leal[3], Salvador Resino[4], Ezequiel Ruiz-Mateos[3], Mathias Lichterfeld[1], Xu G. Yu[1]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]University of Milan, Milan, Italy, [3]Institute of Biomedicine of Seville, Sevilla, Spain, [4]Institute de Salud Carlos III, Majadahonda, Spain
Background: IFN-α can potently reduce HIV-1 replication in tissue culture and animal models, but may also modulate residual viral reservoirs that persist despite suppressive antiretroviral combination therapy. However, mechanisms leading to viral reservoir reduction during IFN-α treatment are unclear.
Methods: We analyzed HIV-1 gag DNA levels in CD4 T cells by digital droplet PCR and CD8 T and NK cell phenotypes by flow cytometry in a cohort of ART-treated HIV-1/HCV co-infected patients (n=67) undergoing treatment for Hepatitis C infection with pegylated IFN-α and Ribavirin for an average of 11 months.
Results: We observed that IFN-α treatment induced a significant decrease in CD4 T cells counts (p<0.0001), in CD4 T cell-associated HIV-1 DNA copies (p=0.002) and in HIV-1 DNA copies per microliter of blood (p<0.0001) in our study patients. Notably, HIV-1 DNA levels were unrelated to HIV-1-specific CD8 T cells responses. In contrast, proportions of total NK cells, of CD56brightCD16- NK cells and of CD56brightCD16+ NK cells were significantly associated with reduced levels of CD4 T cell associated HIV-1 DNA during IFN-α treatment, especially when co-expressing the activation markers NKG2D and NKp30.
Conclusion: These data suggest that the reduction of viral reservoir cells during treatment with IFN-α is primarily attributable to antiviral activities of NK cells.

359 THE THERAPEUTIC VACCINE VACC-4X TARGETS GAG CTL EPITOPES WITH PREEXISTING MUTATIONS

Anni Winckelmann[1], Vincent Morcilla[2], Wei Shao[3], Lars Østergaard[1], Ole S. Søgaard[1], **Martin Tolstrup**[1], Sarah Palmer[2]
[1]Aarhus University Hospital, Aarhus, Denmark, [2]The Westmead Institute for Medical Research, Westmead, NSW, Australia, [3]Frederick National Laboratory for Cancer Research, Frederick, MD, USA

Background: Therapeutic HIV immunisation followed by latency reversal has been suggested as a strategy to achieve a functional cure for HIV. The efficacy of a therapeutic peptide vaccine to improve antiviral immune responses will depend on the presence of potential escape mutations in the target regions. Here we investigate the HIV phylogenetic composition of the four regions targeted by the therapeutic vaccine Vacc-4x in participants in a clinical vaccine trial.
Methods: In a clinical trial, 17 participants on suppressive ART were vaccinated with six doses of the therapeutic HIV gag peptide vaccine Vacc-4x (Bionor Pharma) over 12 weeks, then three doses of romidepsin over three weeks followed by an analytical treatment interruption (ATI). Seven participants were selected for sequencing analysis. We performed single-genome/proviral sequencing of a 2.1 kb region spanning the p24-RT region on HIV-1 DNA and cell-associated RNA from peripheral CD4+ T cells from a total of six time points during the trial, as well as plasma HIV-1 RNA from the ATI. We analyzed HLA-specific CTL epitopes in the four regions targeted by Vacc-4x using the Los Alamos epitope and variant databases. CD8+ immune responses were assessed by intracellular cytokine staining and viral inhibition assays.
Results: In five of the seven participants, we identified CTL epitopes, which contained non-silent mutations in 100% of the sequences obtained from all time points analyzed. Only one participant showed signs of vaccine-induced selection in the rebound plasma virus during the ATI. In this participant, a mutation in one CTL epitope was found in 100% of the plasma RNA sequences, compared to 12% of the proviruses. Notably the rebounding virus formed two distinct clusters in the phylogenetic tree and this participant had the highest rebound doubling time of 2.59 days. Overall, the participants with greater plasma HIV-1 RNA genetic diversity at rebound had a shorter time to viral rebound.
Conclusion: We identified CTL epitope changes at baseline, prior to vacc-4x therapy which may affect the potency of this therapeutic vaccine. However, in two participants we identified no mutations of CTL epitopes and they did not show any improved immune responses to vaccination. These findings highlight the challenges of developing immunogenic therapeutic vaccines for HIV Furthermore, we find that the genetic diversity of the virus at rebound relates to the time it takes for virus to rebound.

360LB WITHDRAWN

361 SEX-BASED DIFFERENCES IN TRANSCRIPTOMIC PROFILES AND HIV RESERVOIR CORRELATES

Eileen P. Scully[1], Khader Ghneim[2], Ashish Sharma[2], Ainsley Lockhart[3], Rowena Johnston[4], Monica Gandhi[5], Rebecca Hoh[5], Sharon R. Lewin[6], Nicolas Chomont[7], Steven G. Deeks[5], Rafick-Pierre Sekaly[2]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]Case Western Reserve University, Cleveland, OH, USA, [3]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [4]amfAR, New York, NY, USA, [5]University of California San Francisco, San Francisco, CA, USA, [6]University of Melbourne, Melbourne, VIC, Australia, [7]Université de Montréal, Montreal, QC, Canada

Background: Biological sex impacts multiple aspects of HIV and the immune response. To identify sex-specific pathways relevant to HIV pathogenesis and cure strategies, we performed transcriptional profiling on a cohort of HIV-positive men and women matched on critical virologic and immunologic factors. Data were analyzed to identify genes and pathways differentially expressed by sex, and gene expression was related to virologic parameters.
Methods: Peripheral blood was collected from men(n=26) and matched reproductive age women(n=26) on fully suppressive ART. RNA was isolated and sequenced with the 3' digital gene expression platform (Broad Institute). Transcripts were analyzed for differential expression of genes and with gene set enrichment analysis(GSEA) to identify selectively enhanced pathways. Transcriptional profiles were regressed to measures of HIV persistence (total and integrated HIV DNA and unspliced and multiply spliced RNA) for each sex.
Results: 20% of variation in transcriptional profiles is attributable to biological sex (multidimensional scaling analysis). 1429 genes and 16 GSEA pathways were differentially expressed (FDR<0.05). The IFNα(p<0.001, FDR 0.008) and IFNγ(p<0.001, FDR 0.02) pathways were upregulated in women, as seen in HIV uninfected subjects previously. Supervised analysis of interferon pathway genes demonstrated higher expression of antiviral genes (IRF7, ISG15 and MX1) in women. Men and women also showed distinct patterns of inflammasome gene expression with NLRP8, CIITA and NLRC5 upregulated in women; these genes are known to counterbalance pro-inflammatory NLRs. Women and men had distinct transcriptional correlates of HIV reservoir (combined HIV DNA and usRNA). Heme metabolism (anti-inflammatory) and UV response (DNA damage inducer of senescence) pathways positively correlated to the measures of HIV persistence in men. Oxidative response, glycolysis, E2F and Myc pathways (all features of active metabolism and functional T cell responses) were positively correlated with reservoir in women.
Conclusion: HIV-infected men and women on fully suppressive ART have distinct transcriptional profiles. Women show enrichment of antiviral pathways along with genes that counterbalance inflammatory components of the inflammasome. Sex-specific analysis of HIV reservoir correlates identifies different gene pathways in men and women. Biological sex determines distinct transcriptional patterns that are related to HIV reservoir, with sex-specific implications for cure strategies

362 THE IMPACT OF ART DURATION ON THE INFECTION OF T CELLS WITHIN ANATOMIC SITES

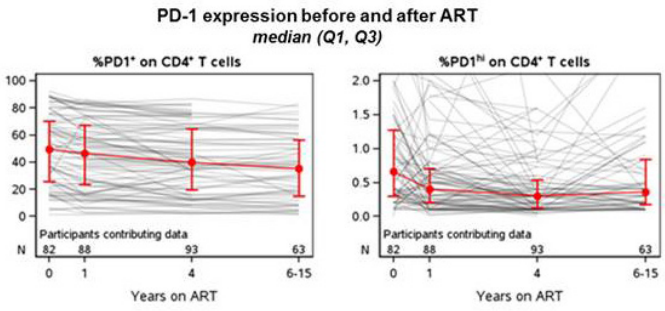
Eunok Lee[1], Susanne von Stockenstrom[2], Vincent Morcilla[1], Wei Shao[3], Wendy Hartogensis[4], Peter Bacchetti[4], Jeffery Milush[4], Rebecca Hoh[4], Ma Somsouk[4], Peter W. Hunt[4], Rémi Fromentin[5], Nicolas Chomont[5], Steven G. Deeks[4], Frederick M. Hecht[4], **Sarah Palmer**[1]
[1]The Westmead Institute for Medical Research, Westmead, NSW, Australia, [2]Karolinska Institute, Stockholm, Sweden, [3]Frederick National Laboratory for Cancer Research, Frederick, MD, USA, [4]University of California San Francisco, San Francisco, CA, USA, [5]Université de Montréal, Montreal, QC, Canada

Background: Understanding the impact of antiretroviral therapy (ART) duration on the dynamics of HIV reservoirs is critical for effective curative strategies. Here, we studied changes in the HIV reservoir size over 3-18 years of ART. We also examined the genetic similarity of HIV sequences found in T cell subsets and plasma viremia.
Methods: Using single-genome/proviral sequencing, we performed cross-sectional inter-participant analysis of 1134 HIV p6-RT RNA sequences from pre- and early-ART plasma; and 3963 HIV DNA sequences from naïve, central (CM), transitional (TM), and effector (EM) CD4+ T cells sorted from peripheral blood (PB), lymph node (LN) and gut tissues from 26 participants on effective ART for 3-18 yrs: 12 who initiated ART during acute/early (AHI) and 14 during chronic HIV infection (CHI). HIV infection frequencies in anatomic and cellular sites were computed by maximum likelihood statistics. Expansions of identical sequences (EIS) were determined as ≥2 identical HIV-DNA sequences across all cell types from all anatomic sites in CHI group.
Results: In PB, the fold-change in infection frequency per year on ART was similar between AHI and CHI groups across all cell types. For the CHI group, the infection frequency was stable in PB-derived EM cells (fold-change=1.0/yr on ART, 95% CI=0.9-1.2). However, the odds of a viral sequence belonging to EIS increased in PB, most substantially in EM cells (p=0.007). No substantial change of HIV infection frequency was observed in cells from the gut. In LN, the AHI group had a larger decline in infection frequencies compared to the CHI group in each cell type (fold-change=0.092-0.48, p-values=0.0056-0.036). Importantly, for the CHI group, EM cells from the LN contained HIV-DNA sequences that were more often genetically identical to pre- and on-ART plasma HIV-RNA sequences than other LN cell types.
Conclusion: The infection frequency of PB-derived EM cells was stable during 3-18 years of ART but the expansions of identical sequences increased which indicates stochastic cellular proliferation and contraction contribute to HIV persistence in these cells. We observed sustained declines in estimated reservoir size in the LN, which changes more substantially among those who started ART during acute infection indicating early ART initiation promotes T cell reconstitution in the LN. However, our data suggest that in LN tissue the replication-competent viral population is more enriched in EM cells.

363 PERSISTENCE OF CD4+PD-1HIGH T CELLS DESPITE LONG-TERM SUPPRESSIVE ART

Bernard J. Macatangay[1], Rajesh T. Gandhi[2], Deborah McMahon[1], Christina Lalama[3], Ronald Bosch[3], Joshua C. Cyktor[1], Christopher Hensel[4], Evelyn Hogg[5], Luann Borowski[1], Joseph J. Eron[6], John W. Mellors[1], Charles Rinaldo[1]
[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]Harvard University, Cambridge, MA, USA, [4]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [5]Social &Scientific Systems, Silver Spring, MD, USA, [6]University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: CD4+ T cells expressing the checkpoint inhibitor PD-1 may be enriched for HIV infection but the impact of ART on their frequency and association with measures of HIV persistence are uncertain.
Methods: We evaluated longitudinal changes in T cell PD-1 expression and their correlation with HIV persistence and immune activation in ACTG A5321 participants who initiated ART during chronic infection and had well-documented sustained viremia suppression. We gated on two T cell populations: positive for PD-1 (PD1+) vs high expression (PD1hi) since the latter subset is reported to have a different functional profile.
Results: Among the 97 participants, there were significant but modest decreases to 1 year of ART in %PD1+ (median 49.5% to 46%) and %PD1hi (median 0.7% to 0.4%) CD4+ T cells (p<0.001; signed rank); the relative reduction in CD4+PD1hi T cells was substantially greater than CD4+PD1+ T cells (median 43% vs 9%; p=0.01). %CD4+PD1+ T cells continued to decrease to year 4 and to 6-15 years on-ART while %CD4+PD1hi T cells only declined to year 4. Pre-ART %CD4+/CD8+PD1+ correlated strongly with frequencies on-ART (Spearman r=0.92-0.95), while correlations for PD1hi expression were not as strong (r=0.28-0.52). %CD4+PD1hi levels positively correlated with cell-associated HIV-1 DNA pre-ART (r=0.22) and at 1 (r=0.25) and 4 years (r=0.24) on-ART, but %CD4+PD1+ levels after ART initiation did not. Residual viremia, measured by single copy assay, ≥4 years on-ART did not correlate with PD1+/PD1hi populations. Similarly, no correlations were observed with cell-associated HIV-1 RNA. %CD4+PD1hi consistently correlated with CD4+ T cell activation (%HLA-DR+CD38+) at years 1 (r=0.40; p<0.001) and 4 (r=0.43; p<0.001) on-ART but not pre-ART. %CD8+PD1hi strongly correlated with %CD4+PD1hi at all timepoints (r=0.80-0.92) but did not consistently correlate with HIV persistence measures or T cell activation. %CD4+PD1+ did not correlate with T cell activation at any timepoint.
Conclusion: PD-1 expression on CD4+ or CD8+ T cells on-ART is most strongly associated with pre-ART expression indicating long-lasting effects despite HIV-1 suppression. Among T cells expressing PD-1, the CD4+PD1hi subset stabilized after initially declining on ART and was positively associated with HIV DNA levels and CD4+ T cell activation, whereas other CD4+PD1+ T-cells were not. Distinguishing CD4+ T cell subsets by levels of PD-1 expression appears to be important for targeting the HIV reservoir.



364 PROVIRAL LANDSCAPE IN HIV-1 POST-TREATMENT CONTROLLERS AND NON-CONTROLLERS

Radwa Sharaf[1], Guinevere Q. Lee[2], Xiaoming Sun[2], Evgenia Aga[3], Ronald Bosch[3], Rajesh T. Gandhi[4], Jeffrey Jacobson[5], Edward P. Acosta[6], Daniel R. Kuritzkes[1], Michael M. Lederman[7], Xu G. Yu[2], Mathias Lichterfeld[2], Jonathan Z. Li[1]
[1]Brigham and Women's Hospital, Boston, MA, USA, [2]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [3]Harvard University, Cambridge, MA, USA, [4]Massachusetts General Hospital, Boston, MA, USA, [5]Temple University, Philadelphia, PA, USA, [6]University of Alabama at Birmingham, Birmingham, AL, USA, [7]Case Western Reserve University, Cleveland, OH, USA

Background: HIV post-treatment controllers (PTCs) represent a natural model of sustained HIV remission, but these individuals are rare and little is known about their viral reservoir. We performed near-full length proviral sequencing to assess the proviral reservoir landscape of a cohort of PTCs and post-treatment non-controllers (NCs). The results were also used to assess the relationship between different proviral species, levels of intracellular HIV RNA expression and host immune responses.
Methods: PBMCs were obtained from the pre-treatment interruption (on-ART) time point for 10 PTCs (controlled for ≥24 weeks) and 15 NCs identified through ACTG. Near-full length proviral sequencing was performed by Illumina next-generation single-genome sequencing (NG-SGS). Unspliced CA-RNA levels were quantified by qPCR. T and NK cell phenotypes were assessed by flow cytometry, and T cell intracellular cytokine staining was performed on PBMCs stimulated with an HIV *gag* peptide pool.
Results: We obtained a total of 1193 proviral genomes. PTCs had approximately 6-fold lower levels of total proviral genomes (TPG, PTCs vs. NCs: median 1.9 vs. 11.2 copies/10^6 PBMCs, P<0.001) and intact proviral genomes (IPG, 0.1 vs. 0.6 copies/10^6 PBMCs, P=0.01). 80% of NCs vs. 0% of PTCs had TPG <5 copies/10^6 PBMCs (P<0.001). There were no significant differences between PTCs and NCs in the percent of proviruses that were intact, harboring deletions, or identical sequences detected more than once (i.e., clonally expanded). Amongst all participants, a median 97% of proviral genomes were defective, most of which harbored large deletions. CA-RNA correlated with levels of defective proviral genomes (DPG, Spearman *r*=0.51, P=0.02), but not with levels of IPG. Higher CD38+ NK cell percentages correlated with lower levels of DPG (*r*=-0.48, P=0.02), as were higher levels of HIV-specific CD4+ cells expressing IFN-γ (*r*=-0.59, P=0.01) and CD8+ cells expressing CD107 (*r*=-0.56, P=0.02).
Conclusion: Prior to treatment interruption, the median total proviral genomes in PTCs was 6-fold lower than in NCs, but the proportions of intact, defective and clonally expanded viral genomes were similar in both groups. The association of defective proviral genomes with levels of CA-RNA, NK activation, and HIV-specific T cell activity support the concept that defective HIV genomes lead to viral antigen production and interact with both the innate and adaptive immune responses.

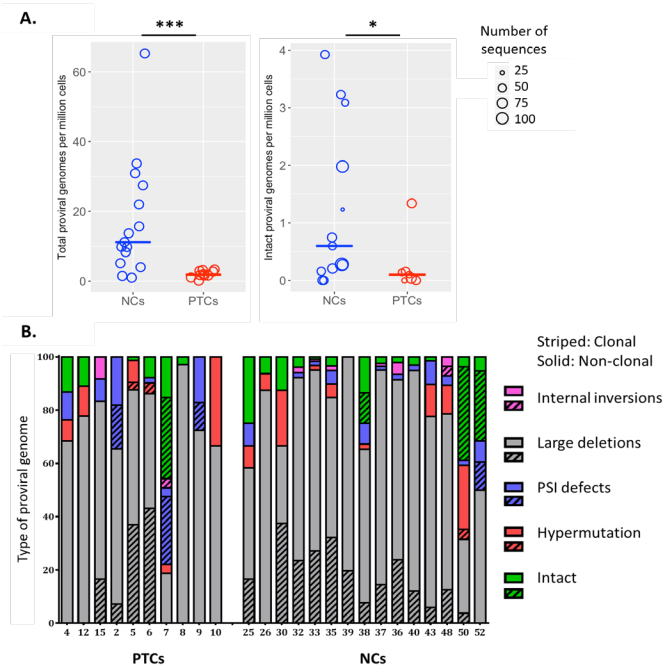


Figure. HIV proviral reservoir analysis of PTCs and NCs by next-generation single-genome sequencing. Comparison of total and intact proviral genome copies *(A)* and distribution of proviral species within each participant *(B)*.

365 HIV VIREMIA IS THE PRODUCT OF A SMALL FRACTION OF HIV INFECTED CELLS

Elizabeth M. Anderson[1], Shawn Hill[1], Jennifer Bell[2], Catherine A. Rehm[3], Sara Jones[2], Rob Gorelick[2], Mary F. Kearney[1], John M. Coffin[4], Frank Maldarelli[1]
[1]National Cancer Institute, Frederick, MD, USA, [2]Leidos Biomedical Research, Inc, Frederick, MD, USA, [3]NIAID, Bethesda, MD, USA, [4]Tufts University, Boston, MA, USA

Background: HIV persistence in replication competent reservoirs during antiretroviral therapy (ART) is a substantial obstacle to HIV cure. Understanding dynamics of HIV viremia and infected T cells is essential to characterizing these reservoirs. Upon initiating ART, plasma HIV RNA undergoes multiphasic decay kinetics reflecting half lives of infected cells. HIV infected cell numbers also decline during ART but kinetics of decay during first weeks of ART have not been well characterized. In particular, it is not known what proportion of infected cells contribute to viremia. To address this issue, we developed sensitive and accurate multiplexed droplet digital approaches (ddPCR) to quantify early HIV-1 decay kinetics.

Methods: HIV infected ART-naïve individuals (N=10) enrolled in a clinical trial of 4 drug ART (2 NRTI+NNRTI+PI) at the NIH Clinical Center, were frequently sampled prior to and throughout first and second phase decline of HIV viremia. Cell-associated HIV DNA from PBMCs obtained pre-ART, during first and second phase viral decay, and after viral suppression was quantified using ddPCR assays targeting HIV *gag*, LTR, and *tat/rev*; a host gene (*CCR5*) was quantified for cell counting. Plasma HIV RNA was measured (bDNA) concurrently. We analyzed the decay kinetics of HIV viremia and of cell-associated HIV DNA during first and second phase decay.

Results: All patients had successful suppression of HIV RNA to <50 cps/mL plasma by a median of 139.5 days on ART. Overall HIV DNA/1e6 CD4+ cells decreased for all 3 assays by an average of 4.5 fold from pre-therapy to viral suppression. Strikingly, while HIV RNA in the blood declined on average 96% after 6 days on therapy, HIV DNA declined an average of only 30% (mean 491 cps HIV DNA/ml; range 49-903 cps/ml) indicating that the majority of viremia is produced by a small fraction of HIV infected cells, and that each infected cell is responsible for a median of 104 cps HIV RNA in plasma (range 21.2-8999 cps/cell). During second phase decline, virus production declined to c. 2.7 cps/cell (range 0.04-13.4 cps/cell).

Conclusion: Prior to ART, plasma viremia is the product of only a small fraction of HIV-infected cells. After initiating ART, HIV reservoirs responsible for persistent viremia are relatively limited and exhibit substantial variation in virus production. Analysis of early HIV RNA and DNA decay kinetics will be useful in characterizing patient-specific differences in establishing HIV reservoirs.

366 THE GENETIC TRAITS OF FULL-LENGTH HIV SEQUENCED FROM MEMORY T CELL SUBSETS

Bethany A. Horsburgh[1], Bonnie Hiener[1], Eunok Lee[1], John-Sebastian Eden[2], Timothy E. Schlub[3], Susanne von Stockenstrom[4], Jeffery Milush[5], Teri Liegler[5], Elizabeth Sinclair[5], Rebecca Hoh[5], Rémi Fromentin[6], Nicolas Chomont[6], Steven G. Deeks[5], Frederick M. Hecht[5], Sarah Palmer[1]
[1]The Westmead Institute for Medical Research, Westmead, NSW, Australia, [2]The University of Sydney, Sydney, NSW, Australia, [3]University of Sydney, Camperdown, NSW, Australia, [4]Karolinska Institute, Stockholm, Sweden, [5]University of California San Francisco, San Francisco, CA, USA, [6]Centre de Research du Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada

Background: A thorough understanding of the distribution and genetic traits of replication-competent virus will be needed to design future HIV eradication therapies. To address this issue, we used the Full-Length Individual Proviral Sequencing (FLIPS) assay to examine the contribution of genetically identical and intact proviruses within memory CD4+ T cell subsets to the latent reservoir during prolonged ART.

Methods: Naïve, central (CM), transitional (TM) and effector (EM) memory CD4+ T cells, as well as CD45RA-HLA-DR+ and CD45RA-HLA-DR- CD4+ T cells were sorted from the peripheral blood of six participants who initiated ART during either acute or chronic infection (n=3 each). Genetic sequences of HIV proviruses from the cell subsets were obtained using the FLIPS assay. FLIPS uses LTR-specific primers to amplify HIV proviruses at limiting dilution followed by next-generation sequencing. Proviruses were characterized as defective (containing INDELs, stop codons or hypermutation) or intact. Expansions of identical sequences (EIS) were determined as ≥2 identical HIV DNA sequences.

Results: Of the 728 sequences isolated, only 5% were considered intact. Intact provirus was found in all cell subsets except the CM subset (0/125 isolated sequences intact). The proportion of intact provirus was different across the cell subsets (EM>TM>CM and HLA-DR+> HLA-DR-; p=0.001). The frequency of cells infected with intact proviruses was higher in HLA-DR+ memory T cells (48 vs <10 infected cells/million cells in HLA-DR+ vs all other subsets). Co-receptor usage was restricted, with 83% of intact proviruses being CCR5 tropic. Overall the percentage of intact and defective sequences contributing to an EIS was 34% (12/35) and 46% (319/693) respectively. In one participant 56 identical sequences contained a deletion in the packaging signal but were intact in the coding region. Despite this defect, the corresponding intracellular RNA sequence was detected.

Conclusion: Genetically intact and therefore likely replication-competent CCR5 tropic HIV is enriched in cells expressing HLA-DR and EM cells. This indicates that the latent HIV reservoir is established early and is maintained by T cell proliferation and differentiation. The lack of intact virus in CM cells suggests that the majority of rebound virus will not be derived from these cells. Defective proviruses can produce viral transcripts indicating that RNA quantification will lead to overestimating the genetically intact HIV reservoir.

367 PULMONARY MUCOSAL T CELLS AS POTENTIAL HIV RESERVOIRS DURING LONG-TERM ART

Syim Salahuddin[1], Omar Farnos[2], Ron Olivenstein[3], Aurelie Le Page[1], Amelie Pagliuzza[4], Christina de Castro[1], Jean Bourbeau[3], Petronela Ancuta[4], Bertrand Lebouché[1], Jean-Pierre Routy[1], Nicolas Chomont[4], Cecilia Costiniuk[1], Mohammad-Ali Jenabian[2]
[1]McGill University Health Centre Research Institute, Montreal, QC, Canada, [2]Université du Québec à Montréal, Montreal, QC, Canada, [3]McGill University Health Centre, Glen site, Montreal, QC, Canada, [4]Université de Montréal, Montreal, QC, Canada

Background: Cellular and anatomical HIV reservoirs remain the primary challenge towards viral eradication. The lungs are potential but relatively understudied anatomical reservoirs in the ART era. CCR6+ and CD32a+ CD4 T-cells as well as double negative (DN) CD4-CD8- T cells have been described as potential cellular reservoirs for HIV in the blood. Here, we assessed their frequency and distribution in the lungs vs the peripheral blood of HIV-infected adults under long-term suppressive ART.

Methods: Cells from bronchoalveolar lavage (BAL), obtained by bronchoscopy, and matched peripheral blood samples were collected from n=16 HIV+ individuals without respiratory symptoms and under long-term suppressive ART (undetectable plasma viral load and CD4 count higher than 350 cells/mm^3 for at least 3 years). T-cell subsets were characterized by flow cytometry, and total and integrated HIV DNA were assessed by ultrasensitive PCR. Paired t-test was used in statistical analyses.

Results: A greater frequency of HIV DNA was observed in the BAL cell pellets compared to blood (p=0.006). Higher frequencies of CCR6+ memory CD4+ T cells were observed within the lungs vs blood (p=0.003). Importantly, CD4 T-cells expressing the Fc receptor CD32a were highly enriched in the pulmonary cells vs blood (p=0.008). Interestingly, pulmonary CD32a+ CD4 T cells demonstrated higher levels of HLA-DR and CCR5 expression compared to blood. A substantial increase in both CD4-CD8α-CD8β- and CD4-CD8-TCRαβ-TCRγδ- DN T-cells (p<0.0001 and p=0.04) was observed in the lungs vs. blood. Pulmonary DN T-cells were characterized by higher levels of immune activation (HLA-DR+, p=0.02), lower levels of immune senescence (CD28-CD57+, p=0.01) and lower marker of recent thymus emigrants (CD31+, p=0.009). Moreover, memory CCR6+ CD4 T-cells and DN T cells exhibited higher expression of CD32a in the lungs compared to blood (p=0.06 and p=0.04).

Conclusion: In virally suppressed HIV+ adults, the lungs contain higher levels of HIV DNA and higher frequencies of various T cell subsets known as preferential HIV reservoirs including CCR6+ and CD32a+ CD4 T cells as well as activated DN T cells when compared to peripheral blood. This particular distribution of mucosal T cells could contribute to the preferential persistence of HIV reservoirs within the lungs.

368 THE BIRC5/OX40 PATHWAY MAINTAINS SURVIVAL OF HIV-1-INFECTED CD4 T CELLS

Hsiao-Hsuan Kuo[1], Rushdy Ahmad[2], Guinevere Q. Lee[1], Hsiao-Rong Chen[1], Matthew J. Szucs[2], Athe Tsibris[3], Eric Rosenberg[4], Steven Carr[2], Xu G. Yu[1], Mathias Lichterfeld[3]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Broad Institute of MIT and Harvard, Cambridge, MA, USA, [3]Brigham and Women's Hospital, Boston, MA, USA, [4]Massachusetts General Hospital, Boston, MA, USA

Background: Infection of CD4 T cells with HIV-1 can lead to cell death through a variety of mechanisms, however, this is counterintuitive to the observation that certain HIV-1-infected cells possess a remarkable long-term stability and can persist for decades in infected individuals treated with suppressive antiretroviral therapy (ART). The mechanisms that maintain such long-term survival of HIV-1-infected CD4 T cells are unknown at present, but may represent important targets for clinical strategies to reduce the viral reservoir.
Methods: CD4 T cells were ex-vivo infected with single or dual-reporter HIV-1, followed by protein expression profiling using comprehensive mass spectrometry and flow cytometry. Molecular profiles of viral reservoirs in sorted CD4 T cell subsets were analyzed using single-genome, near full-length next generation viral sequencing. Functional in vitro assays were performed to analyze effects of small molecule inhibitors of BIRC5 on HIV-1 reservoirs in in vitro and in vivo infected CD4 T cells.
Results: Proteomic analyses of HIV-1-infected CD4 T cells identified distinct signatures of cell survival in HIV-1-infected CD4 T cells that were governed by BIRC5, a member of the inhibitor of apoptosis protein family. BIRC5 and its upstream regulator OX40, a member of the TNF receptor superfamily, were upregulated in productively and latently infected CD4 T cells, and were functionally involved in maintaining their viability, specifically during times of transitioning from productive infection to viral latency. Moreover, OX40-expressing memory CD4 T cells sorted from ART-treated patients were strongly enriched for sequence-intact HIV-1, including clonally-expanded intact proviral sequences. Pharmaceutical inhibition of BIRC5 significantly decreased the frequency of productively and latently in vitro HIV-1-infected CD4 T cells, and diminished the number of patient-derived, in vivo infected CD4 T cells encoding for intact HIV-1 during ex-vivo culture.
Conclusion: Our data show that productive and latent HIV-1 infection of CD4 T cells can activate cellular survival programs directed by the BIRC5/OX40 pathway. In addition, BIRC5/OX40 seem to protect HIV-1-infected CD4 T cells during the vulnerable phase of clonal expansion, a process known to contribute to viral reservoir stabilization. Targeting BIRC5 may represent a promising strategy to reduce the pool of viral reservoir in clinical settings.

369 HIV-2 RESERVOIR DISTRIBUTION IN CD4 T CELLS RELATED TO CXCR6 AND TRIM-5 EXPRESSION

Assia Samri[1], Charlotte Charpentier[2], Mélanie Bertine[2], Mariama S. Diallo[1], Sophie Even[1], Veronique Morin[1], Anne Oudin[1], Gilles Collin[2], Sophie Matheron[2], Rodolphe Thiébaut[3], Rima Zoorob[1], Brigitte Autran[1], Francoise Brun-Vezinet[2]
[1]INSERM, Paris, France, [2]University Paris Diderot, Paris, France, [3]INSERM, Bordeaux, France

Background: HIV-2 infection is characterized by a low pathogenicity and a low virus production compared to HIV-1. We tested the hypothesis of a limited distribution of the HIV-2 reservoir among central-memory CD4 T cells, as in HLA-B*27/57 elite controllers or in models of non pathogenic SIV infection, and analyzed the mechanisms involved.
Methods: 14 ARV-naïve patients with long term non-progressive infection from the ANRS-CO5 HIV-2 cohort were prospectively included. Plasma viral load was <40 c/mL in 12/14 and above 1 c/mL in 4/12 [IQR=1-12]. HIV-2 inducibility was tested by CD8neg T cells culture with anti-CD3+CD28+IL-2+IL-7 for 30 days. Subpopulations were sorted in CD3-CD4+ monocytes, resting naïve (N), central (C), transitional (T) and effector-memory (EM) CD4+ T cells. Cell-associated HIV-2 total DNA was quantified using a real-time PCR assay (LOD=3 c/PCR, LOQ=6 c/PCR). We analyzed the surface markers and the microfluidic transcriptomic profile of sorted subsets related to different pathways (restriction factors, co-receptors, inflammation, chemokine….).
Results: Median total HIV-2 DNA was 1.94 $\log_{10}$ c/106 PBMC [IQR=1.53-2.13]. Virus was inducible in CD8neg T cells from 3 patients. In sorted CD4+ subsets, HIV-2 DNA was undetectable in monocytes but detectable in TN, TCM, TTM and TEM from 3, 12, 9 and 10 patients, respectively. HIV-2 DNA was above the quantification threshold in TTM from only 4 patients (median=2.25 [IQR: 1.99-2.94] $\log_{10}$ c/106 cells) while in TCM from only 1 patient (1.75 $\log_{10}$ c/106 cells). The HIV-2 DNA levels in TTM were positively correlated to those in PBMC ($p=0.008$; $r=0.67$). There was no decrease in CCR5 cell surface expression both ex vivo and in culture. Transcriptome analysis revealed an increased expression of CXCR6 and IL22 genes in TTM compared to TCM ($p= 0.023$ and $p= 0.037$) contrasting with increased Trim5 and TP53 transcripts in TCM compared to TTM ($p= 0.012$ and $p= 0.024$).
Conclusion: Overall, these low circulating HIV-2 reservoirs were mainly distributed in TTM, confirming the hypothesis of a limited reservoir in TCM and supporting the concept of the relative protection of TCM cells as an attribute of low pathogenicity models of HIV/SIV infection. Furthermore, the increased expression of CXCR6, described as an HIV-2 alternative co-receptor, in TTM and the increased expression of Trim5, a restriction factor limiting SIV infection, in TCM could explain the preferential distribution of HIV-2 reservoirs in TTM from these non-progressors.

370 EFFECTOR MEMORY T CELLS CONTRIBUTE TO X4 MONOTYPIC RESIDUAL PLASMA VIRUS PRODUCTION

Hadega Aamer[1], Sherry McLaughlin[1], Michael Dapp[2], Sheila Styrchak[1], Ana Gervassi[3], Janine Maenza[2], Ann Collier[2], James Mullins[2], Lisa Frenkel[1]
[1]Seattle Children's Research Institute, Seattle, WA, USA, [2]University of Washington, Seattle, WA, USA, [3]Center for Infectious Disease Research, Seattle, WA, USA

Background: Although antiretroviral therapy (ART) can limit HIV replication to below the limit of detection, individuals with suppressed replication experience residual viremia. Residual virus is comprised predominately of monotypic viruses, but the cellular origin of this residual plasma virus and whether specific viral variants persist over time on ART is unknown. We aimed to: 1) characterize the dynamics of residual plasma viremia variants over time in chronically infected, long-term suppressed individuals; and 2) decipher the cellular origin of the residual plasma virus by evaluating proviral integration sites (IS) in immune cell subsets. We hypothesized that infected proliferating cells that persist during prolonged ART will consist primarily of effector memory T (Tem) cells and that these cells contribute to the monotypic residual viremia.
Methods: Plasma viral RNA from several time points of 1 chronically infected subject with an undetectable viral load was subjected to single genome amplification of the C2V5 env region. Sequences were assembled into a maximum likelihood phylogenetic tree. Leukapheresis specimens collected after 6yrs of suppressive ART were cell-sorted into naïve, central memory, and Tem cells. HIV IS were identified from sorted cells using multiple displacement amplification-integration site looping assay. The proviral C2V5 env sequence linked with IS were used to compare to plasma C2V5 sequences to identify the potential cellular origin of plasma virus during ART.
Results: Preliminary findings reveal residual plasma viremia was dominated by a large cluster of monotypic, CXCR4-tropic virions that persisted for at least 3 years of ART. Upon IS analysis of sorted cells, a link was found between this monotypic cluster and a provirus in Tem cells integrated in MLLT3. This gene is responsible for transcriptional elongation in the absence of HIV Tat. HIV integration and dysregulation of MLLT3 may enable the low-level production of residual monotypic virions detected in plasma over time on ART.
Conclusion: We found peripheral Tem may contribute to monotypic plasma virus during ART, with the provirus persisting for at least 3yrs. Ongoing studies will examine the genome integrity of this provirus. These findings reveal the potential contribution of peripheral Tem in contributing to HIV persistence during successful ART. Further characterization of integration sites in immune cells will elucidate the potential biological pathways manipulated by HIV to allow persistence during ART.

371 TESTICULAR IMMUNE PRIVILEGE AND HIV-1 PERSISTENCE

Rosalie Ponte[1], Franck P. Dupuy[1], Zabrina Brumme[2], Natalie Kinloch[2], Art Poon[3], Pierre Brassard[4], Maud Bélanger[4], Vikram Mehraj[1], Reina Bendayan[5], Mohammad-Ali Jenabian[6], Jean-Pierre Routy[1]
[1]McGill University Health Centre Research Institute, Montreal, QC, Canada, [2]Simon Fraser University, Burnaby, BC, Canada, [3]Western University, London, ON, Canada, [4]GRS Montreal, Montreal, QC, Canada, [5]University of Toronto, Toronto, ON, Canada, [6]Université du Québec à Montréal, Montreal, QC, Canada

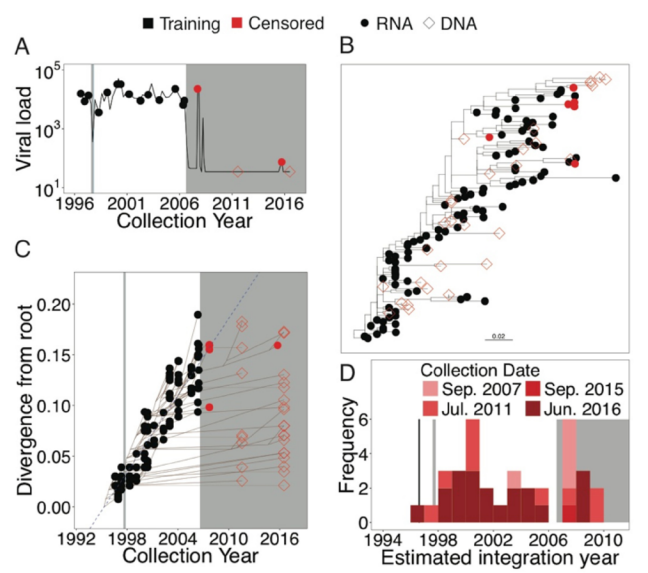
Background: The identification of cellular and anatomic HIV-1 reservoirs constitutes a priority towards a cure. In testis, we demonstrated that the immune privilege is orchestrated by myeloid cells, in part through the production of IDO and induction of suppressive CD39+ Treg. Herein, we hypothesized that the suppressive testicular environment favors local HIV persistence and compartmentalization by promoting the exhaustion/anergy of effector T cells. Therefore, we assessed the expression of T cell exhaustion markers such as PD-1/TIGIT/LAG-3, which have been correlated with HIV reservoir size in the blood, along with their respective ligands PD-L1/CD155/HLA-DR and activation/maturation markers in macrophages (MΦ) and dendritic cells (DC).

Methods: Matched PBMC and testis samples were collected from 3 ART-treated adults and 7 uninfected donors undergoing sex reassignment surgery. The expression of PD-1/TIGIT/LAG-3 in CD4 and CD8 T cells and PD-L1/CD155/HLA-DR/CD80/CD86 in Mϕ/monocytes from testis and PBMC was assessed by flow cytometry. HIV genetic compartmentalization was assessed in 3 donors by applying the Wright's measure of population subdivision (Fst) test to HIV proviral Nef sequences characterized via single-genome amplification.
Results: Among CD45+ immune cells, the frequency of CD4 and CD8 T cells expressing PD-1 or TIGIT was remarkably higher in the testis than in PBMC (93.6% ±6.2 vs. 31.6 ±9.1, p<0.0001 and 98.3% ±6.4 vs. 36.4 ±11.8 p<0.0001), (28.2 ±4.5, vs. 13.7 ±9.3, p=0.0004 and 44.2 ±8.3 vs. 16.1 ±12.1, p<0.0001), respectively. LAG-3 expression was not different between testis and PBMC. Among CD68+CD163+ testicular Mϕ, a proportion of 73.7% (±23.9) expressed PD-L1 and 42.9% (±35.2) expressed CD155, and 92.8% (±39.1) were CD86+ while 10.1% (±9.6) were CD80+. A distinct subset of CD68+CD163- testicular Mϕ with HLA-DR-/lo expression was identified. Both Mϕ and myeloid DC displayed high levels of HLA-DR in testis compared to PBMC (p=0.004). No significant evidence for genetic compartmentalization between testis and PBMC was observed in any studied donor. In one case, multiple identical sequences were isolated from right, left testis and PBMC, consistent with migration of clonally-expanded cell populations between these sites.
Conclusion: For the first time, we identified PD-1/PD-L1 and TIGIT/CD155 pathways as contributors of the human testicular immune privilege. Our results suggest that the testis does not represent a distinct viral compartment in ART-treated persons.

372 RECONSTRUCTING INTEGRATION DATES OF LATENT HIV SEQUENCES WITHIN-HOST

Bradley R. Jones[1], Natalie Kinloch[2], Joshua J. Horacsek[2], Bruce Ganase[1], Marianne Harris[1], P. Richard Harrigan[1], R. Brad Jones[3], Mark Brockman[2], Jeffrey Joy[1], Art Poon[4], Zabrina Brumme[2]
[1]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, [2]Simon Fraser University, Burnaby, BC, Canada, [3]The George Washington University, Washington, DC, USA, [4]University of Western Ontario, London, ON, Canada

Background: Given the continuous nature of within-host HIV evolution and reservoir establishment, and the long-lived nature of latently-infected cells, the reservoir in chronic infection should comprise a genetically heterogenous archive of within-host HIV evolution. Heterogeneity in reservoir age and genetic makeup could complicate immune-based HIV elimination strategies but our understanding of these parameters remains limited, in part due to a lack of methods to infer latent HIV sequence ages. We developed a phylogenetic method to reconstruct HIV integration dates within-host, and applied it to date putative latent HIV sequences in persons with long-term viremia suppression on cART.
Methods: The method involves inference and optimal rooting of a maximum-likelihood phylogeny from longitudinal within-host plasma HIV RNA and putative latent sequences, followed by calibration of a linear model relating root-to-tip distances of plasma HIV RNA sequences to their sampling dates. The model is then used to convert root-to-tip distances of putative latent lineages to their establishment (integration) dates. After validating the method on simulated and published HIV sequences, we used it to reconstruct integration dates of putative reservoir sequences in two individuals with long-term viremia suppression sampled in-depth over a ~20 year period. Dated sequences included HIV isolated directly from PBMC after >10 years on suppressive cART and from low-level viremia blips on cART (presumably representing in vivo HIV release from the reservoir). All sequences were characterized by single-genome amplification.
Results: For both individuals, putative reservoir sequences interspersed throughout within-host phylogenies and exhibited comparable overall diversity to pre-cART plasma RNA sequences sampled over a 10-year period. Historic within-host genetic bottleneck events were also recorded in the reservoir. Inferred proviral integration dates were consistent with the reservoir harboring both ancestral and more recent lineages, with the oldest sequence dating to 20 years prior to sampling. Sensitivity analyses confirmed that linear models can be reliably calibrated from as few as two timepoints, and that the method is robust to rooting method, thus broadening its applicability.
Conclusion: Our method for reservoir dating provides a novel and potentially powerful addition to the HIV persistence research toolkit and reveals a genetically heterogeneous reservoir that recapitulates HIV's within-host evolutionary history.



Reconstruction of within-host latent sequence ages. A) Participant clinical history and sampling timeline. Black points denote sequences used to train the linear model ("training data") and red points denote sequences within, or presumably recently released from, the latent reservoir, whose integration dates we wish to infer ("censored data"). Grey shading denotes cART. B) Optimally-rooted maximum likelihood phylogeny inferred from within-host sequence data. C) Linear model (dotted blue line) relating divergence from the tree root vs. sampling time for training data only, used to infer integration dates of censored sequences. Superimposed light brown lines trace the phylogenetic tree structure. D) Inferred integration dates of censored HIV sequences. The vertical black line denotes the first plasma sampling. The oldest HIV DNA sequence sampled in 2016 is inferred to have integrated 20 years prior.

373 IDENTIFICATION OF MACROPHAGE RESERVOIRS THROUGH TROPISM OF HIV-1 ENVELOPES

Viviane Machado[1], Thaissa Alvarado[1], Mario Stevenson[1], Labelle Barrios[1], Aubrey Morales[1], Mark Sharkey[1], Marco Salemi[2], Carla Mavian[2], Timothy J. Henrich[3]
[1]University of Miami, Miami, FL, USA, [2]University of Florida, Gainesville, FL, USA, [3]University of California San Francisco, San Francisco, CA, USA

Background: Despite advances in antiretroviral treatment (ART), eradication of HIV-1 is still not possible due to viral persistence in cell reservoirs. Macrophages express significantly low levels of the CD4 receptor, yet they are still infected. HIV-1 replicates in tissues that are protected from the effects of ART, including resident tissue macrophages and microglia cells in the CNS, facilitating the presence of persistent viral reservoirs. Since these reservoirs are not eliminated during ART, we hypothesize that macrophages may be a source for HIV-1 reservoir in rebound viremia in individuals undergoing analytical treatment interruption (ATI).
Methods: 71, 97 and 122 HIV-1 full-length envelopes were isolated by single genome amplification from three individuals at rebound plasma viremia followed ATI. To generate infectious recombinant viruses, env sequences were cloned into an infectious HIV-1 backbone, followed by transfection of HEK 293T. Monocyte-derived macrophages were infected with Env-recombinant viruses, and fusogenicity was assessed by a FRET-mediated assay. Replication capacity was monitored for 14 days by reverse transcriptase activity. Phylogenetic analysis was performed to evaluate evolutionary relationships existing among these envelopes.
Results: We found that a small population of Env-recombinant viruses was able to fuse efficiently with macrophages. Of the viruses that fused with macrophages, we identified Env-recombinant viruses that were replication competent, some of which were comparable to the level of the macrophage tropic strains ADA and YU2. Phylogenetic analysis showed the presence of several distinct HIV-1 subpopulations. The relatively low diversity within each clade suggests recent diversification from the common ancestor of each clade. This suggests that several HIV-1 subpopulations persisted in the patient in distinct viral reservoirs that were re-activated during rebound.

Conclusion: The main determinant for macrophage tropism is the HIV-1 envelope. Our findings demonstrate that recombinant viruses containing envelopes isolated at rebound after ATI are able to fuse and spread infection to macrophages. Phylogenetic relationships indicate that from the beginning of rebound to sampling there was not enough time for macrophage tropic variants to evolve from T-tropic ones, suggesting that M-tropic variants may constitute part of an independent HIV-1 reservoir.

374LB HEMATOPOIETIC STEM AND PROGENITOR CELLS ARE A UNIQUE FUNCTIONAL HIV RESERVOIR

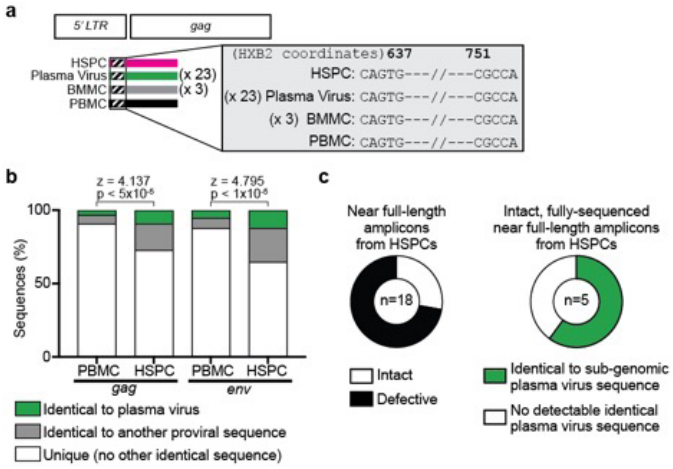
Thomas D. Zaikos, Valeri Terry, Nadia T. Sebastian Kettinger, Andrew J. Neevel, Ryan Yucha, Kathleen L. Collins
University of Michigan, Ann Arbor, MI, USA

Background: Long-lived reservoirs of HIV are a major barrier to cure. Resting memory CD4+ T cells are the best-characterized and largest reservoir of persistent HIV. However, non-T cell reservoirs have also been described. Hematopoietic stem and progenitor cells (HSPCs) have the capacity for life-long survival, self-renewal, and are susceptible to HIV infection. Here, we investigate the contribution of HIV-infected HSPCs to the persistent viral reservoir in 43 optimally-treated, HIV-infected people.

Methods: Nucleic acid was isolated from peripheral blood mononuclear cells (PBMCs), bone marrow-derived HSPCs, HSPC-depleted bone marrow mononuclear cells (BMMCs), and residual plasma virus (rPV) from treated HIV-infected people with undetectable viral loads (<50 copies/mL) for at least 6 months. Single-genome PCR products were directly sequenced to compare the genetic relatedness of HIV from each tissue source.

Results: We obtained HIV sequences from HSPCs of 25 donors and amplified rPV from all but one. Interestingly, proviruses in HSPCs from 8 donors were identical to rPV across the amplified regions. One donor harbored a provirus lacking the primer binding site within the 5′ LTR. This signature deletion was recovered from HSPCs, BMMCs, PBMCs, and rPV (Fig. a). As this defect is predicted to render HIV non-infectious but capable of viral outgrowth, these data support the conclusion that HSPCs can harbor and propagate HIV genomes to other cell types by cellular proliferation and differentiation. Consistent with this, HSPC-derived proviral genomes were more likely than PBMC-derived sequences to exactly match other proviral genomes (27% vs. 9%; Fig. b). In addition, HSPC-derived sequences were 3-fold more likely to be identical to rPV amplicons than those isolated from PBMCs (Fig. b). Remarkably, we also evaluated 18 HSPC-derived near full-length HIV proviral sequences, of which 5 (28%) contained intact open reading frames and cis elements (Fig. c), a much higher proportion than the ~2-5% published for T cells. Moreover, of these 5 intact, near full-length genomes, 3 (60%) were identical to rPV sub-genomic amplicons (Fig. c).

Conclusion: These results provide evidence that HIV-infected HSPCs form a small, but functionally significant reservoir of persistent HIV in infected people. Compared to sequences from other cellular sources, HSPC-associated HIV proviral genomes were more frequently intact and more frequently matched rPV, indicating that they form a unique population with distinct characteristics.



375 SIV PROVIRAL LANDSCAPE DIFFERS FROM THAT OF HIV-1 AND SHOWS GROSS HYPERMUTATION

Alexandra J. Murray[1], Katherine Bruner[1], Mithra R. Kumar[1], Andrew Timmons[1], Po-Ting Liu[2], Janice E. Clements[1], Dan Barouch[2], Janet Siliciano[1], Robert Siliciano[1]
[1]Johns Hopkins Hospital, Baltimore, MD, USA, [2]Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: HIV-1 establishes latency in a small pool of resting memory CD4+ T cells that represent the major barrier to cure. Various cure strategies are being tested in SIV-infected rhesus macaques as a model for HIV-1 infection. While the proviral genomic landscape has been characterized in HIV-1-infected patients, little is known about the proviruses persisting in SIV-infected macaques.

Methods: We developed an unbiased, single-genome-amplification method to capture both intact and defective proviral genomes from CD4+ T cells isolated from 7 long-term chronically SIV-infected ART-suppressed rhesus macaques. PCR primers were designed to amplify near-full-length proviral genomes. PCRs were set up at a limiting dilution, with one or fewer proviruses per well. Reactions were visualized on agarose gels and resulting bands were directly sequenced using either Sanger or Illumina platforms.

Results: At least 75% of proviruses were defective. Strikingly, over half of these proviruses showed gross hypermutation, including a subset that also contained internal deletions. Proviruses containing small, internal deletions at the 3′ end of the genome were also frequently detected. These deletions ranged in size and affected the env, tat, rev, and nef genes, while a distinct subset contained much larger deletions (>6 kb), encompassing most of the genome. In contrast to what was seen in CD4+ T cells isolated from HIV-1-infected patients on ART, a significantly larger proportion of proviruses had intact genomes. These findings differ from the proviral landscape of HIV-1-infected individuals who began ART during chronic infection, in whom 80% of proviruses had internal deletions, 7% were hypermutated, and 8% had both hypermutations and deletions.

Conclusion: The proviral landscape in these SIV-infected macaques is strikingly different than that in HIV-1-infected CD4+ T cells. A marked majority of SIV proviruses were grossly hypermutated. The pattern of hypermutation differs from HIV-1 proviruses in its severity, both across and within proviral genomes. Additionally, far more intact proviruses were detected in SIV-infected, ART-suppressed macaques than in HIV-infected, ART-suppressed patients. Other populations of SIV-infected monkeys will need to be studied, as these major differences between the HIV-1 and SIV pools of latent proviruses have implications for NHP models of HIV latency and treatment.

376 IL-10 SIGNALING IS A KEY MECHANISM OF SIV PERSISTENCE IN ART-TREATED RHESUS MACAQUES

Justin L. Harper[1], **Maria Pino**[1], Luca Micci[1], Susan P. Ribeiro[2], Claire Deleage[3], Hong Wang[1], Colin T. King[1], Daniel Gorman[4], Jacob D. Estes[3], Rafick-Pierre Sekaly[2], Mirko Paiardini[1]
[1]Yerkes National Primate Research Center, Atlanta, GA, USA, [2]Case Western Reserve University, Cleveland, OH, USA, [3]Leidos Biomedical Research, Inc, Frederick, MD, USA, [4]Merck & Co, Inc, Palo Alto, CA, USA

Background: The mechanisms regulating the establishment/maintenance of HIV reservoirs are still to be determined, thus impeding the design of strategies limiting HIV persistence. Interleukin (IL)-10 is a key component of the host anti-inflammatory activities triggered by pathogen induced pro-inflammatory responses. IL-10 signaling inhibits the production of Th1 cytokines and stimulates the production of Th2 cytokines; upregulates the expression of co-inhibitory receptors such as PD-1 and CTLA-4; reduces antigen presentation and increases T cell anergy. As a result of these anti-inflammatory activities, we hypothesized that IL-10 can negatively impact on T cell function, lead to a status of immunosenescence, and favor HIV persistence.

Methods: 15 RMs were infected with SIVmac239 and started on ART (tenofovir, emtricitabine, raltegravir, darunavir, and ritonavir) at day 58 post-infection (p.i.). ART was maintained for 7 months. Blood (PB), lymph node (LN), and rectal biopsy (RB) were collected longitudinally for flow cytometric and DNAscope analyses. Cell-associated SIV DNA was quantified in CD4 T cell subsets, including Tfh.

Results: Plasma and LN levels of IL-10 increased upon SIV infection ($p=0.0001$ as compared to pre infection) and did not fully normalize with ART. Plasma IL-10 at pre-ART correlate with markers of disease progression such as plasma viremia ($p=0.0016$); the depletion of CD4 T cells in PB ($p=0.0003$) and RB ($p=0.0422$); and plasma IP-10 ($p=0.0001$). Additionally, plasma IL-10 at pre-ART correlates

in LN with the percentage of Tfh cells proliferating (Ki-67+ ; p=0.0002) or harboring SIV-DNA (p=0.0256). We observed a selective enrichment during ART of SIV-DNA+ cells being IL-10+ in LN within the BCF (>85%; p=0.0095) as compared to untreated RMs, with the SIV-DNA+ IL-10+ cells being remarkably more stable between the pre- and on-ART time points than their IL-10 negative counterpart. Furthermore, plasma IL-10 at pre-ART predicts several key parameters of residual disease after 7 months of suppressive ART: CD4 T cell counts in PB (p=0.0305), %Ki-67+ CD4 T cells in PB (p=0.0163), %Tfh cells in LN (p=0.0002), SIV-DNA content in PB CD4 T cells (p=0.0218) and in RB (p=0.0383).

Conclusion: Plasma and LN content of IL-10, which is induced by SIV infection and not fully normalized with ART, critically contributes to SIV persistence by promoting maintenance of SIV-DNA+ cells, including TFH. Modulation of IL-10 represents a novel therapeutic avenue towards an HIV cure.

377 NOVEL SHIVS ENCODING TRANSMITTED/FOUNDER ENVS FOR LATENCY AND CURE RESEARCH

Anya Bauer[1], Fang-Hua Lee[1], Hui Li[1], Ronald Veazey[2], Meagan Watkins[2], George Shaw[1], Katharine J. Bar[1]

[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Tulane National Primate Research Center, Covington, LA, USA

Background: A novel, robust simian-human immunodeficiency virus (SHIV)-macaque model of HIV-1 latency is critical to investigate eradicative and suppressive strategies that engage Env. We have developed a novel strategy to generate designer SHIVs encoding native TF (transmitted/founder) or primary Envs with tier 2 neutralization that consistently confer productive infection, high peak viremia, and desirable early viral kinetics. Here, we evaluate two promising TF SHIVs, SHIV.D.191859 and SHIV.C.CH848, which encode TF subtype D and C HIV-1 Envs, respectively, for their viral kinetics and persistence during suppressive combination antiretroviral therapy (cART) and treatment interruption in rhesus macaques (RM).

Methods: 12 Indian RM were intravenously or mucosally inoculated with SHIV.D.191859 and followed longitudinally. A second cohort of 8 RM were intravenously inoculated with SHIV.C.CH848. Viral kinetics through the establishment of peak and setpoint viremia, 24 weeks of cART, and treatment interruption were assessed via plasma RT-PCR. Single genome sequencing of plasma virus was used to characterize the diversity of rebounding viruses.

Results: Inoculation of 12 RM with SHIV.D.191859 led to productive infection with peak viral loads between 10^5-10^8 copies/ml. In 11 of 12 animals, viremia was maintained for at least 6 months. At between 6 and 18 months of infection, 4 RM with high setpoint viremia (viral load of 10^3-10^7 copies/mL) were placed on cART for 24 weeks. Viral suppression was rapidly achieved and durably maintained. Viral rebound between day 7 and 17 was observed in all four rhesus macaques upon cessation of ART. Sequencing of rebound plasma vRNA revealed multiple genetically distinct virus populations at or near first detectable rebound in all four animals. Inoculation of 8 RM with SHIV.C.CH848 produced desirable viral kinetics with peak viremia of 10^7-10^8 and set point viremia between 10^3-10^5 copies/ml. After 16 weeks of infection, 4 RM were placed on cART and viral suppression was rapidly achieved and maintained for 24 weeks. Viral rebound occurred at day 12-29 after treatment interruption. In both SHIV.D and SHIV.C infected RM, time to rebound correlated with setpoint viremia.

Conclusion: The antigenic properties and viral kinetics before, during, and upon interruption of cART make SHIV.D.191859 and SHIV.C.CH848 promising reagents for a SHIV model of HIV-1 latency and cure.

378 CLONES WITH INTACT PROVIRUSES ARE FOUND IN MULTIPLE CD4+ T CELL MATURATION SUBSETS

Andrew Musick[1], Eli A. Boritz[2], Jonathan Spindler[1], Michael J. Bale[1], Michele Sobolewski[3], Wei Shao[4], Stephen H. Hughes[1], John M. Coffin[5], John W. Mellors[3], Frank Maldarelli[1], Mary F. Kearney[1]

[1]NIH, Frederick, MD, USA, [2]NIH, Bethesda, MD, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA, [4]Leidos Biomedical Research, Inc, Frederick, MD, USA, [5]Tufts University, Boston, MA, USA

Background: An important mechanism for maintaining the HIV reservoir is the proliferation of cells that were infected with replication-competent (intact) proviruses prior to ART initiation. It is not known in which CD4+ T cell subsets clonally-expanded, intact proviruses persist. To address this question, we assayed naïve, central and transitional memory (CTM), and effector memory CD4+ T cell subsets (EM) for sequence matches to expanded clones with intact proviruses, and compared their distribution to those with defective proviruses, and to those with proviruses without obvious defects but that did not produce replicating virus in VOA (non-induced).

Methods: Using p6-PR-RT single genome sequencing (SGS), we identified 84 different WT proviruses that were likely in clonally expanded cells (i.e. multiple identical sequences detected) in PBMC from "Patient 1" in Simonetti, et al. (PNAS 2016). At this same timepoint, the plasma contained a mixture of diverse, replicating drug-resistant (DR) variants and a population of identical WT virus produced by a highly-expanded clone. PBMC from the same sample were sorted into naïve, CTM, and EM subsets and SGS was performed to identify sequence matches to proviruses in probable clonally-expanded cells.

Results: Three of the 84 probable clones matched replicating viral sequences in VOA, 10 were defective (contained stop codons), and 71 were non-induced. About 45,500 naïve, 60,000 CTM and 57,000 EM cells were analyzed and 22, 48, and 37 SGS were obtained, respectively. A test for panmixia suggested that each cell subset had a different proviral population (probability of panmixia <10-6). DR proviruses were found primarily in naive cells (14/20 in naïve, 5/20 in CTM, 1/20 in EM (p=0.01)). Sequences matching the intact AMBI-1 provirus, the source of the WT clonal plasma virus in the patient, were found primarily in EM (14/37 proviruses) and, to a lesser degree, in CTM (3/48) (p=6x10-4). A second sequence matching infectious provirus was found only in a single naïve T cell, and a third only in two EM cells. Sequences matching defective and non-inducible proviruses were found in each of the three T cell subsets.

Conclusion: We identified intact proviruses that appear to have been present in clonally-expanded cells in each of the CD4+ T cell maturation subsets. This study suggests that the HIV reservoir resides in multiple T-cell subsets, all of which will need to be targeted to eradicate HIV infection.

379 MULTI-COMPARTMENT DISSEMINATION OF GENOME-INTACT HIV-1 RESERVOIR CLONES

Guinevere Q. Lee[1], Riddhima Banga[2], Matthias Cavassini[3], Jean-Marc Corpataux[3], Xu G. Yu[1], Giuseppe Pantaleo[3], Matthieu Perreau[3], Mathias Lichterfeld[4]

[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]University of Lausanne, Lausanne, Switzerland, [3]Lausanne University Hospital, Lausanne, Switzerland, [4]Brigham and Women's Hospital, Boston, MA, USA

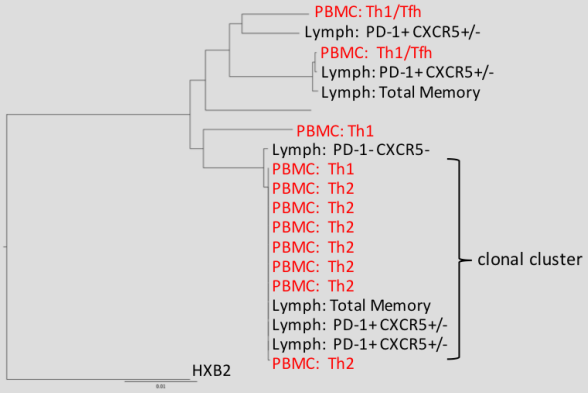
Background: Latently infected CD4 T cells provide a highly durable reservoir for HIV-1, but the ability to support viral persistence appears to differ considerably among different CD4 T cell populations. Here, we used single-template near full-length viral deep sequencing to map proviral sequences across nine different CD4 T cell subsets from blood and lymph nodes (LN).

Methods: PBMC from three HIV-infected patients treated with suppressive ART were sorted into the following CD3+ CD4+ T cell subsets: CD45RA- cells (total memory), CXCR3+CXCR5- (Th1-enriched), CCR4+CCR6- (Th2-enriched), CCR4+CCR6+ (Th17-enriched), CXCR3-CXCR5+ (circulating Tfh-like cells) and CXCR3+CXCR5+ (enriched for Th1/Tfh-like cells). Simultaneously, the following CD3+ CD4+ subsets were isolated from autologous LN: CD45RA- (total memory), PD-1- CXCR5-, PD-1- CXCR5+, PD-1+ CXCR5+/- (enriched for Tfh), and CD45RA+ naïve T cells. Total DNA was extracted, diluted for single-template full-HIV-1 genome PCR, and Illumina deep-sequenced. HIV sequences were classified into "genome-intact" or "defective" using established criteria.

Results: A total of 312 HIV proviral sequences were detected from 3 patients. Frequencies of genome-intact sequences relative to defective copies did not notably differ between blood (17/135, 12.6%) and lymph nodes (20/177, 11.3%) (p=0.73, Fisher's). Except for lymph node naïve cells, genome-intact HIV DNA was detected in all analyzed CD4 T cell subsets from both blood and lymph nodes. In LN, proportions of intact proviruses were highest in CXCR5+ or PD-1+ CD4 T cells, while in blood, distribution of intact proviral sequences was more variable. Proviral sequences from blood and LN phylogenetically intermingled without obvious compartmentalization (Slatkin-Maddison test p=1, 0.2, 0.1). Notably, we observed a cluster of clonally-expanded intact provirus derived from cells with discrete functional polarization from blood and LN (Figure1). Clonally-expanded defective HIV-1 sequences with mixed contributions from blood and lymph nodes were also observed.

Conclusion: This study suggests dynamic interchanges between "genome-intact" viral reservoir cell populations from blood and lymphoid tissues. Clusters of clonally-expanded intact proviruses encompassing sequences from cells with distinct anatomic localization and functional polarization suggest infection of common precursor cells as a driving force for viral reservoir stabilization.

Figure 1. In a patient on suppressive ART for 19 years, a 10-member genome-intact HIV proviral clonal cluster was detected across PBMC- and lymph node-derived CD4 T cell subsets.



380 WITHDRAWN

381 HIV INTEGRATES IN GENES REGULATING CELL CYCLE, DNA DAMAGE, & VIRAL TRANSPORT

Sulggi Lee[1], Kevin G. Haworth[2], Cassandra Thanh[1], Lauren E. Schefter[2], Zachary K. Norgaard[2], Christopher D. Pilcher[1], Frederick M. Hecht[1], Jeffrey N. Martin[1], Timothy J. Henrich[1], Steven G. Deeks[1], Hans-Peter Kiem[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]University of Washington, Seattle, WA, USA

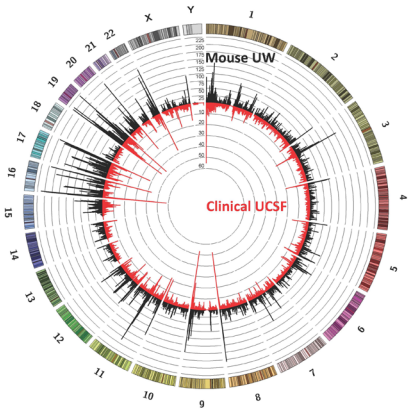
Background: HIV integration is a key step in the viral replication cycle. Prior studies disagree on whether HIV preferentially integrates in oncogenes leading to clonal proliferation. We performed HIV integration site analysis from HIV+ participants and a humanized mouse model.

Methods: HIV+ adults on effective antiretroviral therapy (ART) were sampled from the UCSF SCOPE cohort. We extracted human DNA from PBMCs, enriched for CD4+ T cells, and quantified cell-associated HIV total DNA and unspliced RNA by qPCR. HIV integration sites were identified using nested PCR (Illumina MiSeq) with primers for HIV genome and linker sequences. A novel humanized mouse model challenged with a CCR5-tropic virus allowed in vivo comparisons of HIV integration. Sequences were aligned using UCSC Genome BLAT (hg38 assembly). Gene set enrichment analyses were performed using COSMIC Cancer Gene and Gene Ontology Consortium databases.

Results: Twenty-six (96% male) participants were included with median age of 46 years, timing of ART from HIV infection of 2.6 years, and ART suppression of 5 years. Among a total of 31,890 detected integration sites, there was a high degree of similarity in integration site loci (7,504 sites) and frequency between clinical and humanized mouse samples (Figure 1). Only 4.5% of integrations occurred within oncogenes. Integrations occurred in genes involved in cell cycle, DNA damage, membrane and nuclear envelope disassembly, viral transport, and DNA unwinding (all >2.26-fold enrichment, false discovery-adjusted P<1.21x10 2). The most frequently observed gene, NPLOC4, regulates spindle disassembly during mitosis, negatively regulates type I interferon to promote degradation of RIG-I, an important antiviral factor. The frequency of unique integration sites was inversely correlated with $\log_{10}$copies of unspliced HIV RNA (Spearman R=-0.52, P=0.0075) but not with total HIV DNA (R= 0.27, P=0.18). Timing of ART was also inversely associated with the frequency of unique sites (N=22, R= 0.44, P=0.039) but not with the %expanded clones.

Conclusion: We observed consistent integration site patterns between HIV+ patient and in vivo humanized mouse samples. The majority of insertions occurred in genes that may serve to promote viral latency, supported by the observation that a higher number of unique integration sites correlated with lower levels of residual viral transcription, and the observation that integrations were enriched in genes associated with cell cycle, response to DNA damage, and viral transport.

Figure 1. HIV integration site analysis of 26 HIV+ patient samples (red Circos plot) and humanized mouse samples (black Circos plot) demonstrates similar genomic regions and frequencies of integration. Concentric rings denote axis increments of 15 integration sties. The top 10 genes observed in the highest number of patient samples are shown below.



Top 10 Observed Genes in 26 HIV+ Patient Samples

Gene	Summary[a]	N[b]	Unique IS[c]	Oncogene[d]	Cell Regulation[e]
NPLOC4	Regulates spindle disassembly during mitosis and type I IFN to promote degradation of RIG-I	19	116	N	Y
MROH1	Involved in actin-regulated late vesicular sorting	18	202	N	N
FANCA	DNA repair post-replication, cell cycle checkpoint	16	115	Y	Y
PPP6R2	Essential mitotic kinase, responds to TNF-alpha	16	91	N	N
MIR1268A	Unknown function microRNA	15	74	N	N
DNMT1	Essential in DNA methylation	15	58	N	N
QRICH1	Contains caspase activation recruitment domain, may be involved in inflammation, apoptosis	14	54	N	N
PTK2	Critical for cell growth and signal transduction	14	68	N	Y
HSF1	Role in mitotic progression, binds to HIV-1 long terminal repeat to reactivate transcription	14	56	N	Y
AXIN1	Controls cell growth, apoptosis, development, and enhances TGF-β signaling	13	27	Y	Y

[a]Summary adapted from Gene Cards (www.genecards.org). [b]Number of participants. [c]Total number of unique integration sites within the specific gene. [d]Oncogene defined as genes in which a single allele variant contribute to oncogenesis; the COSMIC: Cancer Gene database (http://cancer.sanger.ac.uk/cosmic). [e]Genes involved in cell cycle regulation as defined by the Gene Ontology database (http://www.geneontology.org).

382 INTEGRATION SITE-INDEPENDENT ENHANCEMENT OF LATENCY REVERSAL BY HIV-1 NEF

Xiao Mei T. Kuang, Steven W. Jin, Tristan M. Markle, Mark Brockman
Simon Fraser University, Burnaby, BC, Canada

Background: Nef is a crucial accessory protein that enhances HIV pathogenesis, in part through its ability to evade host immunity, but Nef's contribution viral latency reversal remain elusive. Nef is reported to modulate T cell signaling events, which may alter cellular reactivation in the context of latent infection. To investigate this, we examined the reactivation efficiency of latent HIV+ T cell lines harboring functional or defective Nef.

Methods: Latent CEM-A02 (CLat) T cell clones were generated using NL4.3ΔEnv viruses encoding Nef and GFP marker (SF2GFP, G2AGFP or NL4.3IeG). The nef gene was subsequently disrupted in selected CLat clones using CRISPR/Cas9. Viral reactivation induced by TNFα, panobinostat and/or prostratin was assessed using flow cytometry to measure GFP or intracellular Gag-p24 expression.

Results: We generated a panel of CLat-SF2GFP [N=11] and CLat-G2AGFP [N=38] clones and tested latency reversal using a combination of LRAs (TNFα, panobinostat and prostratin). In general, viral reactivation was lower in clones encoding defective G2A Nef (GFP MFI=149 [IQR 123-187]) compared to those encoding WT SF2 Nef (GFP MFI=375 [272-474]; p<0.0001), resulting in a reduced number of Gag-p24+ cells. Similar results were obtained when these clones were treated with individual LRAs. Consistent with previous literature, we showed that HIV reactivation efficiency was dependent in part on the proviral DNA integration site. To overcome potential bias associated with these differences between clones, we used two pairs of sgRNA to disrupt the Nef gene in four different CLat clones encoding either SF2GFP or NL4.3-IeG. Total reactivation and Gag-p24 expression were reduced in all four bulk-Nef KO cell lines. To investigate further, we generated and characterized Nef KO clones that lacked the ability to downregulate CD4 and HLA-A02. These KO clones displayed variable reactivation profiles, but notably, the reactivation intensity (GFP MFI) and % Gag-p24+ cells were lower in Nef KO clones compared to their corresponding parental cell line (see table). Additional sequence characterization revealed Nef inversion and/or large HIV sequence deletion in majority of KO clones, an unexpected outcome using CRISPR/Cas9.

Conclusion: These results highlight a potential role for Nef in modulating viral reactivation from latency in response to LRAs. Additional studies to assess the impact of natural nef sequence variation on this activity are necessary to determine the clinical relevance of this observation.

		CLat-Nef$_{NL4.3}$-IRES-GFP			CLat-Nef$_{SF2}$GFP
	Group	% Reactivation	Reac. Intensity	% Gag-p24	% Gag-p24
TNFα	WT	***97.2***	***236***	***96.9***	***79.0***
	KO$_1$	83.5 [44.0-93.0]	66.9 [55.0-114.0]	22.0 [16.0-36.1]	N/A
	KO$_2$	88.8 [57.3-96.0]	94.2 [43.6-126.8]	27.8 [12.7-51.1]	33.6 [5.0-74.9]
Pano.	WT	***62.6***	***246***	***55.5***	***65.2***
	KO$_1$	38.6 [16.8-64.2]	62.3 [51.7-102.0]	2.0 [0.8-3.3]	N/A
	KO$_2$	47.4 [21.3-69.1]	67.6 [38.8-94.8]	2.4 [1.0-8.8]	21.4 [0.6-44.8]
Pros.	WT	***62.7***	***102***	***51.9***	***72.9***
	KO$_1$	52.2 [18.4-71.7]	58.0 [44.1-79.2]	2.5 [1.0-5.3]	N/A
	KO$_2$	50.2 [34.8-73.5]	47.7 [39.2-60.4]	3.0 [0.4-16.9]	18.0 [1.0-23.0]

Note - CLat-Nef$_{NL4.3}$-IRES-GFP: N=15 for KO$_1$ and N=14 for KO$_2$. CLat-Nef$_{SF2}$GFP: N=6 for KO$_2$.

383 HIGHER RECTAL P24 LEVELS CORRELATE WITH POOR CD4 RECOVERY IN TREATED HIV INFECTION

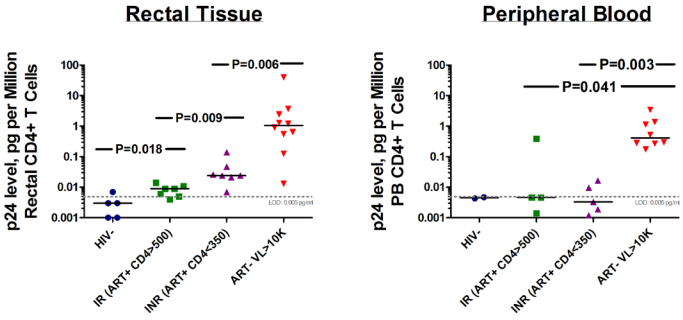
Bonnie J. Howell[1], Guoxin Wu[1], Shih Lin Goh[1], Paul Zuck[1], Montha Pao[2], Monika Deswal[2], Rebecca Hoh[2], Jeffrey N. Martin[2], Steven G. Deeks[2], Ma Somsouk[2], Daria Hazuda[1], Peter W. Hunt[2]
[1]Merck & Co, Inc, West Point, PA, USA, [2]University of California San Francisco, San Francisco, CA, USA

Background: Gut-associated lymphoid tissue is a major persistent reservoir of HIV DNA and RNA during antiretroviral therapy (ART)-mediated viral suppression, but less is known about HIV protein expression in this compartment, which is required for immune-based clearance strategies and may be more likely than total HIV transcripts to impact systemic immune activation and CD4+ T cell recovery.

Methods: HIV gag p24 protein was measured using an ultrasensitive digital ELISA in CD4+ T cells isolated from cryopreserved rectal tissue biopsies (and PBMC in those with available samples) from viremic (n=10 with plasma HIV RNA level >4 $\log_{10}$ copies/ml), ART-suppressed (n=7 immunologic non-responders [INR] with CD4+ T cell counts <350 and n=7 immunologic responders [IR] with CD4+ T cell counts>500 cells/mm^3) and HIV-uninfected participants (n=5) in the SCOPE cohort. Correlations between rectal p24, peripheral blood p24, plasma HIV RNA levels, and immunologic status were assessed with non-parametric tests.

Results: Levels of HIV gag p24 protein in rectal and peripheral blood (PB) CD4+ T cells were moderately correlated among all participants (r: 0.54, P=0.0169); however, when restricted to ART-suppressed participants, there was no evidence for a correlation between peripheral blood and rectal CD4+ T cell p24 levels (P=0.35). Rectal p24 levels were also not well correlated to plasma viral load in viremic participants. Nevertheless, rectal CD4 p24 levels discriminated between viremic, ART-suppressed, and HIV-uninfected participants much better than PB CD4 p24 levels (see Figure). Furthermore, while there was no evidence for a difference in PB p24 levels, ART-suppressed immunologic non-responders had significantly higher median rectal p24 levels than immunologic responders (0.024 vs. 0.009 per million rectal CD4+ T cells, P=0.009). Among all ART-suppressed participants, higher rectal p24 levels were associated with lower CD4 counts (r: -0.69, P=0.006) and a trend toward lower CD4/CD8 ratio (r: -0.48, P=0.079).

Conclusion: Greater HIV gag p24 protein expression in rectal tissue is strongly associated with poor CD4+ T cell recovery in PB during ART-mediated viral suppression and may not be accurately reflected by PB p24 expression. These findings suggest a potential impact of gut HIV protein expression on immune recovery during ART and highlight the need to assess HIV protein expression in gut tissue (as opposed to simply PB) in studies of immune-based clearance interventions.



384 ALTERED PD-1/PD-L1 INTERACTIONS IN GERMINAL CENTERS OF TREATED HIV-INFECTED SUBJECTS

Riddhima Banga, Caterina Rebecchini, Francesco Procopio, Stephanie D. Georget, Fabio Candotti, Matthias Cavassini, Jean-Marc Corpataux, Laurence de Leval, Giuseppe Pantaleo, Matthieu Perreau
Lausanne University Hospital, Lausanne, Switzerland

Background: One of the major obstacles to HIV cure resides in the capacity of HIV to establish a transcriptionally silent reservoir, which is not targeted by the immune system or by ART. However, under certain circumstances, HIV transcription might be reactivated. In this context, we recently demonstrated that the levels of HIV transcription in PD-1+/Tfh cells were significantly higher as compared to any other blood and lymph node (LN) memory CD4 T-cell populations. On the basis of this observation, we hypothesized that increased HIV transcription in Tfh cells may be facilitated by the reduction in the inhibitory signals delivered through PD-1/PD-L1 interaction in the germinal centers (GCs).

Methods: To test this hypothesis, we assessed 1) the expression of PD-1 and PD-L1 by mass cytometry and immunohistochemistry (IHC) and 2) the impact of PD-1/PD-L1 interaction on HIV production in blood and LN memory CD4 T cells from viremic and aviremic, ART-treated HIV-infected subjects.

Results: We show that PD-1 was highly expressed in blood and LN memory CD4 T-cell populations and particularly in Tfh cells. In contrast, PD-L1 expression was predominant in extra-follicular areas and restricted to macrophages and dendritic cells (P<0.05). Interestingly, IHC revealed that the PD-1/PD-L1 ratio was significantly higher in GCs as compared to extra-follicular areas of aviremic, ART-treated HIV-1 infected subjects (P<0.05). In addition, PD-1/PD-L1 ratio in GCs was about 20-fold higher in ART-treated than viremic, HIV-infected subjects (P<0.05), suggesting that PD-1/PD-L1 interactions might be altered in GCs of ART-treated HIV-infected subjects. We then showed that TCR-mediated HIV production from latently infected memory CD4 T cells was significantly inhibited in presence of PD-L1 recombinant protein (P<0.05), indicating that PD-1/PD-L interactions substantially reduced TCR-induced HIV production. Finally, we demonstrated that the anti-PD-1 mAb, pembrolizumab efficiently reactivated HIV replication from latently infected blood memory CD4 T cells (P<0.05).

Conclusion: This study suggests that an imbalance in the PD-1/PDL-1 signaling may contribute to the persistence of HIV in memory CD4 T cells and to the presence of active HIV transcription in LN Tfh cells. Taken together, these data provide the rationale for the development of intervention strategies targeting PD-1 and/or PD-L1 to reactivate HIV replication.

385 CD32 EXPRESSION IS ASSOCIATED TO T CELL ACTIVATION AND UPREGULATED BY HIV

Roger Badia, Edurne García Vidal, Maria Pujantell, Bonaventura Clotet, Miguel Angel Martinez, Ester Ballana, Eva Riveira-Muñoz, Jose A. Este
IrsiCaixa Institute for AIDS Research, Badalona, Spain

Background: HIV infection establishes a subset of latently infected CD4+ T cells thought not to produce viral proteins and remain indistinguishable from uninfected cells. However, the overexpression of the gene encoding for the transmembrane protein FCGR2A (CD32a+) has been proposed as a potential marker of HIV+ latently infected cells. The study of molecular signatures that allow the identification of resting, latently infected cells would facilitate the development of new therapeutic approaches.

Methods: Cell surface markers, including CD32 and activation markers HLA-DR and CD69, were measured in PBMC and CD4+ T lymphocytes from healthy donors and HIV+ individuals by flow cytometry and mRNA by qPCR. Effect of

HIV-1 infection on CD32 expression was determined in FACS-sorted CD4+ T lymphocytes stimulated with or without IL-2 (16 U/ml) and PHA (4 µg/ml) and/or infected with an HIV-1 NL4-3-GFP virus modified to express Vpx (NL4-3*GFP-Vpx). Contribution of CD32+ cells to the viral reservoir was determined in sorted CD4+ T cells from healthy donors infected in vitro or from HIV+ patients by qPCR of integrated HIV-1 DNA.

Results: Stimulation of CD4+ T cells with IL-2/PHA induced the expression of CD32 concomitant to the activation markers CD69 and HLA-DR. Infection with HIV-1 NL4-3*GFP-Vpx of non-stimulated or activated CD4 T cells increased CD32 expression that was strongly associated to HLA-DR or CD69 expression. Addition of the NNRTI efavirenz inhibited CD32 expression, indicating a virus replication induced effect. CD32 expression in CD4+ T cells from HIV+ individuals (n:12) under antiretroviral treatment indicated that a mean of 85% (70-94) of cells were CD32+/HLA-DR+. We found higher proviral DNA copies/cell in resting CD4+/CD32- T cells (n:5) infected in vitro with HIV-1 NL4-3*GFP-Vpx, except in one donor with significantly higher basal CD4 T cell activation (HLA-DR+/CD69+ cells). There were no statistically significant (p:0.76, n:6) differences in the mean viral DNA copies/cell in CD32+ or CD32- CD4+ T cells from HIV+ individuals under therapy but 3 of 6 patients showed higher DNA copies/cell in CD32+ cells. However, total DNA copies were higher in the CD32- compartment in all patients (mean 18-fold).

Conclusion: CD32 expression is a marker of CD4+ T cell activation in healthy donors and HIV+ patients. The viral reservoir lay outside the CD32+ component as the majority of HIV DNA copies are harbored in CD32- cells. HIV-1 latency may not be preferentially associated to CD32+ cells.

386 HIV-SEROREVERSION DYNAMICS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

Maria Salgado[1], Victoria González[2], Belén Rivaya[2], Cristina Gálvez[1], Mi Kwon[3], Jon Badiola[4], Alessandra Bandera[5], Björn Jensen[6], Linos Vandekerckhove[7], Kavita Raj[8], Monique Nijhuis[9], Jose Luis Diez[3], Annemarie Wensing[9], **Javier Martinez-Picado**[1]

[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [2]Hospital Germans Trias i Pujol, Barcelona, Spain, [3]University Hospital Gregorio Marañon, Madrid, Spain, [4]University Hospital Virgen de las Nieves, Granada, Spain, [5]San Gerardo Hospital, Monza, Italy, [6]Heinrich Heine University Hospital, Düsseldorf, Germany, [7]HIV Cure Research Center, Ghent University, Ghent, Belgium, [8]King's College Hospital, London, UK, [9]University Medical Center Utrecht, Utrecht, Netherlands

Background: Allogeneic stem cell transplantation (allo-SCT) in HIV-infected subjects with severe hematological malignancies is the only described strategy capable to dramatically reduce HIV latent reservoir. Whether this putative eradication strategy is associated with seroreversion has not been established yet. Within the IciStem Consortium, we explored the longitudinal serostatus of HIV+ individuals after allo SCT.

Methods: Longitudinal plasma samples from 13 HIV+ allo-transplanted patients under cART were analyzed. HIV-1 serostatus was tested in a qualitative western blot assay (New Lav Blot I, Biorad). For 7 subjects with longer follow up (>2years) additional analysis was done using the standard and low-sensitive (LS) versions of the VITROS anti- HIV-1 assay (Ortho-Clinical Diagnostics) and the LAg avidity assay.

Results: Evolution of the HIV-specific antibodies in plasma was studied for 13 allo-SCT patients, all of them under cART. We observed that p24 and/or p31 disappeared in 9/13 patients, sometimes only three months after allo-SCT. gp140, gp160, and gp120 bands persisted in most individuals. Surprisingly, in two cases we found an undetermined (Pt#19 and Pt#28) western blot. LAg avidity assay was negative in 6/7 individuals with longer follow. LS-VITROS detuned assay showed that transplanted patients presented lower antibody levels than viremic and successfully suppressed HIV+ controls. These levels started to decrease directly after allo-SCT. Remarkably Pt#19 and Pt#28 presented antibody levels close to HIV negative donors.

Conclusion: We conclude that allo-SCT not only remarkably decreased the HIV latent reservoir, but also reduced the level of HIV antibodies in presence of cART. We have observed evidence of seroreversion a few years after allo-SCT. Future cART discontinuation will unravel the role of the antibodies dynamics in the HIV cure.

387 IMMUNE ACTIVATION CORRELATES WITH EXPRESSION OF CD32 ON CD4+ T CELLS OF HIV PATIENTS

Melanie Wittner, Gabor Dunay, Johanna Eberhard, Julian Schulze zur Wiesch

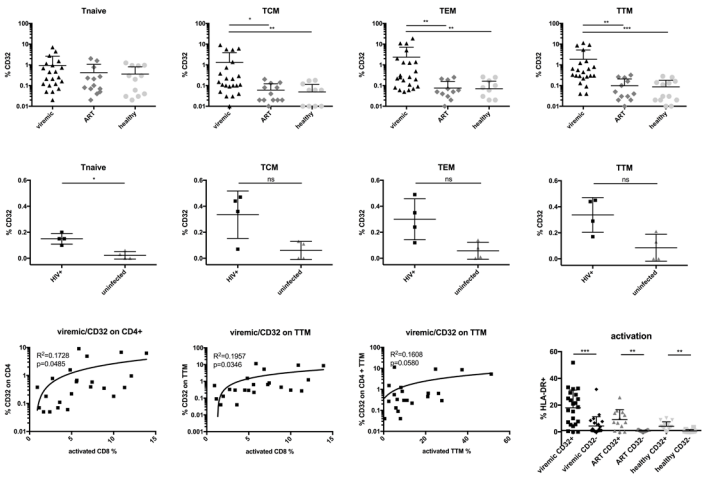
University Hospital Hamburg–Eppendorf, Hamburg, Germany

Background: Recently, CD32, a low-affinity receptor for the IgG Fc fragment with no previously reported expression on T cells, has been described as specific surface marker of latently HIV infected CD4+ T cells. As most of the current findings are based on in vitro experiments and little is known about the frequency and distribution, we studied the CD32 expression on CD4+ T cell naïve and memory populations in blood and lymph nodes of HIV patients and healthy individuals.

Methods: We analyzed peripheral blood samples of 36 HIV-1 infected patients (n=23 viremics/13=ART treated) and healthy individuals (n=14) using a multi-parametric flow cytometry determining surface expression of CD3, CD8, CD4, CD45RA, CCR7, CD27, CD25, CD127, CCR5, CCR6, CXCR4. Additionally, cells from 8 lymph nodes of HIV patients and uninfected individuals were examined.

Results: Overall, expression of CD32 differed only slightly on total peripheral CD4+ T cells between viremic HIV patients, ART-treated and healthy individuals. The highest expression was found in peripheral memory CD4+ T cell sub populations of viremic patients. CD32+ CD4+ T cells showed higher immune activation and higher expression of CCR5+. Furthermore, expression of CD32 on total CD4+ T cells and memory T cell populations of viremic patients correlated with general cellular immune activation and integrated viral DNA. Compared to blood, CD32 expression was generally lower in lymph nodal CD4+ T cells.

Conclusion: In line with previous reports on the nature of reservoir cells, effector memory cells expressed CD32 with a higher frequency. However, we hypothesize that the relationship between CD32 and the reservoirs of latently infected T cells is more complex as other host factors and immune activation seem to influence CD32 expression. Follow-up studies will have to re-evaluate CD32 as definite marker of latently HIV-infected CD4+ T cells.



388 THE HIV RESERVOIR RESIDES MAINLY IN CD32A− /CD4+ T CELLS IN PERINATAL INFECTION

Adit Dhummakupt[1], Lilly V. Siems[1], Dolly Singh[1], Ya Hui Chen[1], Thuy Anderson[1], Aleisha Collinson-Streng[1], Purvish Patel[2], Hao Zhang[1], Allison Agwu[1], Douglas Watson[3], Deborah Persaud[1]

[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Quanterix Corporation, Lexington, MA, USA, [3]University of Maryland, Baltimore County, Baltimore, MD, USA

Background: CD32a uniquely marks the latent HIV reservoir in CD4+ T cells in infected adults, with up to a 3,000-fold increase in inducible replication-competent proviruses compared with CD32a−/CD4+ T cells. The generalizability of these findings to perinatal infection is unknown. We undertook a cross-sectional study in virally suppressed, perinatally-infected youth to determine CD32a CD4+ T cell expression and the size of this reservoir.

Methods: Peripheral blood mononuclear cells were assessed by FACS (N=7) for CD32a+ and CD32a−/CD4+ T cells in perinatally-infected youth on ART. In 4 participants with sufficient cells, total CD4+ T cells were sorted into CD32a+

and CD32a– cells, and placed in a quantitative viral outgrowth assay. Inducible, replication-competent latent HIV genomes were assayed at days 7, 14 and 21 using standard p24 ELISA (LOD=6.25 pg/mL) and Quanterix ultrasensitive p24 Simoa (LOD=0.003 pg/mL).

Results: The mean age of participants was 16 years (range 15-23) and average duration of virologic suppression was 7.85 years (range 2.45-19). The proportion of CD32a+/CD4+ T cells ranged from 0.04%–0.31% (median=0.055, IQR=0.074), higher than reported in adults. Replication-competent virus was readily detected by standard ELISA in 50% of 4 participants with 7.2%, 14.3% and 21.4% of one million cell wells (mean wells cultured=7) in the CD32a–/CD4+ T cells, at days 7, 14 and 21 respectively, but not in the CD32a+ fraction (mean cells cultured=19,880). Using Simoa, inducible latent HIV was identified in CD32a–/CD4+ T cells in 25% and 32.1% of one million cell wells at day 7 and 14, respectively; p24 was detected in CD32a+/CD4+ T cells in the same two participants. The concentration of p24 antigen was significantly higher in CD32a– cells than in CD32a+/CD4+ T cells at day 14 (p=0.04) and there was a significant increase in replication over time in CD32a–/CD4+ T cells only (p=0.03)(Figure 1).

Conclusion: Despite high concentrations of CD32a+/CD4+ T cells in perinatal infection, the replication-competent CD4+ T cell reservoir resides predominantly in CD32a–/CD4+ T cells. However, while CD32a–/CD4+ T cells harbor a larger replication-competent proviral pool, CD32a+/CD4+ T cells are enriched 125-2,713-fold for cells producing virus with minimal replication-competence. Whether this inducible reservoir is capable of producing infectious virus under different stimulation conditions is unknown. The significance in perinatal infection and the implication for cure strategies requires further study.

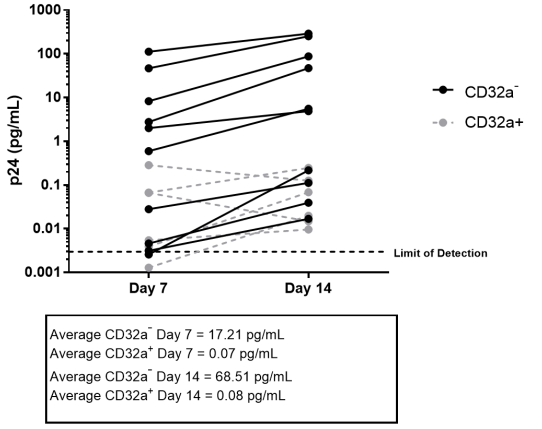


Figure 1. Change in p24 concentration (pg/mL) from Day 7 to Day 14 for $CD32a^-$ and $CD32a^+/CD4^+$ T cells by Quanterix Simoa. A significant increase in p24 concentration was observed in $CD32a^-/CD4^+$ T cells (p=0.03), but not in $CD32a^+/CD4^+$ T cells (p=0.43)

389 CD4+ T CELLS EXPRESSING CD32 FROM HIV-1+ PATIENTS ARE NOT ENRICHED FOR PROVIRAL DNA

Adam M. Spivak[1], Racheal Nell[1], McKenna L. Coletti[1], Luis Montaner[2], Vicente Planelles[1]
[1]University of Utah, Salt Lake City, UT, USA, [2]Wistar Institute, Philadelphia, PA, USA

Background: A recent publication described enrichment of the latent proviral reservoir in resting CD4+ T cells expressing the low-affinity Fc receptor CD32. This finding has not yet been reproduced. Identification of a cell surface marker that distinguishes the minority of cells harboring latent HIV-1 provirus from the larger pool of circulating, uninfected CD4+ T cells would represent a crucial scientific advance with potential therapeutic implications for HIV-1 eradication. Using cells obtained from aviremic HIV-1-positive participants, we hypothesized that CD32 expression would identify a CD4+ T cell population enriched for proviral DNA.

Methods: Resting CD4+ T (rCD4) cells were purified via negative magnetic bead isolation from peripheral blood mononuclear cells obtained from aviremic HIV-1-positive study participants (n=6). CD32-positive rCD4 cells were purified via magnetic bead isolation, and quantitative proviral DNA PCR was carried out on CD32-negative, CD32-positive, and total rCD4 cell populations. Changes in CD32 expression upon T cell activation, de novo or reactivated HIV-1 infection were evaluated in rCD4 cells from both HIV-1-positive and negative donors. In parallel, flow cytometric evaluation of T cell activation markers was carried out to assess for co-expression of CD25, CD69 or HLA-DR with CD32. Based on strong correlations between HLA-DR and CD32 expression, total CD4 cells from aviremic HIV-1-positive participants (n=3) underwent flow sorting into populations expressing either HLA-DR, CD32, both markers or neither to evaluate for proviral enrichment. Viral reactivation was quantified in sorted populations.

Results: rCD4 cells from aviremic HIV-1-positive donors expressing CD32 did not contain significantly more proviral DNA than the CD32-negative population or total rCD4 cells (repeated measures one-way ANOVA, P=0.48). CD32 expression increased significantly with T cell activation and de novo HIV-1 infection in vitro. CD32 expression did correlate with expression of the activation marker HLA-DR (R2=0.99, P<0.001), but not with CD69 or CD25. Viral reactivation did not differ between CD32+, CD32- and total CD4 sorted cell populations (P=0.49).

Conclusion: CD32 expression on CD4+ T cells from aviremic HIV-1-positive participants was associated with the activation marker HLA-DR but did not identify a population of cells enriched for replication-competent proviral DNA.

390 PRODUCTIVE HIV-1 INFECTION UPREGULATES CD32 IN VITRO AND IN VIVO

Carla Serra Peinado[1], Judith Grau-Expósito[1], Meritxell Genescà[1], Laura Luque-Ballesteros[1], Cristina Gálvez[2], Josep Castellví[3], Rein Willekens[1], Luis Montaner[4], Vicenç Falcó[3], Javier Martinez-Picado[2], María J. Buzón[1]
[1]Vall d'Hebron Research Institute, Barcelona, Spain, [2]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [3]Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, [4]Wistar Institute, Philadelphia, PA, USA

Background: The cell surface receptor protein CD32a has recently been postulated as a marker of a CD4+ T-cell HIV reservoir harboring replication-competent proviruses in ART-suppressed subjects. The expression of CD32 in different CD4+ T-cell subsets in HIV-infected patients and expression in persistent infected cells retained within lymphoid tissue after ART are important questions that still need to be evaluated.

Methods: The expression of CD32 in different CD4+ T-cell subpopulations was measured in 9 ART-treated patients by fluorescence activated cell sorting (FACS) immunophenotyping using antibodies that recognized CD3, CD4, CD27, CD45RO, CD32 and HLA-DR. HIV and CD32a RNA expression in tissue was measured by fluorescent in situ hybridization (FISH) in lymph node sections from 2 aviremic and 4 viremic HIV-infected patients. Ex vivo HIV-1 infection kinetics was measured by the RNA/flow technique during 6 days after the initial infection of healthy donor unstimulated PBMCs, and in a cervico-vaginal tissue explant model of HIV infection. Wilcoxon signed rank and spearman's rank correlation tests were used for statistical analysis.

Results: Terminally-differentiated CD4+ T cells expressed significantly higher proportions of CD32 receptor compared to other CD4+ T subpopulations (p<0.05 for all comparisons). The majority of CD4+CD32+ cells had a naïve phenotype (CD45RO–CD27+) followed by central memory (CD45RO+CD27+) and terminally-differentiated phenotype (CD45RO–CD27–). In vivo, the vast majority of productively infected cells in lymph node tissues from HIV aviremic and viremic patients also co-expressed the CD32a marker (90% of all infected cells), while most of CD32a single positive cells were absent from the B cell follicle, one of the major reservoirs for HIV. HIV infection of unstimulated PBMCs and cervico-vaginal histocultures upregulated the expression of CD32 in approximately 10-20% of all infected cells. CD32+ infected cells expressed more frequently the activation marker HLA-DR compared to CD32- infected cells (92% vs 77%) and the immune check-point PD-1 (46% vs 25%).

Conclusion: CD32 is preferentially detected in HIV transcriptionally active cells in tissues after ART and was identified to be co-expressed with activation markers in in vitro infected cells suggesting its expression is also associate with active HIV-infected cells

391 HIV-1 BURDEN IN PERIPHERAL BLOOD AND GUT CD4+ T CELLS EXPRESSING CD30 AND CD32

Louise Hogan[1], Joshua Vasquez[1], Kristen Hobbs[1], Emily Hanhauser[1], Brandon Aguilar-Rodriguez[1], Cassandra Thanh[1], Erica Gibson[1], Alexander Carvidi[1], Louis Smith[1], Ma Somsouk[1], Daniel R. Kuritzkes[2], Steven G. Deeks[1], Timothy J. Henrich[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]Harvard University, Cambridge, MA, USA

Background: Identification of specific, cell-surface markers of residual HIV infection is a top research priority. We studied CD30 (TNF superfamily receptor) and CD32 expression in blood and gut-associated lymphoid tissue (GALT), determined the HIV burden within CD4+ T cells expressing these markers, and evaluated response to ex vivo anti-CD30 therapy.
Methods: CD4+ T cells from blood or gut tissue were sorted based on expression of CD30 and CD32 followed by quantification of cell-associated HIV-1 DNA and RNA. In situ HIV RNA hybridization studies were performed on GALT, and PBMC from ART-suppressed individuals were co-cultured in the presence of the cytotoxic antibody-drug-conjugate, brentuximab vedotin, an approved cancer therapy that targets CD30.
Results: Overall, the frequency of CD30 expressing peripheral CD4+ T cells was significantly higher in ART suppressed (n=17; P=0.002) and viremic (N=9; P=0.045) individuals compared to HIV-uninfected controls. CD30+ T cells expressed higher levels of HLA-DR, CD69 and PD1, although very few activated CD4+ T cells expressed CD30. Cell-associated HIV-1 RNA was significantly enriched in CD30 expressing peripheral CD4+ T cells from ART suppressed (n=17; P=0.008) and viremic participants (n=9; P=0.007). Despite the rarity of CD30+ T cells (<4% of CD4+ T cells), an average of 21% and 28% of HIV-1 RNA burden was attributed to CD30+ cells in suppressed and viremic groups. >90% of detectable cell-associated HIV-1 RNA was found within CD30+CD4+ T cells in samples from 5 individuals, and >50% of cell-associated HIV-1 DNA was attributed to CD30+CD4+ T cells from 3 participants on ART. Interestingly, HLA-DR expression in gut CD4+ T cells was highest in dual CD30+CD32+ expressing cells. Despite the finding that only 0.1% of GALT cells expressed CD30+ RNA determined by in situ hybridization, 88% of all HIV-1 RNA+ cells from ART-suppressed participants expressed CD30 RNA. 78% of HIV RNA+ GALT cells from suppressed individuals expressed CD32, but 80% of GALT cells expressed CD32 in uninfected controls. Finally, ex vivo treatment with brentuximab vedotin, significantly reduced the mean level of HIV-1 DNA in PBMC obtained from seven ART-suppressed individuals (Figure 1).
Conclusion: Our results suggest that CD30+ expression appears to be a marker of residual HIV-1 transcriptional activity in the setting of suppressive ART and that targeting CD4+ T cells from ART-suppressed individuals may reduce overall HIV DNA burden.

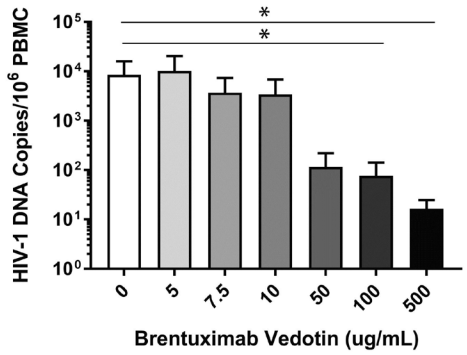


Figure. Anti-CD30 therapy reduces total HIV-1 DNA burden in PBMC *ex vivo* following 5 days of culture with ART. Significant intergroup differences were determined using paired, nonparametric Friedman tests incorporating Dunn's tests for multiple comparisons.

392 HIV ANTIBODY AND T CELL RESPONSES ON ART ARE ASSOCIATED WITH HIV DNA BUT NOT RNA

Sheila M. Keating[1], R. Brad Jones[2], Christina Lalama[3], Ronald Bosch[3], Deborah McMahon[4], Dylan Hampton[1], Evelyn Hogg[5], Joshua C. Cyktor[4], Joseph J. Eron[6], John W. Mellors[4], Michael P. Busch[1], Rajesh T. Gandhi[7]
[1]Blood Systems Research Institute, San Francisco, CA, USA, [2]The George Washington University, Washington, DC, USA, [3]Harvard University, Boston, MA, USA, [4]University of Pittsburgh, Pittsburgh, PA, USA, [5]Social &Scientific Systems, Silver Spring, MD, USA, [6]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [7]Massachusetts General Hospital, Boston, MA, USA

Background: HIV-specific immune responses decline after initiation of antiretroviral therapy (ART). Infected cells that persist during ART are thought to be invisible to the immune system, but if there is intermittent antigen expression and recognition, HIV antibody (Ab) and T cell responses may correlate with measures of HIV persistence.
Methods: Plasma and PBMC samples were obtained from 100 individuals on suppressive ART in the ACTG A5321 cohort. Cell-associated (CA) HIV DNA and unspliced RNA levels (using qPCR targeting pol) and Ab concentrations and avidity to Env/p24 (using LS-VITROS and Avidity Vitros assays, respectively) were measured longitudinally at yr 1, 4 and (for some participants) yr 6-15 after ART initiation. Plasma HIV RNA by single copy assay and T cell responses (IFN-γ ELISPOT) against Gag, Pol, Env, Nef/Tat/Rev, Vpr/Vpu/Vif were measured at the last time point (yr 4-15; median 7 yr of ART).
Results: HIV Ab levels and avidity declined with increasing time on ART and were positively associated with HIV DNA at yr 1, 4 and 4-15 of ART (r=0.35 and 0.38, respectively, p<0.001 at the last time point). Nef/Tat/Rev-specific T cell responses, but not responses against other gene products, correlated with HIV DNA levels (r = 0.23, p = 0.03). Neither Ab levels nor T cell responses correlated with cell-associated HIV RNA or plasma RNA by single copy assay. HIV Ab and avidity correlated with T cell responses to HIV Pol (r=0.3, p=0.01 and r =0.26, p=0.04, respectively) and to Nef/Tat/Rev (r =0.35; p =0.005 and r =0.39, p=0.001). There were no correlations between HIV Ab measures and T cell responses to HIV Gag or Env, or to CMV and EBV controls.
Conclusion: In individuals on long-term ART, HIV-specific Ab to ENV/p24 and T cell responses to Nef/Tat/Rev correlate with each other and with HIV DNA levels but not with CA HIV RNA or residual plasma viremia. These findings suggest that the total frequency of HIV-infected cells (HIV DNA) may be a better marker of antigen expression that drives immune responses on ART than CA RNA in blood or residual viremia, which reflect activity of only a small fraction of proviruses that can be induced to express antigen. The positive correlation between HIV immune responses and HIV DNA suggests that the immune system is sensing, but not clearing, infected cells, perhaps because of immune dysfunction. Sensing of infected cells by immune responses suggests that tracking these measures may be a method of assessing the impact of reservoir reducing strategies.

393 BLINDED EVALUATION OF ULTRASENSITIVE ASSAYS OF HIV IN PLASMA

Sheila M. Keating[1], Mars Stone[1], Xutao Deng[1], Sonia Bakkour[1], John W. Mellors[2], Douglas D. Richman[3], Rob Gorelick[4], Jeffrey D. Lifson[4], Cheryl Jennings[5], Martin Stengelin[6], Guoxin Wu[7], Bonnie J. Howell[7], Peter Bacchetti[8], Michael P. Busch[1]
[1]Blood Systems Research Institute, San Francisco, CA, USA, [2]University of Pittsburgh, Pittsburgh, PA, USA, [3]University of California San Diego, La Jolla, CA, USA, [4]Leidos Biomedical Research, Inc, Frederick, MD, USA, [5]Rush University Medical Center, Chicago, IL, USA, [6]Meso Scale Diagnostics, LLC, Rockville, MD, USA, [7]Merck & Co, Inc, West Point, PA, USA, [8]University of California San Francisco, San Francisco, CA, USA

Background: A major barrier to developing HIV cure interventions is the lack of validated assays that reliably quantify HIV in plasma below the limit of detection of current clinical assays. We sought to objectively assess the performance characteristics of newer, more sensitive assays to quantify plasma viremia.
Methods: The HIV Reservoir Assay Validation and Evaluation Network (RAVEN) project was created to assess the sensitivity, specificity, limits of detection and quantitative ranges of blood-based assays of HIV persistence. To accomplish this for HIV detection in plasma, blinded 50-sample panels containing subtype B and C HIV including duplicate, virus-spiked analytic standards (2 subtype-specific 5-step, 3-fold dilution series with highest concentrations ranging from 45 to 6 copies/mL to lowest concentrations ranging from 0.33 to 0.07 copies/mL), clinical samples with expected low-level viremia and negative controls were distributed to 8 laboratories for HIV quantification using 9 assays. Four assays included centrifugation to concentrate virus prior to HIV RNA nucleic acid extraction and PCR amplification; two included replicate testing using diagnostic HIV RNA assay platforms; while two utilized ultrasensitive detection of p24 Ag without virus enrichment. Results were analyzed for sensitivity, specificity, reproducibility, and ability to accurately quantify HIV in standards.
Results: Data from five laboratories using 6 assays were included in this analysis. Four of five RNA-amplification based assays detected virus in the standards down to ~1 copy/mL in at least 1 of the 2 replicates; negative controls were all negative. All RNA-amplification-based assays had strong correlations between replicates across the standards (p<0.05, rho>0.8). Four assays quantified standards with little bias (mean recovery 69-218% of nominal HIV [RNA]) whereas one assay overestimated copies/mL by >300%. Ultrasensitive p24 Ag assays were not able to quantitatively measure HIV in the diluted

standards. One p24 assay detected HIV protein in virus-spiked samples, with observed specificity of 90%.
Conclusion: p24 assays can detect virus in seronegative plasma without virus enrichment, but dynamic sensitivity was lacking at <45 copies/mL. Ultrasensitive RNA-amplification assays following virus enrichment or with replicate testing can quantitatively measure HIV RNA down to ~1 copy/mL, which is necessary to assess the impact of experimental curative interventions on residual viremia.

394 QUANTIFYING THE TURNOVER OF LATENT HIV: APPLICATIONS TO ANTI-PROLIFERATIVE THERAPY

Jeffrey Gerold[1], Michael J. Bale[2], Zheng Wang[3], Guinevere Q. Lee[4], Mathias Lichterfeld[4], Robert Siliciano[3], Mary F. Kearney[5], Alison L. Hill[1]
[1]Harvard University, Cambridge, MA, USA, [2]NIH, Frederick, MD, USA, [3]Johns Hopkins University, Baltimore, MD, USA, [4]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [5]NIH, Bethesda, MD, USA

Background: The latent reservoir for HIV consists of provirus stably integrated into long-lived lymphocytes and represents a barrier to a cure. This reservoir decays with a half-life of ~44 months during long-term suppressive ART, but the relative role of intrinsic T cell longevity vs proliferation in this persistence is unknown. Recent characterization of integration sites and full-genome sequences has suggested that clonal proliferation contributes to reservoir stability, but this rate has yet to be quantified. Estimating the value of this turnover rate is necessary to understand whether anti-proliferative therapy is a viable treatment option.
Methods: Here we develop a method to infer the underlying dynamics of cells in the latent reservoir from clone size distributions in sampled cells. We created a dynamic, stochastic mathematical model for cells in the latent reservoir, and fit this model to data using a Bayesian Markov Chain Monte Carlo estimation procedure that includes the size of the latent reservoir before ART initiation, the time on ART, and the later sampling of infected cells. The inference algorithm was applied to two sources of data: HIV integration site frequencies and intact provirus determined by full-genome sequencing.
Results: Using HIV DNA integration site data and a simple homogeneous model of latent cell division and death, we estimated that on average latent cells divide around 10 times/yr [95% CI 5-20/yr], a much higher turnover than predicted by the total decay rate of 0.2/yr (e.g. half-life 44 months). For individual patients, the best-estimated turnover rate varied by up to an order of magnitude [2-30/yr]. Results were similar using intact virus only, though more uncertain due to smaller sample sizes. We used simulated populations to confirm our inference method was unbiased and required ~500 samples from each patient to reduce the uncertainty in turnover rate to +/-40% (95% CI). We found that an augmented model which also allowed for rare, burst-like proliferation could explain the clone size distribution better than the simple model. These findings suggest that therapy which reduced proliferation by 50% could reduce reservoir half-life to a few months, raising the potential for eradication with a few years of ART.
Conclusion: Our findings suggest that proliferation of latently-infected cells is a major contributor to the stability of the total and intact DNA reservoir and that reducing this proliferation may have potential as a curative intervention.

395 SINGLE CELL ANALYSIS OF HIV LATENCY REVEALS DIVERSE PROVIRAL AND HOST CELL BEHAVIOR

Edward P. Browne[1], Todd Bradley[2], Guido Ferrari[2], Barton F. Haynes[2], David M. Margolis[1]
[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]Duke Human Vaccine Institute, Durham, NC, USA

Background: The latent reservoir is inherently diverse with each infected cell exhibiting a potentially unique combination of integration site, epigenetic modifications, and host cell phenotype. However, most studies of HIV latency have relied on assays of bulk cultures in which information about the behavior of individual cells is lost. As such, the application of single cell level methods to HIV latency model systems may reveal previously unappreciated levels of heterogeneity. We hypothesized that latently infected cells exhibit diverse characteristics with respect to proviral reactivation and host cell phenotype, and that characterizing this diversity will be important for optimizing approaches for clearing the latent reservoir.
Methods: We have characterized a cell line model and a novel primary cell model of HIV latency with two single cell assays – single cell qPCR (sc-qPCR) for viral RNA (vRNA), and single cell RNAseq (scRNAseq). These systems were examined both at rest, and after stimulation with two latency reversing agents (LRAs)– vorinostat, and prostratin.
Results: sc-qPCR for vRNA revealed that a subset of latently infected cells transcribe detectable viral RNA in the absence of stimulation, and that stimulation with LRAs induces a wide range of vRNA levels in infected cells. For transformed cell lines, an apparent threshold of ~500 copies of vRNA was required before virally encoded antigen was detected by flow cytometry, while primary cells exhibited a more complex relationship between vRNA and viral protein expression. Compared to prostratin, vorinostat induced lower levels of viral antigen expression, even in cells with equivalent expression of vRNA, suggesting a post-transcriptional block to viral gene expression. Single cell RNAseq of >2000 latently infected primary cells using the 10x Genomics platform revealed diverse transcriptomic profiles within the infected cell population. Interestingly, cells which exhibited the greatest levels of HIV silencing were enriched for a specific set of host genes that define naïve and central memory T cells, suggesting a role for T cell subset identity in the establishment of latency.
Conclusion: Altogether, these data reveal heterogeneous behaviors of HIV proviruses and host cells at rest, and after stimulation with LRAs, and illustrate the power of single cell methods to provide insights into HIV latency.

396 ULTRASENSITIVE P24 DIGITAL ELISA CAN LEAD TO AN OVERESTIMATE OF HIV RESERVOIR SIZE

Francesco R. Simonetti[1], Subul A. Beg[2], Jun Lai[2], Purvish Patel[3], Hao Zhang[2], Gregory Laird[2], Lynn N. Bertagnolli[2], David Kulick[3], Robert Siliciano[2], Janet Siliciano[2]
[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Johns Hopkins University, Baltimore, MD, USA, [3]Quanterix Corporation, Lexington, MA, USA

Background: The quantitative viral outgrowth assay (qVOA) estimates the size of the HIV reservoir based on the frequency of cells harboring inducible, replication-competent proviruses. The ultrasensitive SIMOA p24 assay, developed by Quanterix, can quantify p24 with a limit of detection up to 1000 times lower than standard ELISA. We investigated whether SIMOA can be used as a reliable read out to calculate the frequency of infected cells in qVOA experiments. In addition, we tested if SIMOA can be biased by defective proviruses still capable of producing p24.
Methods: Total CD4+ T-cells from 3 patients on suppressive ART were sorted based on CD32, recently characterized by Descours et al. CD4+CD32- cells (14-24x10^6) were plated in 5-fold dilutions. CD4+CD32+ cells, present at very low frequency, were plated in replicate with low cell input (2.2-62 x 10^3 total cells). qVOAs were conducted as described by Laird et al, 2014. The SIMOA p24 2.0 commercial kit was used to assay supernatants collected at days 5, 9, 14 and 21. We used droplet digital PCR to quantify HIV RNA from cells and supernatants, and performed RNA single genome sequencing from U5 to gag (HXB2 nt 551-1330).
Results: The lower limit of quantification of SIMOA (0.01 pg/ml) allowed earlier p24 detection in CD32- wells that were positive by ELISA at day 21 (63% positive wells at day 5, 95% at day 9, 100% at day 14, n=19). However, of these wells positive by SIMOA, only 53% (19/36) showed exponential viral outgrowth from day 5 to 21, while the others had stable, low p24 levels (mean 0.21 pg/ml). In two of these wells with no outgrowth we found high HIV RNA copies in both cells and supernatants. SGS revealed 3 variants with an intact gag ORF, 2 of them carrying defects in the major splice donor site. The extreme sensitivity of SIMOA allowed detection of low level of p24 released from cells with defective proviruses. The frequency of latently infected cells showed a 4-fold increase when the assay had high cell input. However, in 2 out of the 3 qVOAs with a low input of CD32+ cells (all negative by ELISA), SIMOA caused a dramatic overestimate of infected cell frequency (554 and 3184 IUPM).
Conclusion: SIMOA allows earlier detection of p24 compared to ELISA. However, longitudinal sampling is necessary to distinguish viral outgrowth from low-level p24 likely produced by defective proviruses. Our results advice caution in using SIMOA on a single timepoint, as it can lead to an overestimate of IUPM, particularly for qVOA with low cell input.

397 NEXT-GEN VIRAL OUTGROWTH ASSAYS AS PROXIES FOR CLASSIC QVOA TO MEASURE HIV RESERVOIR

Mars Stone[1], Daniel S. Rosenbloom[2], Peter Bacchetti[3], Xutao Deng[1], Melanie Dimapasoc[1], Sheila M. Keating[1], Douglas D. Richman[4], John W. Mellors[5], Steven G. Deeks[3], Janet Siliciano[6], Nicolas Chomont[7], Roger Ptak[8], Michael P. Busch[1]
[1]Blood Systems Research Institute, San Francisco, CA, USA, [2]Columbia University, New York, NY, USA, [3]University of California San Francisco, San Francisco, CA, USA, [4]University of California San Diego, San Diego, CA, USA, [5]University of Pittsburgh, Pittsburgh, PA, USA, [6]Johns Hopkins University, Baltimore, MD, USA, [7]Université de Montréal, Montreal, QC, Canada, [8]Southern Research Institute, Frederick, MD, USA

Background: Evaluations of HIV curative interventions require efficient assays that reliably quantify the latent reservoir (LR) of replication-competent HIV-1. The "classic" quantitative viral outgrowth assay (QVOA) monitors limiting-dilution co-culture of resting CD4+ T cells and stimulated donor PBMCs for 3 weeks by p24 Ag ELISA. While regarded as a "gold standard," QVOA is prohibitively resource- and labor-intensive for widespread use. We compared five induced outgrowth assays employing PCR or ultrasensitive p24 readout of short-term resting CD4+ T cell cultures ("next-gen assays") to assess their suitability as scalable proxies for QVOA.
Methods: Next-gen viral outgrowth assays were performed and compared to classic QVOA results on samples derived from single leukapheresis collections from 5 ART-suppressed HIV+ participants and one HIV- control, with 3 aliquots of cryopreserved cells and one fresh sample tested at each lab. A certain amount of variation between split samples is inevitable due to Poisson sampling variation, so we used Markov chain Monte Carlo methods to estimate extra-Poisson variation at the aliquot, batch, and lab levels. Models also estimated the effect of using frozen versus fresh samples.
Results: Next-gen assays had similar estimates of variation to QVOA, with random variation at aliquot, batch, and lab levels having overlapping credible intervals. Overall, RNA-based assays reported higher IUPM than classic p24-based assays. Assaying split samples in the same batch had 2.5-fold extra-Poisson variation (95% CI 2.1 – 3.5) for next-gen assays. Assay performance by two separate labs increased total extra-Poisson variation to 3.4-fold (95% CI 2.6 – 5.4). Frozen storage did not substantially alter IUPM (–18%, 95% CI –52% – +39%). Within this cohort, two of the next-gen assays using short-term stimulation and PCR or ultrasensitive p24 readout had moderately high correlation with all four classic assays ($R2 > 0.5$ for all four comparisons, $R2 > 0.8$ for at least one comparison).
Conclusion: The data offer cautious support for use of next-gen assays as proxies for more laborious outgrowth-based co-culture QVOA, while providing greater sensitivities and dynamic ranges. Measurement of LR in eradication strategies would benefit from development of assays that are high-throughput and scalable.

	Estimated extra-Poisson variation (fold), Posterior Median (95% credible interval)	
	Classic QVOA (4 Assays)	Next-gen QVOA (5 Assays)
Aliquot Level	**1.5 (1.1-2.1)**	**2.4 (2.0-3.1)**
Batch Level (alone)	**1.8 (1.0-2.4)**	**1.1 (1.0-1.8)**
Aliq + Batch	2.0 (1.6-2.7)	2.5 (2.1-3.4)
Assay-Level (alone)	**1.5 (1.0-2.5)**	**2.5 (1.0-4.4)**
Aliq + Batch + Assay	2.3 (1.8-3.5)	3.7 (2.9-5.7)
Frozen Effect	**+4% (-44%, +97%)**	**-18% (-50%, +39%)**

398 QVOA COUPLED WITH DIGITAL P24 ANALYSIS ENHANCES HIV RESERVOIR QUANTIFICATION

Elizabeth R. Wonderlich[1], Yury V. Kuzmichev[1], Carol Lackman-Smith[1], Marie K. Mankowski[1], Christine N. Raney[1], Hayley P. Madeira[1], Jiayi Wei[1], Rebecca M. Bernbaum[1], Krupa Subramanian[1], Rachel L. Jarrett[1], Ellen R. Nordgren[1], Mars Stone[2], Michael P. Busch[2], Roger Ptak[1], Deanna Kulpa[3]
[1]Southern Research Institute, Frederick, MD, USA, [2]Blood Systems Research Institute, San Francisco, CA, USA, [3]Emory University, Atlanta, GA, USA

Background: Latently infected resting CD4+ T cells (rCD4+) contribute to HIV persistence in individuals receiving long term suppressive ART. The low frequency of latently infected cells among the rCD4+ population presents challenges in quantifying the latent reservoir, which is critical to evaluate HIV eradication strategies. Several assays have been developed to quantify HIV persistence, however all present limitations; PCR-based assays overestimate the HIV reservoir, while QVOA has been shown to underestimate it. To support the development of effective HIV eradication therapeutics, there is an urgent need to develop a robust and precise assay that more accurately quantifies the frequency of infected cells carrying replication-competent HIV. To address this need, we modified QVOA to include a digital p24 endpoint that not only allowed for a shorter assay duration, but also increased sensitivity.
Methods: rCD4+ cells were enriched from cryopreserved PBMC from 5 ART-suppressed, HIV+ individuals provided by the Reservoir Assay Validation and Evaluation Network (RAVEN). Standard QVOA was performed, with culture supernatant collection on days 8, 12, and 20. IUPM were calculated by assessing the frequency of p24 positive culture supernatants at each time point as determined by Quanterix Simoa digital p24 system or ELISA.
Results: The digital p24 endpoint readily detected HIV+ samples that were below the limit of detection by ELISA. Analysis revealed patterns of viral growth kinetics at p24 levels not detected by ELISA, supporting identification of replicating virus present in QVOA that are missed by standard approaches. While ELISA efficiently detected robustly replicating virus with greatest sensitivity at day 20, digital p24 enabled enhanced detection as early as day 8 with greatest sensitivity at day 12 (Table). Overall, use of digital p24 coupled with QVOA reduced assay duration and increased the estimated size of the latent reservoir (~7-fold) compared to day 20 IUPM measured by ELISA.
Conclusion: Digital p24 permits early and more sensitive detection of HIV outgrowth in QVOA enabling the duration of the assay to be reduced by 8-12 days, coupled with an approximate one log increase in the calculated IUPM. These data support that digital p24 offers an approach to improve the sensitivity of QVOA in quantifying the HIV reservoir, a critical component for effective development of HIV eradication strategies.

RAVEN ID#	Mean Fold Change in IUPM Digital p24/Day 20 ELISA (SD)		
	Day 8	Day 12	Day 20
1126 (n=3)	5.48 (0.82)	15.57 (0.79)	10.60 (0.71)
2026 (n=3)	4.07 (0.25)	3.41 (0.51)	3.81 (0.65)
2147 (n=3)	3.38 (1.17)	3.09 (0.45)	4.88 (0.63)
2208 (n=3)	1.70 (0.65)	4.44 (0.83)	8.85 (0.86)
3068 (n=3)	15.54 (1.47)	8.55 (1.10)	3.40 (1.12)
Average	**6.03 (0.55)**	**7.01 (0.31)**	**6.31 (0.41)**

399 QUANTIFICATION OF REPLICATION COMPETENT LATENT HIV-1 IN GALT AND SEMEN

Anwesha Sanyal[1], Ian McGowan[1], Ma Somsouk[2], Charles Rinaldo[1], Nicolas Sluis-Cremer[1], **Phalguni Gupta**[1]
[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]University of California San Francisco, San Francisco, CA, USA

Background: The latent replication-competent HIV-1 reservoir represents a major obstacle to a cure. This reservoir has been well-characterized in resting CD4+ (rCD4+) T cells in blood. However, few studies have quantified the frequency of replication-competent latent HIV-1 in tissue, primarily due to the limitation of the sensitivity of current assays. We recently developed a reporter cell-based assay to quantify inducible, replication-competent latent HIV-1 in the blood (Sanyal et al., Nat. Med. 2017. 23:885) which is sensitive, requires only a small blood volume, and is less labor intensive than other available technologies. The goal of this study was to adapt this assay (termed TZA) to quantify replication competent HIV-1 in GALT and semen from virally suppressed individuals.
Methods: The TZA was adapted to quantify inducible replication-competent HIV-1 in tissue samples. Using this assay, we quantified inducible latent virus in total CD4+ T cells from the blood and semen of 2 infected individuals on ART, and from the blood and GALT of 6 infected individuals on ART.
Results: We routinely isolated 2-3×106 CD4+ T cells of high purity from rectal tissue using the gentleMACSTM Octo Dissociator (Miltenyi). We found in 6 patients that there was more replication competent HIV-1 in the GALT than

in the blood. The mean IUPM value for blood was determined to be 3.5 (range: 0.5 -3.76); whereas the mean IUPM value for tissue was 16.2 (range 0.5-51). Interestingly, we also observed more replication competent HIV-1 in the semen compared to blood. In one subject tested, the IUPM value was calculated to be 2.0 and 17.0 in the blood and semen, respectively. In the second subject, infectious virus could not be recovered from the blood, but an IUPM of 58.0 was determined in the semen.

Conclusion: We have adapted the TZA to quantify inducible replication-competent HIV-1 in the GALT and semen of HIV-1 infected subjects on ART. Preliminary studies suggest a higher frequency of HIV in both GALT and semen compared to blood.

400 CLASSIFYING COGNITIVE STATUS IN HIV-INFECTED MEN BY MULTIVARIATE NORMATIVE COMPARISON

Zheng Wang[1], Yu Cheng[1], Samantha A. Molsberry[2], Lawrence Kingsley[1], Andrew Levine[3], Eileen Martin[4], Eric N. Miller[3], Cynthia Munro[5], Ann B. Ragin[6], Ned Sacktor[5], Eric C. Seaberg[7], James T. Becker[1]

[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]Harvard University, Cambridge, MA, USA, [3]University of California Los Angeles, Los Angeles, CA, USA, [4]Rush University Medical Center, Chicago, IL, USA, [5]The Johns Hopkins Hospital, Baltimore, MD, USA, [6]Northwestern University, Chicago, IL, USA, [7]The Johns Hopkins University, Baltimore, MD, USA

Background: Estimates of the extent of cognitive impairment among individuals infected with HIV vary widely. This work used a relatively new method of multivariate normative comparisons (MNC) to identify individuals with impaired cognition, and to compare the results with those using the original (Antinori) and modified (Gisslén) Frascati criteria. MNC is a statistical method to control for the increased false discovery rate associated with using multiple intercorrelated measures of cognitive function.

Methods: This project used data collected prior to October 2014 from bisexual/gay men in the Neuropsychological (NP) Substudy of the Multicenter AIDS Cohort Study. These participants have been regularly assessed over 30+ years with a battery of tests measuring performance in working memory & attention, learning, motor speed & coordination, executive functioning, speed of information processing, and memory. The study cohort included 2904 men (mean age 39.7yr, 52.7% HIV-infected, 1314 classified in the preART era) who had complete data in all six domains at their first NP evaluation. T-scores were computed for each domain, adjusting for age, race, and education. The MNC was applied to detect impairment among seronegative and seropositive groups; the seronegative men were treated as healthy controls. For comparisons, the number of impaired men that were identified by Antinori's and Gisslén's criteria were also determined.

Results: In the seronegative group, the MNC method classified 5.8% of men as being cognitively impaired; as the subjects in the seronegative group were treated as healthy controls, the MNC successfully controlled the false discovery rate at 5% level. Using the Antinori and Gisslén criteria, 24.2% and 11.2% of the HIV- men were classified as impaired, respectively. Among the HIV+ men, the MNC classified 7.1% as impaired; the Antinori and Gisslén criteria identified 25% and 11.6% impaired cases, respectively. The rates of abnormality did not differ between groups, nor did they differ in the mean domain T-scores.

Conclusion: Among seronegative individuals, the MNC method successfully controlled the false discovery rate at the predetermined error level. In contrast, both the Antinori and Gisslén criteria produced inflated prevalence rates, suggesting low specificity of these two methods. More research is needed to evaluate the sensitivity of this method in a seropositive population which may be sicker or older than the current study sample.

401 USE OF NON-ANTIRETROVIRAL MEDICATIONS THAT MAY IMPACT NEUROCOGNITION

Kendra K. Radtke[1], Peter Bacchetti[1], Leah H. Rubin[2], Kathryn Anastos[3], Howard Crystal[4], Daniel Merenstein[5], Roksana Karim[6], Kathleen M. Weber[7], Andrew Edmonds[8], Anandi N. Sheth[9], Margaret Fischl[10], David Vance[11], Ruth Greenblatt[1]

[1]University of California San Francisco, San Francisco, CA, USA, [2]Johns Hopkins University, Baltimore, MD, USA, [3]Albert Einstein College of Medicine, Bronx, NY, USA, [4]SUNY Downstate Medical Center, Brooklyn, NY, USA, [5]Georgetown University, Washington, DC, USA, [6]University of Southern California, Los Angeles, CA, USA, [7]John H. Stroger Jr. Hospital of Cook County, Chicago, IL, USA, [8]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [9]Emory University, Atlanta, GA, USA, [10]University of Miami, Miami, FL, USA, [11]University of Alabama at Birmingham, Birmingham, AL, USA

Background: Neurocognitive impairment (NCI) is a frequent and often disabling comorbidity of HIV. In addition to antiretroviral (ARV) therapies, individuals with HIV infection may commonly use non-ARV medications that are known to cause neurocognitive adverse effects (NC-AE). The contribution of NC-AE to NCI is rarely considered in the context of HIV and could explain part of the variability in neurocognitive performance among individuals with HIV.

Methods: This study was conducted with data from the Women's Interagency HIV Study (WIHS); a prospective, multisite, observational study of U.S. women with and without HIV. After a literature review, 98 non-ARV medications with NC-AE were identified, 78 of which (excluding statins) were reported by WIHS participants. We examined factors associated with self-reported use of these medications over a 10-year period among WIHS women. Multivariable logistic regression was used to assess socio-demographic, behavioral, and clinical characteristics associated with NC-AE medication use.

Results: 3,300 women (70.6% with HIV) and data from ~42,000 visits were studied. HIV infection was associated with NC-AE medication use (odds ratio =1.52 (95% confidence interval: 1.35-1.71)). HIV-infected women were more likely ($p<0.001$) to report using antianxiety, opioid, antihistamine, gastrointestinal, or antidepressant NC-AE medications (see Table). After adjustment for HIV infection status, having health insurance, multiple depressive symptoms, prior clinical AIDS, non-injection recreational drug use, and an annual household income <$12,000 were each predictors of NC-AE medication use (all $p<0.004$). NC-AE medication use was less likely among women who drank 1-7 or 8-12 alcoholic drinks/week (vs. abstaining) (both $p<0.04$).

Conclusion: HIV infection was associated with NC-AE medication use which may influence determinations of HIV-associated NCI. Providers should consider the impact of NC-AE medications when evaluating patients with HIV and concurrent neurocognitive symptoms.

Medication Class	HIV-infected n visits (%)	HIV-uninfected n visits (%)	Odds Ratio (95% CI)	*p*-value
Anticonvulsant	1274 (4.3)	450 (3.6)	0.96 (0.74-1.24)	0.74
Antianxiety	3706 (12.4)	1047 (8.4)	1.41 (1.17-1.70)	0.0004
Anticholinergic	676 (2.3)	218 (1.7)	1.20 (0.86-1.67)	0.29
Antipsychotic	2074 (7.0)	903 (7.2)	0.93 (0.76-1.15)	0.52
Amphetamine	78 (0.3)	34 (0.3)	0.79 (0.28-2.20)	0.66
Opioid	3420 (11.5)	1102 (8.8)	1.35 (1.15-1.60)	0.0003
Beta Blocker	1004 (3.4)	304 (2.4)	1.29 (0.90-1.86)	0.17
Gastrointestinal	807 (2.7)	186 (1.5)	1.78 (1.27-2.50)	0.0009
Antihistamine	2053 (6.9)	645 (5.2)	1.42 (1.17-1.73)	0.0004
Muscle Relaxant	718 (2.4)	316 (2.5)	0.87 (0.66-1.16)	0.35
Antidepressant	6231 (20.9)	1539 (12.3)	1.58 (1.35-1.85)	<0.0001

402 BRAIN NEUROTRANSMITTER GENOMICS AND EFAVIRENZ CENTRAL NERVOUS SYSTEM (CNS) EFFECTS

David Haas[1], Yuki Bradford[2], Anurag Verma[2], Shefali S. Verma[2], Sarah A. Pendergrass[2], Joseph J. Eron[3], Roy M. Gulick[4], Sharon Riddler[5], Paul E. Sax[6], Thomas Campbell[7], Eric Daar[8], Gene D. Morse[9], Edward P. Acosta[10], Marylyn D. Ritchie[2]

[1]Vanderbilt University, Nashville, TN, USA, [2]Geisinger Health System, Danville, PA, USA, [3]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [4]Weill Cornell Medicine, New York, NY, USA, [5]University of Pittsburgh, Pittsburgh, PA, USA, [6]Brigham and Women's Hospital, Boston, MA, USA, [7]University of Colorado, Aurora, CO, USA, [8]University of California Los Angeles, Los Angeles, CA, USA, [9]State University of New York at Buffalo, Buffalo, NY, USA, [10]University of Alabama at Birmingham, Birmingham, AL, USA

Background: Efavirenz (EFV) is widely prescribed for HIV-1 infection but CNS adverse effects (AEs) are common. CYP2B6/CYP2A6 genotypes predict risk for EFV CNS AEs. Interactions of EFV with neurotransmitter transporters/receptors are thought to cause CNS AEs. We assessed whether predicted brain expression or polymorphisms (SNPs) in candidate genes in brain (SLC6A2, SLC6A3, PGR, HTR2A, HTR2B, HTR2C, HTR6, AR) were associated with EFV CNS AEs.

Methods: Antiretroviral therapy (ART)-naïve patients were randomly assigned to EFV-containing ART in protocols ACTG 384, A5095, A5142 and A5202. Genetic consent was obtained under protocol A5128. Cases had new onset grade ≥2 EFV-consistent CNS AEs within 48 weeks of study entry while receiving EFV.

Controls had no EFV-consistent CNS AEs while receiving EFV for ≥96 weeks after entry. Neither group had neuropsychological signs or symptoms at entry. Genotypes were imputed from Illumina genome-wide assays. Tissue-specific RNA expression levels for about 10,000 genes were inferred from genotypes using PrediXcan (Nat Genet 2015; 47:1091-8). Associations were tested with multivariable logistic regression, adjusted for CYP2B6/CYP2A6 genotype, baseline age, sex and 2 ancestry principal components.

Results: A total of 2863 participants were assigned to EFV-containing ART, of whom 2171 consented for genetic testing, 1798 had CYP2B6/CYP2A6 genotypes, and 1425 had imputed genome-wide genotypes and principal components. Of these participants, 820 met criteria for cases (n=167) or controls (n=653). CYP2B6/CYP2A6 genotype was associated with CNS AEs (p=0.001). For candidate gene expression in 10 brain regions, the lowest P-value was for PGR (progesterone receptor) in hippocampus (p=0.012), and for all genes was for RCE1 (CAAX prenyl protease 2) in cerebellum ($p=5.3x10^{-4}$). For candidate gene (±100kB) SNPs, the lowest P-value was for rs12393326 in HTR2C (serotonin receptor 2C, $p=6.7x10^{-4}$), and for all SNPs was for rs7143465 in SLC8A3 (zinc transporter 10, $p=2.1x10^{-9}$).

Conclusion: In ART-naïve patients randomly assigned to EFV-containing ART in ACTG protocols, grade ≥2 EFV CNS AEs were not associated with predicted neurotransmitter transporter/receptor gene expression levels in brain or with SNPs in these genes, after correcting for multiple testing. We confirmed an association of CYP2B6/CYP2A6 genotype with EFV CNS AEs. Variable susceptibility to EFV CNS AEs may not be explained by brain neurotransmitter transporter/receptor genomics.

403LB POORER NEUROCOGNITIVE PERFORMANCE ASSOCIATED WITH CSF HIV DNA DESPITE LONG-TERM ART

Kevin Robertson[1], Ronald Bosch[2], Serena S. Spudich[3], Rajesh T. Gandhi[4], Joshua C. Cyktor[5], Hanna Mar[2], Bernard J. Macatangay[5], Christina Lalama[2], Charles Rinaldo[5], Ann Collier[6], Catherine Godfrey[7], Joseph J. Eron[1], Deborah McMahon[5], John W. Mellors[5]

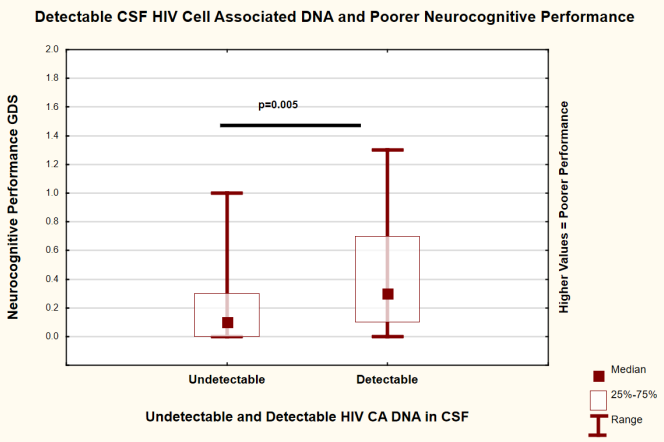
[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]Harvard University, Boston, MA, USA, [3]Yale University, New Haven, CT, USA, [4]Brigham and Women's Hospital, Boston, MA, USA, [5]University of Pittsburgh, Pittsburgh, PA, USA, [6]University of Washington, Seattle, WA, USA, [7]NIH, Bethesda, MD, USA

Background: We have found that almost half of individuals with suppressed viremia (<50 copies/ml) on long-term antiretroviral therapy (ART) have persistence of HIV-infected cells in cerebrospinal fluid (CSF), but the neurocognitive significance of this finding is unknown. We assessed neurocognitive performance in a large cohort of individuals on long-term ART who had CSF sampling.

Methods: In ACTG A5321, participants underwent lumbar puncture, blood collection and neurocognitive assessments. Participants had sustained long-term viremia suppression after initiating ART during chronic HIV infection. Cell-associated (CA) HIV DNA, unspliced HIV mRNA, and cell-free HIV RNA were quantified. Markers of inflammation (IL-6, IP-10, neopterin, MCP-1, sCD14, and sCD163) in CSF and plasma were assessed. Neurocognition was measured with a 15-test battery covering Language, Attention, Executive, Learning, Memory, Speed of Processing, and Fine Motor domains, standardized into z and deficit scores to create the neurocognitive total z score and global deficit score (GDS) as the summary neurocognitive measures.

Results: The 65 participants were 97% male, 75% white, had a median age 50 years and median duration of ART 8.6 years; median current and pre-ART CD4+ cells of 696/mm^3 and 292/mm^3, respectively. All participants had at least a high school education. The median neurocognitive total z score was 0.2 (range -1.1, 1.5), and median GDS was 0.2 (0.0, 1.3). Detectable CSF HIV DNA (46%) was significantly associated with poorer neurocognitive total z-score (p = 0.044, Wilcoxon) and GDS (p = 0.005, figure 1). This association persisted after adjusting for pre-ART, current CD4 count and age. By contrast, soluble biomarkers of immune activation in CSF were not associated with neurocognitive performance.

Conclusion: Poorer neurocognitive performance despite long-term effective ART is associated with the persistence of detectable HIV-infected cells in the CSF. We do not know whether this is due to the legacy effects of HIV infection on the CNS prior to ART initiation, or alternatively that persistent HIV in the CNS is driving neurocognitive injury. No association with inflammatory biomarkers suggests that current inflammation was not driving present function, but does not rule out prior inflammation as the underlying cause of neuronal injury. These findings underscore the importance of the CSF compartment as a reservoir with clinical significance that needs additional evaluation.



404 DETERMINANTS OF COGNITIVE FUNCTION DIFFER IN A EUROPEAN AND A KOREAN COHORT

Davide De Francesco[1], Alan Winston[2], Jun Yong Choi[3], Rosan van Zoest[4], Jonathan Underwood[2], Judith Schouten[4], Nam Su Ku[3], Woo Joo Kim[5], Peter Reiss[4], Caroline Sabin[1]

[1]University College London, London, UK, [2]Imperial College London, London, UK, [3]Yonsei University, Seoul, South Korea, [4]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands, [5]Korea University, Seoul, South Korea

Background: HIV-associated cognitive impairment (CI) remains relevant in people living with HIV (PLWH) treated with antiretroviral therapy. However, risk factors for CI may differ in populations of PLWH of different ethnicity. We compared the prevalence and determinants of CI in a Northern European and a Korean cohort of PLWH, and assessed the ability of individual cognitive tests to discriminate between those with and without CI.

Methods: Cognitive performances were assessed using a comparable battery covering 6 domains in 134 PLWH aged ≥45 years in the EU-funded COBRA study (Netherlands, UK), and 194 PLWH aged ≥18 years from the NeuroAIDS Project (Korea). Cognitive scores were standardized using population-specific normative scores and averaged into an overall score. Determinants of cognitive function were evaluated using linear regression. Factors that were associated with cognitive function in univariate analyses were selected for inclusion in a multivariable model. The discriminative ability of individual cognitive tests to detect CI, as defined by an overall score ≤0.5 standard deviations (SD) below the mean, was assessed using the area under the receiver operating characteristic curve (AUROC).

Results: The 134 COBRA PLWH (mean age: 57 yrs, 93% male, 88% white ethnicity, 100% on cART) had a higher CD4 (mean (SD): 646 (214) cells/μL) and lower rate of anaemia (8.3% with haemoglobin ≤13 g/dL) compared to the 194 Korean PLWH (45 yrs, 94% male, 90% on cART, mean (SD) CD4: 481 (236) cells/μL, 19.1% with anaemia). The prevalence of CI was 18.8% in COBRA PLWH and 18.0% in Korean PLWH (p=0.86). In COBRA, being of African descent was the main determinant of cognitive function (p<0.01) whereas in the Korean cohort anaemia (other than years of education) was the main risk factor (p=0.1, Table). The discriminative ability of CI screening was highest for tests of attention (AUROC of 0.81 to 0.84) and executive function (0.80-0.88) in COBRA PLWH and for tests of processing speed (0.73-0.80) and motor skills (AUROC=0.78) in Korean PLWH.

Conclusion: Two cohorts of PLWH from different geographic regions show similar CI rates when assessed using similar cognitive tests. However, determinants of cognitive performance in the two cohorts differ considerably with ethnicity and anaemia being important determinants in one but not the other cohort. These findings suggest that differences in ethnicity and other diseases should be taken into consideration when comparing CI rates in different geographic regions.

Table: Estimates from multivariable regression to identify determinates of the standardised overall cognitive score (mean=50, SD=10) in cohorts from Europe (COBRA) and Korea (NeuroAIDS Project)

COBRA			NeuroAIDS Project		
Risk factor	*Reg. coef. (95%CI)*	*p-value*	*Risk factor*	*Reg. coef. (95%CI)*	*p-value*
Male vs Female	-0.7 (-6.7, 5.3)	0.82	Years of education	0.4 (0.3, 0.6)	<0.001
Black-African vs White	-11.0 (-14.4, -7.6)	<0.001	Anaemia	-1.1 (-2.6, 0.3)	0.12
Likely route of transmission		0.98			
Heterosexual sex vs MSM	0.4 (-4.3, 5.1)	0.86			
Other vs MSM	0.5 (-5.0, 5.9)	0.87			
BMI (kg/m²)	-0.1 (-0.3, 0.1)	0.39			
Anaemia	-0.2 (-4.4, 4.0)	0.93			

NB: Anaemia is defined as a blood haemoglobin concentration ≤13 g/dL

405 HIV SUBTYPE AND RISK OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDER IN RAKAI, UGANDA

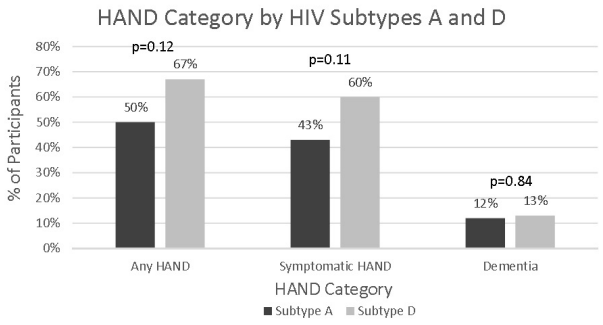
Ned Sacktor[1], Deanna Saylor[1], Gertrude Nakigozi[2], Kate Grabowski[1], Noeline Nakasujja[3], Xiangrong Kong[1], Kevin Robertson[4], Ronald H. Gray[1], Maria Wawer[1]
[1]Johns Hopkins Hospital, Baltimore, MD, USA, [2]Rakai Health Sciences Program, Kalisizo, Uganda, [3]Makerere University, Kampala, Uganda, [4]University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: HIV-1 subtype B is predominant in the US while subtypes A, C and D predominate in Sub-Saharan Africa. The clade subtype may have an impact on HIV disease progression. Subtype D is associated with a more rapid CD4 cell count decline and faster disease progression compared to individuals with subtype A. Differences in co-receptor usage have been hypothesized to explain the differences in progression rates, as the probability of having an X4 virus was higher in subtype D infections than in subtype A infections. Previous studies also suggest that HIV subtype D is associated with an increased risk of HIV dementia (HAD) than subtype A among HIV+ individuals with advanced but not moderate immunosuppression. The objective of this study was to assess the association of HIV subtype with HIV-associated neurocognitive disorder (HAND) stage among HIV+ individuals with both moderate and advanced immunosuppression in rural Rakai, Uganda.

Methods: 190 antiretroviral naïve HIV+ individuals with CD4 counts less than 200 and CD4 counts between 351-500 from the Rakai Community Cohort Study were evaluated by detailed neurological history, examination, neuropsychological tests and functional assessments and full length HIV sequencing on serum samples collected at baseline. HAND stage was determined using Frascati criteria. Subtype was determined by sequencing a portion of the gag and env regions.

Results: HIV subtype frequency was D (24%, n=45), A (22%, n=42), D-A recombinant (31%, n=59), C (0.5%, n=1), other recombinants (22%, n=43). There was no difference in age between HIV+ individuals with subtype D (mean age= 35.2 years) and subtype A (mean age= 34.9 years). 67% of HIV+ individuals with subtype D had HAND, compared to 50% with subtype A (p=0.12) (see Figure). 60% of HIV+ individuals with subtype D had symptomatic HAND [mild neurocognitive disorder (MND)/ HAD], compared to 43% with subtype A (p=0.11). There was no association between the presence of HAD and HIV subtype (subtype D=13%, subtype A =12%, p=0.84). There were no differences between the presence of HIV subtype D vs. A and either HAND, symptomatic HAND, or HAD when stratified by CD4 counts.

Conclusion: A trend was seen for an increased rate of either HAND or symptomatic HAND (MND/HAD) among HIV+ individuals with subtype D vs. A. However, HAD was not more common among HIV+ individuals with subtype D compared to those with subtype A. Additional analyses including results from the pol gene are on-going.



406 VITAMIN D IS NOT ASSOCIATED WITH HIV-ASSOCIATED NEUROCOGNITIVE DISORDER IN UGANDA

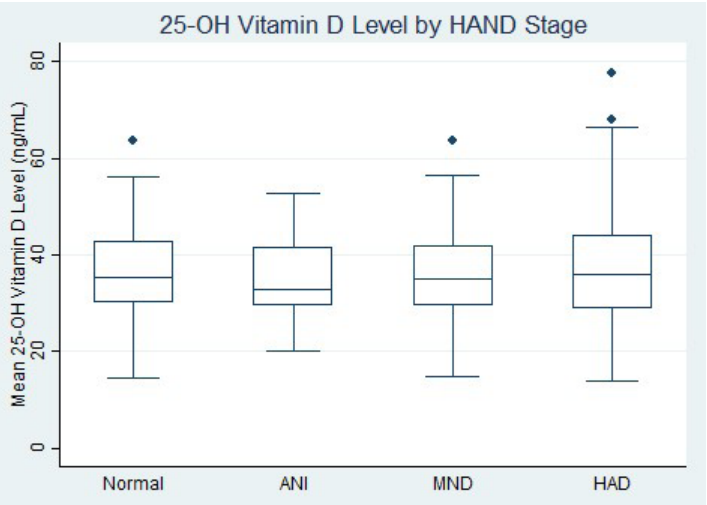
Deanna Saylor[1], Gertrude Nakigozi[2], Noeline Nakasujja[3], Kevin Robertson[4], Ronald H. Gray[5], Maria Wawer[5], **Ned Sacktor**[1]
[1]Johns Hopkins Hospital, Baltimore, MD, USA, [2]Rakai Health Sciences Program, Kalisizo, Uganda, [3]Makerere University, Kampala, Uganda, [4]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [5]The Johns Hopkins University, Baltimore, MD, USA

Background: The exact pathophysiologic mechanisms of HIV-associated neurocognitive disorder (HAND) are unknown. Increased deposition of amyloid-beta-42 (Aβ42) in the brain and altered Aβ42 metabolism leading to subsequent neuronal dysfunction have been proposed to contribute to the development of HAND. Vitamin D has been shown to suppress Aβ42 production and plaque aggregation in vitro. Vitamin D deficiency has been linked with an increased risk of Alzheimer Disease, which is also attributed to Aβ42 pathology. Therefore, we hypothesized that vitamin D deficiency may also contribute to the development of HAND.

Methods: 399 HIV+ adults from the Rakai Community Cohort Study underwent a detailed neurological history and examination, comprehensive neurocognitive battery, functional status assessments, and peripheral blood draw at baseline. 333 (84%) underwent repeat assessment after 2 years. HAND stage was determined using Frascatti criteria and local normative data derived from 400 HIV- adults in Rakai. Baseline serum 25-hydroxy-vitamin D (25OH-D) was determined via LIAISON chemiluminescence assays, and vitamin D binding protein (VDBP) levels were determined using ELISA. 25OH-D levels were categorized as low (<20 ng/mL), sufficient (20 – 40 ng/mL), and optimal (>40 ng/mL). ANOVA was used to compare 25OH-D and VDBP levels by HAND status. Chi-square analyses were used to compare HAND status by 25OH-D category.

Results: 53% of participants (n=211) were male, mean age was 35 (SD 8) years, and mean education was 5 (SD 3) years. All were antiretroviral therapy (ART) naïve at baseline, and 94% (n=312) were taking ART at follow-up. Mean 25OH-D level was 36 (SD 10) ng/mL with 63% of participants with sufficient levels, 33% with optimal levels, and 4% with low levels. Mean VDBP was 316 (SD 61) µg/mL. At baseline, 41% of participants had normal cognition, 6% had asymptomatic neurocognitive impairment (ANI), 38% had minor neurocognitive disorder (MND), and 15% had HIV-associated dementia (HAD). At follow-up, 48% were normal, 13% had ANI, 33% had MND, and 5% had HAD. Mean 25-OHD was not significantly associated with HAND status at baseline (Figure) or follow-up. HAND stage was not associated with vitamin D category. Mean VDBP did not vary by HAND stage at baseline or follow-up.

Conclusion: Vitamin D status was not associated with HAND stage at baseline or after two years of follow-up among HIV+ adults in Uganda. Vitamin D supplementation is unlikely to provide benefit in treating HAND in this population.



407 VACS INDEX PREDICTS SYMPTOMATIC HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS IN UGANDA

Deanna Saylor[1], Gertrude Nakigozi[2], Noeline Nakasujja[3], Kevin Robertson[4], Ronald H. Gray[5], Maria Wawer[5], **Ned Sacktor**[1]

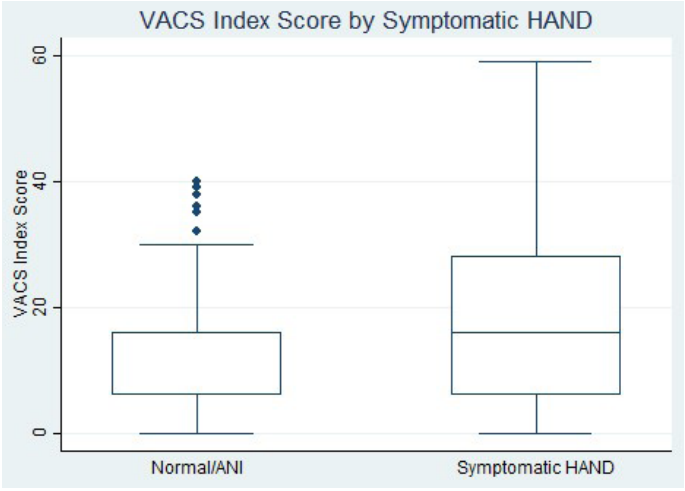
[1]Johns Hopkins Hospital, Baltimore, MD, USA, [2]Rakai Health Sciences Program, Kalisizo, Uganda, [3]Makerere University College of Health Sciences, Kampala, Uganda, [4]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [5]The Johns Hopkins University, Baltimore, MD, USA

Background: The Veterans Aging Cohort Study (VACS) Index, a clinical score originally developed in HIV+ military veterans to predict hospitalizations, mortality, and other adverse health outcomes, was recently found to correlate with HIV-associated neurocognitive disorder (HAND) in cohorts from the United States, Canada and Italy, but this relationship varies by ethnicity. It has never been studied in Sub-Saharan Africa. We investigated the relationship between HAND stage and VACS Index score among HIV+ patients in rural Uganda.

Methods: 141 HIV+ adults from the Rakai Community Cohort Study underwent a detailed neurological history and examination, a comprehensive neurocognitive battery, functional status assessments, and peripheral blood draw for CD4 count, viral load, complete blood count, and comprehensive metabolic panel. HAND stage was determined using Frascatti criteria and local normative data derived from 400 HIV- adults in Rakai, Uganda. HAND diagnoses were then classified into symptomatic (minor neurocognitive disorder, HIV-associated dementia) and asymptomatic (normal cognition, asymptomatic neurocognitive impairment) HAND. Because prior community-based studies in Rakai have found very low rates of hepatitis C infection, VACS Index scores were calculated assuming all participants were hepatitis C negative. Scores between HAND groups were compared using t tests.

Results: Participants were 48% male (n=68) with mean age of 37 (SD 9) years. 140 participants (99%) were taking antiretroviral therapy. Median CD4 count was 363 cells/μL (Interquartile Range 245-490), and 77% (n=109) had undetectable HIV plasma viral loads. Those with symptomatic HAND (n=51) had significantly higher VACS Index scores (19.4 (SD 14.9)) than those without symptomatic HAND (n=90; 14.9 (SD 9.1); p=0.04) (Figure). For every one quartile increase in VACS Index score, odds of symptomatic HAND increased by 42% [OR 1.42, 95% CI (1.03, 1.96), p=0.03]. This difference was most strongly associated with the VACS component scores for age (2.4 vs 0.4, p=0.008) and FIB4 score (2.1 vs 1.0, p=0.02). Other component scores were not significantly different between those with and without symptomatic HAND.

Conclusion: VACS Index scores were significantly higher among HIV+ adults with symptomatic HAND than those with normal cognition or asymptomatic neurocognitive impairment in rural Uganda. This suggests that the VACS Index may be a useful indicator of symptomatic HAND in African populations in addition to Western populations.



408 NEUROPSYCHOLOGICAL PHENOTYPES IN THE MACS

Samantha A. Molsberry[1], Yu Cheng[2], Lawrence Kingsley[2], Lisa Jacobson[3], Andrew Levine[4], Eileen Martin[5], Eric N. Miller[4], Cynthia Munro[3], Ann B. Ragin[6], Ned Sacktor[3], James T. Becker[2]

[1]Harvard University, Cambridge, MA, USA, [2]University of Pittsburgh, Pittsburgh, PA, USA, [3]The Johns Hopkins University, Baltimore, MD, USA, [4]University of California Los Angeles, Los Angeles, CA, USA, [5]Rush University Medical Center, Chicago, IL, USA, [6]Northwestern University, Chicago, IL, USA

Background: HIV infection can affect brain function; prior to the development of combination anti-retroviral therapies (cART), HIV infected individuals often performed poorly on tests of cognition and, in many cases, became severely demented. In the cART era mild forms of HIV-associated neurocognitive disorder (HAND) remain prevalent.This study's objective was to identify neuropsychological subgroups within the Multicenter AIDS Cohort Study (MACS) based on the participant-based latent structure of cognitive function and to identify factors associated with subgroups

Methods: Using MACS Neuropsychological substudy participants' domain scores from the time of their first neurocognitive classification [HIV+: n=1531; HIV-: n=1370], we applied a cluster variable selection algorithm to identify the optimal subset of neuropsychological domains that have cluster information. We then conducted a latent profile analysis based upon scores from the identified domains. Exploratory analyses were conducted to identify factors associated with cluster membership. For those factors found to be associated with cluster membership, post-hoc analyses were conducted to determine the drivers of the observed results.

Results: Cluster variable selection identified all domains as containing cluster information except for the working memory domain. A three-cluster solution with variable distribution, variable volume, and equal shape and orientation (VVE) was identified as the best fit for the data. Profile 1 performed below average on all domains; Profile 2 performed at average on executive functioning, motor, and speed and below average on learning and memory; Profile 3 performed at or above average across all domains (See figure). Approximately 20% of men identified most closely with Profile 1, 35% with Profile 2, and 45% with Profile 3. Demographic, cognitive, and social factors but not HIV-related factors were found to be associated with profile membership. Post-hoc analyses of these associations demonstrated that they were generally driven by differences between Profile 1 and the other two profiles.

Conclusion: There is an identifiable pattern of neuropsychological domain scores among MACS members and this pattern is determined by all domains except for the working memory domain. Neither HIV nor HIV-related biomarkers were related with cluster membership, which is consistent with other recent findings that patterns of neuropsychological test performance do not map directly onto HIV serostatus.

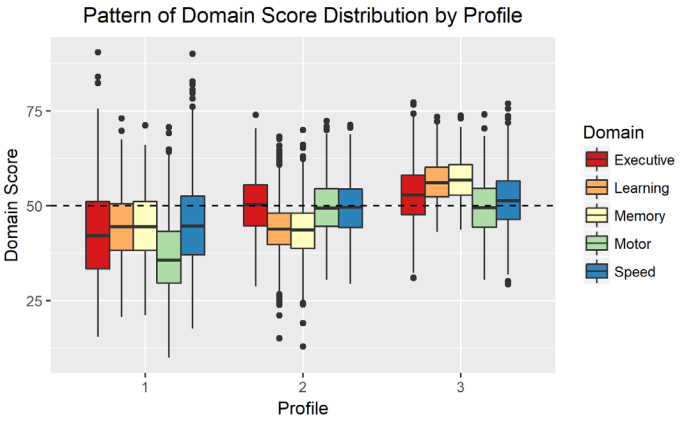


Figure: Boxplot of cognitive domain score distribution based on MACS participants identifying most closely with each latent profile

409 PREVALENCE OF HIV NEUROCOGNITIVE IMPAIRMENT IN A RURAL TANZANIAN COHORT

Montserrat Sanmartí[1], Ana-Claire Meyer[2], Angels Jaen[1], Kevin Robertson[3], Nora Tan[4], Leila Samson[5], Regina Ndaki[5], Marcel Tanner[6], Manuel Battegay[6], David Dalmau[1], Emilio Letang[6]

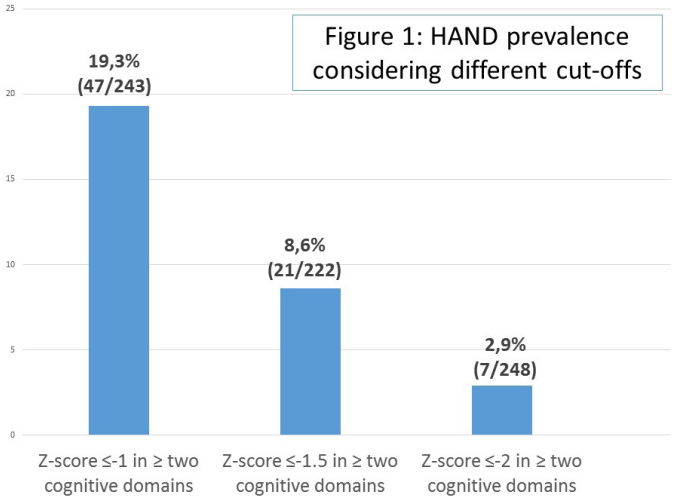
[1]Hospital Universitari Mútua de Terrassa, Terrassa, Spain, [2]Yale University, New Haven, CT, USA, [3]North Carolina Division of Public Health, Raleigh, NC, USA, [4]Stanford University, Stanford, CA, USA, [5]Ifakara Health Institute, Dar es Salaam, Tanzania, United Republic of, [6]Swiss Tropical and Public Health Institute, Basel, Switzerland

Background: HIV-associated Neurocognitive impairment (HNI) is still highly prevalent and is associated with lower quality of life despite the advances in antiretroviral therapy (ART). Few studies have assessed the neurobehavioral status of people living with HIV (PLWH) on ART in sub-Saharan Africa. We conducted a study to evaluate the prevalence and associated factors for HNI in a rural Tanzanian HIV-infected cohort.

Methods: Cross sectional study among a random sample of adult PLWH on ART for >1 year without neither immunological failure nor pre-existing neurological disease, prospectively enrolled in the Kilombero-Ulanga Antiretroviral Cohort and visited between 06 and 08/2015. A neuropsychological test battery was administered, including: verbal fluency test, digit symbol, digit span, WHO/UCLA auditory verbal learning test and grooved pegboard. Demographically–adjusted normative data were obtained from a sample of 400 HIV-negative adults from Rakai (Uganda). A definition of HNI was applied, requiring a mean Z-score≤-1 in ≥two cognitive domains. Multiple logistic regression identified risk factors for HNI.

Results: Among 243 recruited patients, the median age was 44 years (IQR 36-52), 71% were female, 98% were infected heterosexually and 35% had primary education or less. Median nadir CD4 was 243 cells/µL (IQR 80–302) and 53% had a WHO Stage 3 or 4. The median time on ART was 5 years (IQR 3-7), and 68% were on an efavirenz-based regimen. Nearly all patients (97%) reported good self-adherence to ART. The prevalence of HNI was 19.3% (47/243) (figure 1). Group mean Z-scores for memory (Z=-0.22) and psychomotor (Z=−0.81) domains demonstrated the highest impairment. Age (adjusted odds ratio (aOR) 1.6 for 10 years increase; 95% CI 1.1-2.3) and alcohol consumption (aOR 2.7; 95% CI 1-6.7) independently predicted HNI. Also, a trend was observed for a higher risk of HNI in patients who had not disclosed their HIV status (OR 1.7; 95% CI 0.8-3.3).

Conclusion: This is the first study evaluating cognition from Tanzania HIV population using normative data from a large African HIV-negative cohort. We have found a moderate prevalence of HNI considering that only healthy and HIV stable population were included. Classical risk factors were not associated to HNI, except age. Further analysis is needed to better understand the association of alcohol consumption with HNI and the protective effect of HIV disclosure. Our results raise differences among patients with HNI from different geographical settings.



410 PREDICTORS OF HIV-RELATED COGNITIVE IMPAIRMENT IN EAST AFRICA

Benedetta Milanini[1], Isabel E. Allen[1], Emmanuel Bahemana[2], Yakubu Adamu[3], Francis Kiweewa[4], Jonah Jonah Maswai[5], John Owuoth[6], Christina Polyak[7], Julie Ake[7], Victor Valcour[1]

[1]University of California San Francisco, San Francisco, CA, USA, [2]Walter Reed Program–Tanzania, Mbeya, Tanzania, United Republic of, [3]Walter Reed Program–Nigeria, Abuja, Nigeria, [4]Makerere Univ Walter Reed Proj, Kampala, Uganda, [5]KEMRI/Walter Reed Proj, Kericho, Kenya, [6]KEMRI/Walter Reed Proj, Kisumu, Kenya, [7]Walter Reed Army Institute of Research, Silver Spring, MD, USA

Background: Studies in developed countries show that HIV infection is associated with cognitive impairment (CI). We investigated the clinical and demographic predictors of CI in the African cohort study.

Methods: HIV+ individuals from Kenya, Uganda, and Tanzania underwent a 30-minute cognitive testing battery that assessed multiple cognitive domains. CI on neuropsychological testing was defined as -1SD on two tests or -2SD on one test when performance was compared to demographically similar seronegative individuals at the same sites. We performed multivariate logistic and linear models to examine factors associated with CI and global neuropsychological testing performance (NP6; i.e. average of the individual scores).

Results: We enrolled 2208 HIV+ participants from Kenya (n=1384), Tanzania (n=368) and Uganda (n=456). The mean (SD) age was 40(10), 39(12) and 39(10), respectively (p=0.007). 1508(68%) were on cART, 554(40%) had plasma viral loads <500 copies/ml and 813(37%) met criteria for WHO clinical stage 1. The overall prevalence of CI was 38% (n=844) and independent of cART use (p=0.178) or plasma viral load (p=0.328). Tanzanians showed higher CI rate (51%) compared to Ugandans (31%) and Kenyans (37%;p<0.001). In the overall multivariate logistic regression model, inability to read (aOR:2.93;95%CI: 2.15-4.00;p<0.001), site (aOR: 0.85;95%CI: 0.76-0.96), and WHO clinical stage 4 compared to stage 1 (aOR:1.73;95%CI:1.08-2.76; p=0.022) were associated with higher risk of CI. Multivariate logistic regression models within country showed similar findings with significant effects of literacy in all countries, WHO stage 4 in Kenya and CD4 cell count between 200 and 500 in Uganda (ps<0.02). The only noted difference in the predictive model of NP6 compared to CI was a significant protective effect of CD4 cell count>500 (b=0.09;95%CI:0.02/0.16;p=0.018) and negative effect of WHO stage 3 (b=-0.08;95%CI:-0.15/-0.01;p=0.024) on NP6. Restricting the logistic analysis to literate participants, we found a significant increased risk for CI with WHO stage 4 (aOR:2.25;95%CI:1.06-4.79;p=0.035) and plasma viral load (aOR:1.1;95%CI:1.00-1.31;p=0.046).

Conclusion: We found 38% prevalence of CI in our sample; that was independent of cART use. Inability to read, site and higher WHO stage were strongly associated with increased risk of CI. Further studies are needed to better explore the prevalence of CI among HIV+ individuals on cART with higher degrees of viral suppression in African settings.

411 PLASMA D-DIMER RELATES TO PHYSICAL HEALTH AND MOTOR SKILLS ACROSS THE AGE SPAN IN HIV

Jessica L. Montoya, Scott L. Letendre, Ronald J. Ellis, Dilip V. Jeste, David J. Moore

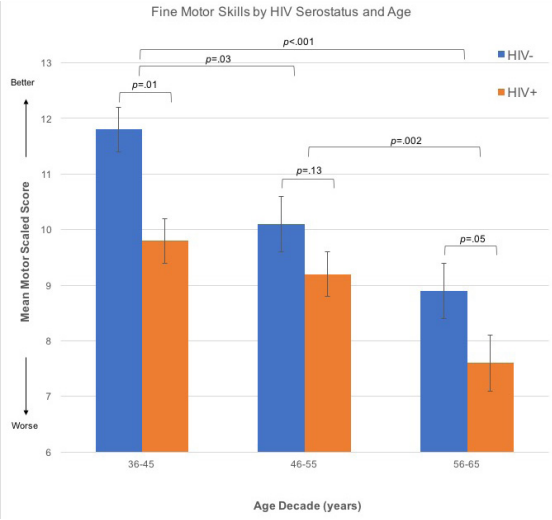
University of California San Diego, La Jolla, CA, USA

Background: Inflammatory processes have been suggested as culprits for early neurologic abnormalities among persons living with HIV (PLWH), which have been purported to remit with effective antiretroviral treatment (ART). We hypothesized that inflammatory processes likely continue throughout the disease and may be associated with poorer physical health and worse fine motor skills as persons age with HIV.

Methods: The sample consisted of 107 PLWH and 95 HIV-uninfected adults, ages 36 to 65, with balanced recruiting in each age decade (36-45, 46-66, 56-65). Biomarkers of inflammation (d-dimer, IL-6, MCP-1, soluble CD14, and TNF-α) were measured. Participants completed the Medical Outcomes Study SF-36 to derive a physical health summary score, and fine motor skills were evaluated using the Grooved Pegboard Test. Standard statistical techniques were used for 1) group comparisons (i.e., Welch's F Test or Wilcoxon rank sum test), 2) associations among continuous variables (i.e., Pearson's or Spearman correlations), and 3) overall models (multivariable linear regressions to control for the effects of covariates that showed univariable association with outcome at α <.10).

Results: Compared to the HIV-uninfected group, PLWH had higher levels of sCD14 (p=.03), MCP-1 (p<.001), and TNF-α (p=.001) and reported poorer physical health (p<.001). Presence of HIV (p<.001) and older age decade (p<.001) were associated with poorer fine motor skills (i.e., lower scaled scores) (Model F=14.2, p<.001; figure). Among the biomarkers, only D-dimer (ρ=-.17, p=.01) and MCP-1 (ρ=-.24, p=.001) were associated with physical health. D-dimer (r=-.19, p=.01), IL-6 (r=-.15, p=.04), MCP-1 (r=-.16, p=.02), and TNF-α (r=-.17, p=.01) had linear associations with fine motor skills, while sCD14 showed a quadratic association (p=.008), such that lower and higher values of sCD14 were associated with worse fine motor skills. Only d-dimer remained as a statistically significant predictor (p=.02) of fine motor skills in a multivariable model controlling for covariates.

Conclusion: Inflammatory processes may contribute to worse physical health, including worse fine motor skills throughout the course of HIV disease. Although neurologic findings (e.g., deficits in motor speed/dexterity) commonly associated with HIV infection have been suggested to largely remit with ART, our analysis indicates continued and worsening fine motor skills across the adult age continuum of PLWH beyond that expected from normal aging alone.



412 CARDIOVASCULAR RISK FACTORS ASSOCIATED WITH NEUROCOGNITIVE IMPAIRMENT DIFFER BY SEX

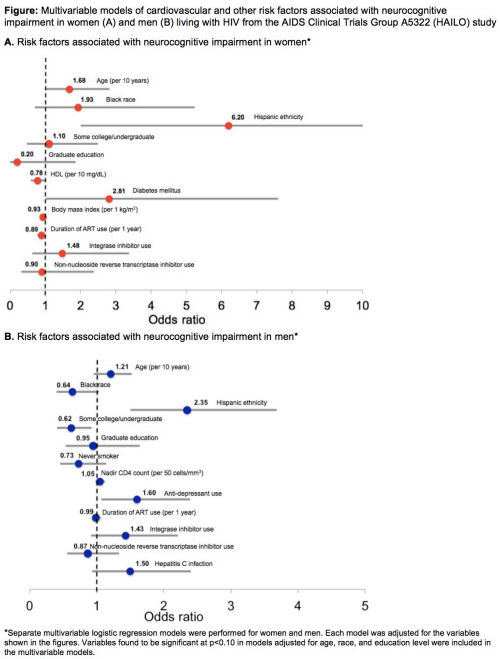
Felicia C. Chow[1], Kunling Wu[2], Katherine Tassiopoulos[2], Baiba Berzins[3], Kevin Robertson[4], Babafemi Taiwo[3]
[1]University of California San Francisco, San Francisco, CA, USA, [2]Harvard University, Cambridge, MA, USA, [3]Northwestern University, Chicago, IL, USA, [4]University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: Cardiovascular (CV) disease has been consistently linked with neurocognitive impairment (NCI) in persons living with HIV (PLWH). Despite recognized differences in CV risk profiles between women and men, most studies investigating the association between CV risk and NCI in PLWH have not stratified by sex or have been in men-only cohorts. We investigated sex differences in CV risk factors associated with NCI at entry into a prospective cohort of older PLWH who initiated antiretroviral therapy (ART) in a randomized trial and were followed longitudinally in the AIDS Clinical Trials Group (ACTG) A5322 study.

Methods: Participants who underwent a neurocognitive screen (Trailmaking A and B, Hopkins Verbal Learning Test-Revised, Digit Symbol) at A5322 entry were eligible. NCI was defined as ≥1 standard deviations (SD) below the mean on ≥2 tests or ≥2 SD below the mean on ≥1 test. We used separate logistic regression models for women and men to investigate differences in factors associated with CV and NCI.

Results: Of 988 participants, 20% (n=195) were women. Mean age was similar between women and men (51 versus 52 years). Fifty-two percent of women were black and 22% white, while 56% of men were white and 25% black. Women had fewer median years of education than men (12 versus 14 years). Women had significantly higher total and high-density lipoprotein (HDL) cholesterol and body mass index (BMI) compared with men, and a trend toward a higher prevalence of diabetes mellitus, anti-hypertensive use, and current smoking. In a multivariable model, older age (adjusted odds ratio [aOR] 1.68 per 10 years, p=0.05) and diabetes mellitus (aOR 2.81, p=0.04) were associated with higher odds of NCI for women, while higher HDL (aOR 0.78 per 10 mg/dL, p=0.05), higher BMI (aOR 0.93 per 1 kg/m2, p=0.01) and longer duration of ART (aOR 0.89 per year, p=0.04) were protective. Among men, older age (aOR 1.21 per 10 years of age, p=0.10), hepatitis C infection (aOR 1.50, p=0.09), nadir CD4 count (aOR 1.05 per 50 cells/mm^3, p=0.08), and anti-depressant use (aOR 1.60, p=0.02) were risk factors for NCI, although only anti-depressant use reached statistical significance.

Conclusion: Several traditional CV risk factors were associated with NCI in older women living with HIV, whereas similar relationships were not found in men. These data suggest that interventions to prevent NCI in PLWH may differ between women and men.



413 IMPACT OF DETERMINANTS OF INCREASED VASCULAR RISK ON NEUROCOGNITION IN HIV+ PATIENTS

Ilaria Mastrorosa, Patrizia Lorenzini, Carmela Pinnetti, Alessandra Vergori, Gabriele Fabbri, Raffaella Libertone, Maria Maddalena Plazzi, Pietro Balestra, Martina Ricottini, Rita Bellagamba, Mauro Zaccarelli, Adriana Ammassari, Stefania Cicalini, Andrea Antinori
Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy

Background: HIV associated neurocognitive disorder (HAND) remains prevalent also with effective antiretroviral therapy (ART). Chronic inflammation, due either to HIV per se, vascular and metabolic comorbidities, or viral co-infections, has been hypothesized to affect neurocognition. Thus, we investigated the association of determinants of increased vascular risk factors (VasR) with cognitive performances in a large cohort of HIV infected (HIV+) patients (pts).

Methods: This was a cross-sectional analysis of all neuropsychological (NP) evaluations performed by HIV+ pts between 2000 and 2017. HAND was assessed through a comprehensive battery of 14 tests on 5 different domains and classified according to Frascati's criteria. Diabetes (DB), dyslipidemia (DL) and hypertension (HT) were determined by i) patient self-report, ii) co-medications, iii) for DB, fasting glucose > 125 mg/dl, iv) for DL, at least two among: fasting total cholesterol >200 mg/dl, LDL >100 mg/dl, HDL <40 mg/dl for females or <50 mg/dl for males, triglycerides >150 mg/dl for. Body Mass Index (BMI) was calculated. Multivariable logistic model was built to assess link between VasR and HAND after adjustment by all main confounding covariates.

Results: We included 3,433 evaluations from 2,031 pts: male 79%, median age 48 years (IQR 40-55), median education 13 years (IQR 8-13), IDUs 20%, median CD4+ nadir 205/mm^3 (IQR 90-325) and current 515/mm^3 (IQR 305-725), HIV-RNA <50 cp/ml 63%, on ART 87%, HCV co-infection (HCV+) 19.5%. Prevalence of

VasR: overweight 26.4%, obesity 4.8%, HT 18.7%, DB 7.3%, DL 28%, current smoking 29%, prior cerebro/cardiovascular event 2.7%. When excluding pts with confounding factors, HAND was limited to 825 out of 2656 evaluations (24%): Asymptomatic Neurocognitive Impairment 12%, Mild Neurocognitive Disorder 9.7%, HIV-Associated Dementia 2.4%. Among factors associated to HAND, the risk was increased with DB and HCV+, and reduced with overweight (Table 1).

Conclusion: Diabetes and HCV coinfection, both characterized by a pro-inflammatory status and linked to accelerated vascular disease, are strong risk factors of HAND. Being overweight, a proxy of better medical and nutritional care and a measure of generalized rather than central obesity, seems to have a protective role on cognition. Traditional vascular risk-reduction strategies and HCV cure could improve neurocognitive performance in HIV+ persons.

	OR	95% CI		p	OR	95% CI		p
	Univariable				Multivariable			
Gender (male vs female)	0.99	0.81	1.21	0.935				
Age (per 10 years increase)	**1.24**	**1.15**	**1.35**	**<0.001**	**1.35**	**1.21**	**1.50**	**<0.001**
MSM	**0.60**	**0.51**	**0.71**	**<0.001**	1.12	0.91	1.38	0.300
Mode of HIV transmission								
MSM	1.00							
IDUs	1.95	1.54	2.46	<0.001				
heterosexual	1.66	1.37	2.01	<0.001				
other/unknown	1.07	0.74	1.55	0.707				
Years from HIV test	1.00	0.99	1.01	0.676				
Nadir CD4 < 200 cell/mm^3	0.97	0.92	1.02	0.197				
HIV-RNA at NPA								
detectable	1.00				**1.00**			
<40 cp/ml	**0.72**	**0.58**	**0.88**	**0.002**	**0.80**	**0.62**	**1.02**	**0.070**
undetectable	**0.44**	**0.36**	**0.54**	**<0.001**	**0.64**	**0.48**	**0.84**	**0.001**
CD4 at NPA*								
0-350 cell/mm^3	**1.00**				**1.00**			
351-500 cell/mm^3	**0.48**	**0.37**	**0.61**	**<0.001**	**0.56**	**0.43**	**0.73**	**<0.001**
501-700 cell/mm^3	**0.34**	**0.27**	**0.42**	**<0.001**	**0.43**	**0.33**	**0.56**	**<0.001**
701+ cell/mm^3	**0.28**	**0.22**	**0.36**	**<0.001**	**0.39**	**0.30**	**0.52**	**<0.001**
Education (per 1 year more)	**0.83**	**0.81**	**0.85**	**<0.001**	**0.85**	**0.83**	**0.87**	**<0.001**
Body Mass Index								
underweight	**1.94**	**1.32**	**2.86**	**0.001**	**1.41**	**0.92**	**2.18**	**0.117**
normal	**1.00**				**1.00**			
overweight	**0.78**	**0.64**	**0.95**	**0.013**	**0.71**	**0.57**	**0.88**	**0.002**
obesity	**0.99**	**0.67**	**1.49**	**0.980**	**0.79**	**0.50**	**1.24**	**0.300**
HCV co-infection								
antibodies -	**1.00**				**1.00**			
antibodies +	**1.71**	**1.41**	**.2.06**	**<0.001**	**1.28**	**1.02**	**1.61**	**0.031**
Hypertension	**1.27**	**1.03**	**1.57**	**0.024**	1.02	0.79	1.32	0.855
Diabetes	**1.84**	**1.36**	**2.50**	**<0.001**	**1.79**	**1.22**	**2.62**	**0.003**
CV Event*	0.74	0.39	1.39	0.346				
Dyslipidemia	1.01	0.85	1.20	0.919				
Current Smoking	0.92	0.77	1.10	0.370				
Fib4								
<1.45	**1.00**				1.00			
1.45-3.25	**1.40**	**1.11**	**1.78**	**0.005**	0.82	0.62	1.09	0.174
>3.25	**1.87**	**1.29**	**2.73**	**0.001**	0.80	0.52	1.23	0.317
Year of NPA*								
2000-2005	**1.00**				1.00			
2006-2011	**0.82**	**0.66**	**1.03**	**0.093**	1.00	0.71	1.41	0.995
2012-2017	**0.49**	**0.40**	**0.61**	**<0.001**	0.73	0.49	1.08	0.113

Table 1. Univariable and multivariable logistic regression models to define risk factors of HIV-associated neurocognitive disorder (HAND) including vascular and metabolic variables.
* NPA: neuropsychological assessment; CV event: stroke/transient ischemic attack/myocardial infarction/myocardial ischemia.

414 ENDOTHELIAL ACTIVATION IN HIV-ASSOCIATED ISCHEMIC STROKE AND MYOCARDIAL INFARCTION

Susan M. Graham[1], Susanna Harju-Baker[1], Junmei Chen[2], Jennie Le[2], Dominic W. Chung[2], Mark M. Wurfel[1], Yu Ni[1], Robin M. Nance[1], Peter W. Hunt[3], David Tirschwell[1], Alice S. Ryan[4], Jeffrey N. Martin[3], Heidi M. Crane[1], Jose A. Lopez[2], W. C. Liles[1]
[1]University of Washington, Seattle, WA, USA, [2]Bloodworks Northwest Research Institute, Seattle, WA, USA, [3]University of California San Francisco, San Francisco, CA, USA, [4]University of Maryland, Baltimore, MD, USA

Background: HIV infection, whether treated or untreated, leads to endothelial activation, which promotes platelet adhesion and accelerates atherosclerosis. We determined whether key biomarkers were elevated in individuals on antiretroviral therapy (ART) in the 12 months before an ischemic stroke or primary myocardial infarction (MI), relative to biomarker levels in matched controls who experienced no stroke or MI.

Methods: We conducted a case-control study nested in the CFAR Network of Integrated Clinical Systems cohort, comparing adjudicated cases with an ischemic stroke or primary (type 1) MI after ≥6 months of ART to controls matched on regimen and time since ART initiation. Biomarkers including angiopoietin 1, angiopoietin 2 (ANG-2), plasminogen activation inhibitor 1, serum amyloid A, interleukin 6 (IL-6), C-reactive protein (CRP), and soluble vascular cell adhesion molecule 1, intercellular adhesion molecule 1, P-selectin, and CD14 were measured in stored plasma. Conditional logistic regression identified biomarkers associated with stroke or MI status, with and without adjustment for potential confounders including age, race, sex, diabetes, tobacco use, hypertension, and statin use. Biomarkers were log-transformed. Odds ratios (OR) represent the odds of a stroke or MI for each log increase in biomarker level.

Results: Among 42 stroke cases and 83 matched controls, 76.2% and 88.0% had viral load <400 copies/mL, respectively ($\chi 2$ p=0.09). In bivariable analyses, ANG-2 was the only biomarker associated with stroke (OR 2.02, 95% confidence interval [CI] 1.03-3.97). In multivariable modeling, ANG-2 remained associated with stroke (adjusted OR 2.22, 95% CI 1.05-4.67). Among 69 MI cases and 138 matched controls, 82.6% and 77.5% had viral load <400 copies/mL, respectively ($\chi 2$ p=0.40). In bivariable analyses, ANG-2 (OR 1.84, 95% CI 1.09-3.13), IL-6 (OR 1.49, 95% CI 1.01-2.20), and CRP (OR 1.25, 95% CI 1.05-1.49) were each associated with MI. In multivariable models ANG-2 remained associated (aOR 1.73, 95% CI 1.01-2.95), CRP had a borderline association (aOR 1.22, 95% CI 0.98-1.51), and IL-6 had no association with MI.

Conclusion: ANG-2 levels were elevated in treated HIV-infected individuals in the 12 months prior to an ischemic stroke or primary MI, compared to treated HIV-infected controls. Because ANG-2 is a potential target for therapeutic intervention, additional study of its role in HIV-associated cardiovascular disease and related therapeutic interventions is warranted.

415 HAND IMPROVEMENT IS ASSOCIATED WITH INCREASED CPE SCORE AFTER ARV INTENSIFICATION

Gilles Force[1], Idir Ghout[2], Elodie Bouaziz-Amar[2], Karim Dorgham[2], Dhiba Marigot-Outtandy[2], Didier Troisvallets[3], Valerie Hahn[4], Helene Defferriere[2], Natacha Darchy[1], Jacques Ropers[2], Jean-Louis Laplanche[2], Constance Delaugerre[2], Gilles Peytavin[2], Guislaine Carcelain[2], Pierre de Truchis[2]
[1]Institut Hospitalier Franco-Britannique, Levallois-Perret, France, [2]AP–HP, Paris, France, [3]Centre Hospitalier de Gonesse, Gonesse, France, [4]Centre Hospitalier Sainte Anne, Paris, France

Background: Neuro+3 is a pilot open-label prospective study of ARV intensification in controlled patients (pts) with HAND. Initial treatment was switched for a new combination with better CPE score (ΔCPE ≥+3 for total score ≥9) and same cognitive tests were assessed at W48 and W96.

Methods: Among 63 screened pts, 31pts with HAND were included with at least 2 ability domains >1SD for the following tests and Beck Depression Inventory BDI II assessment: Grooved Pegboard (d and nd), Verbal Fluency, CVLT, Digit span, PASAT, Digit symbol, WCST (6 domains). Primary objective was to demonstrate improvement in Global Deficit Score (GDS) and HAND classification (HC), with ITT and PerProtocol analysis with updated 2016 genotype algorithm. Plasma and CSF virological and immunological assessment, neopterin and NFL, were followed.

Results: Initial median CPE score of 6 increased to 10 after intensification (MVC addition 10pts, add or switch InSTI 21pts, NNRTI 6pts, DRV/r 6pts, ABC 4pts). Median GDS improved from 1.4 at baseline to 0.8 at W48 (p=0.012) and 1.0 at W96 (p=0.009); HC (16 HAD, 8 MND, 7 ANI) became at W48 (8, 5, 11, and 7 pts with only one altered domain)(p=0.002) and at W96 (6, 3, 17, 2, and 3 pts with normal tests)(p<0.001). At W96 we observed both GDS improvement (GI) (GDS reduction ≥0.2) and HC improvement in 12 pts (39%) and improvement of one of the items (GI or HC) in 13 pts (42%). Lowest CPE score at baseline was predictive for GI at W48 (rho=0.5;p=0.017). In comparison with improved GDS group (19 pts), failing GDS group (12 pts) at W96 had more frequently positive CSF VL 67% vs 26% (p=0.084), had bad evolution for ΔBDI score -0.5 vs -6 (p=0.024), had lesser ΔCPE 2016 score +3 vs +4 (p=0.041), had persistent inflammation in plasma with Δneopterin +1.9 vs -0.4 (p=0.028). Enhanced CPE 2016 score was predictive for GI at W48 (rho=-0.46;p=0.03): no GI if ΔCPE ≤+2, 50% with ΔCPE +3, 67% with +4, and 83% if ≥+5. We compared the 22 patients with enhanced CPE 2016 score vs the 9 others, and ΔGDS was -0.4 vs +0 (p=0.018), ΔBDI score -5 vs +1 (p=0.029). No correlation was found between

GI and a specific drug class intensification, except ABC for which we observed deterioration of Working Memory +1.5 vs 0 at W96 (p=0.008).
Conclusion: Intensification strategy demonstrated clear improvement in GDS and HC, particularly with effective CPE 2016 ≥9, and correlation with enhanced CPE 2016 score. For ARV controlled pts, an updated CPE score taking in account potential drug toxicity could be useful.

416 CROSS-SECTIONAL AND CUMULATIVE LONGITUDINAL CPE SCORES ARE NOT ASSOCIATED WITH HAND

Galia Santos[1], **Katharine Darling**[1], Isabella Locatelli[1], Melanie Metral[1], Alexandra Calmy[2], Thanh Doco-Lecompte[2], Christoph Hauser[3], Helen Kovari[4], Philip E. Tarr[5], Marcel Stoeckle[6], Caroline Di Benedetto[7], Patrick Schmid[4], Renaud Du Pasquier[1], Matthias Cavassini[1]
[1]Lausanne University Hospital, Lausanne, Switzerland, [2]University Hospitals of Geneva, Geneva, Switzerland, [3]University of Bern, Bern, Switzerland, [4]University Hospital Zurich, Zurich, Switzerland, [5]University of Basel, Basel, Switzerland, [6]University Hospital Basel, Basel, Switzerland, [7]Ospedale Regionale di Lugano, Lugano, Switzerland

Background: Higher Central nervous system Penetration Effectiveness (CPE) scores have been associated with better control of HIV replication in the central nervous system (CNS) but the link between CPE score and neurocognitive function remains controversial. Studies to date examining CPE score and HAND have used the CPE score as a cross-sectional variable. The potential association between HAND and a cumulative CPE score, representing the entire longitudinal history of a patient's cART exposure over years, has not been explored. We hypothesized that a cumulative CPE score (summarizing scores from cART initiation to the time of neurocognitive assessment) would better predict the presence of HAND than a cross-sectional CPE score (a single measure at the time of neurocognitive assessement).
Methods: The Neurocognitive Assessment in the Metabolic and Aging COhort (NAMACO) is an ongoing prospective longitudinal observational sub-study of the Swiss HIV Cohort Study (SHCS), set up to study the cognitive and neurological impact of HIV infection on an aging HIV-positive population. In this study, 981 HIV-positive SHCS participants aged ≥45 years underwent a standardized neurocognitive assessment. The cross-sectional and cumulative CPE scores were tested as potential predictors of the presence of HAND in multivariate logistic regression models.
Results: The majority of patients were male (80%) and Caucasian (92%). Undetectable HIV-RNA in the plasma was recorded in 96%. Neurocognitive impairment was present in 40%. Overall, 27% were considered to have HAND with 26%, 0.8% and 0.6% classified as asymptomatic neurocognitive impairment, mild neurocognitive disorder and HIV-associated dementia, respectively. Non-HIV-associated factors contributed to neurocognitive impairment in 13% of the population. None of the cross-sectional and cumulative CPE scores tested was statistically significantly associated with neurocognitive impairment or with HAND.
Conclusion: In this large and well-treated HIV-positive cohort, 27% were diagnosed with HAND. Cross-sectional and cumulative CPE scores were not associated with HAND or with non-HAND neurocognitive impairment. However, further longitudinal analysis will provide a valuable means of establishing factors in the future which may be associated with the appearance, persistence or resolution of neurocognitive impairment. The impact of modifying cART, and potentially CPE score, on neurocognitive performance will be examined in future longitudinal studies within the NAMACO study.

417 EXOSOMAL MICRO-RNA EXPRESSION ASSOCIATES WITH NEUROPSYCHOLOGICAL FUNCTION DURING ART

Tess O'Meara[1], Yong Kong[1], Brinda Emu[1], Kevin Robertson[2], Richard W. Price[3], Sarah Yosief[2], Xinran N. Liu[1], Rabib Chaudhury[1], Serena S. Spudich[1], Lingeng Lu[1]
[1]Yale University, New Haven, CT, USA, [2]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [3]San Francisco General Hospital, San Fransisco, CA, USA

Background: Mechanisms of persistent neurological impairment during antiretroviral therapy (ART) are poorly understood. Exosomes, nanoparticles exocytosed from cells, contain bioactive molecules that affect cellular activity. We performed deep sequencing and pathway analyses of plasma exosomal miRNA (exo-miRNA) to examine associations between exo-miRNA signaling and neuropsychological (NP) performance after ART initiated in early infection.
Methods: Participants who started ART in early infection were divided into 2 two groups based on Total-Z (TZ) score (motor, executive function, processing speed, memory, and learning): higher (NP+, TZ>0) and lower scoring (NP-, TZ<0). Exosomes were precipitated from plasma using a polyethylene glycol solution and assessed with NanoSight nanoparticle tracking analysis (NTA), transmission electron microscopy (TEM), and exoELISA-Ultra assay for CD63 expression. After massive parallel sequencing of extracted exo-miRNA, differential expression between NP- and NP+ was assessed as -1≥log2 fold-change≥1, base-mean expression level>10, p<0.05, with patient age as a covariate. KEGG pathway analyses were performed on microT-CDS-predicted miRNA targets, with p value representing the probability of the pathway enriched by differentially expressed miRNAs.
Results: Samples were collected from 19 men with median age 43 years, CD4+ count 641 cells/ul, plasma HIV RNA <50 copies, 0.6 years of pre-ART infection, and 1.2 years-duration of ART. Median TZ scores were 0.35 for NP+ (n=12) and -0.50 for NP- (n=7). Exosome extraction was confirmed by visualization of vesicles with TEM, measurement of their diameters by NTA, and detection of surface CD63 expression. After miRNA sequencing, 15 differentially expressed miRNAs were identified between NP+ and NP- groups (p<0.05). miR-708 was the most differentially expressed exo-miRNA, with 37-fold higher levels in NP- vs NP+ (p=9.6E-4). Let-7a-5p was expressed at 3-fold higher levels in NP+ vs NP- (p=3.7E-3). KEGG analysis implicated 12/15 identified exo-miRNAs in glycosphingolipid biosynthesis pathways (p=1.7E-11).
Conclusion: High-throughput analyses revealed differentially expressed plasma exo-miRNAs in higher versus lower NP performing participants despite early suppressive ART. Many of these miRNAs are predicted to target pathways related to neurological function, including sphingolipid biosynthesis, previously related to neurodevelopment and cognition. Exo-miRNAs may associate with cerebral function and deserve further investigation.

418 NO CHANGE IN NEUROCOGNITIVE FUNCTION AFTER SWITCHING FROM EFAVIRENZ TO RILPIVIRINE

Giuseppe Lapadula[1], Davide P. Bernasconi[2], Francesca Bai[3], Antonio Di Biagio[4], Emanuele Focà[5], Stefano Bonora[6], Francesco Castelli[7], Claudio Viscoli[8], Alessandra Bandera[1], Antonella D'Arminio Monforte[3], Andrea Gori[1]
[1]San Gerardo Hospital, Monza, Italy, [2]University of Milano–Bicocca, Milan, Italy, [3]University of Milan, Milan, Italy, [4]IRCCS AOU San Martino-IST, Genoa, Italy, [5]Spedali Civili di Brescia, Brescia, Italy, [6]University of Turin, Turin, Italy, [7]University of Brescia, Brescia, Italy, [8]University of Genoa, Genoa, Italy

Background: Efavirenz (EFV) association with neuropsychiatric side effects is well known. However, a link between EFV and neurocognitive (NC) impairment is controversial. Whether switching from EFV to rilpivirine (RPV) can improve NC performances is still debated.
Methods: Randomized open-label controlled trial. Eligible patients (pts) had confirmed HIV-RNA <50 cp/ml for >6 months under treatment with co-formulated TDF/FTC/EFV and at least one among: (i) Z-transformed score <-1 in at least 1 of 6 cognitive domains explored by NC assessment; (ii) depression or anxiety, defined as scores >90th percentile in Beck Depression Inventory-II (BDI-II) or Beck Anxiety Inventory (BAI); (iii) low quality of sleep (i.e., a Pittsburgh Sleep Quality Index [PSQI] score >5). Pts were randomized 1:1 to continuing TDF/FTC/EFV or switching to co-formulated TDF/FTC/RPV. Treatment efficacy, NC function and symptoms were evaluated 12 and 24 weeks after randomization.
Results: 74/125 screened patients fulfilled inclusion criteria and were randomized to switch arm (36 patients) or continuation arm (38 patients). 89.2% of pts were male, mean age was 47 (SD:10.3) and current and nadir CD4+ counts were 702 (SD:265) and 299 (SD:139) cells/mm^3. At baseline, total NC functioning z-score was -0.02 (0.78); 63% and 23.4% of the pts had z-scores below -1 in ≥1 or 2 domains. The proportion of pts with altered scores in BDI-II, BAI and PSQI was 31.1%, 17.6% and 44.6%. At week 24, 71 pts were re-evaluated by NC assessment. Overall, NC performances improved, but no statistically significant difference was found comparing the two arms (table 1). Depression and anxiety reduced over time, with no statistically significant difference between arms (at week 24, 14.8% vs. 17.1%, P=1 and 0% vs. 8.3%, P=0.25 for switch and continuation arm). A significant improvement in CNS symptoms, quality of sleep and self-reported cognitive failures was reported by pts in the switch but not in the continuation arm (table 1). At week 24, 97.1% and 97.3% of pts had HIV-RNA <50 copies/ml in the switch and continuation arm, respectively (P=0.24). No protocol defined virological failure, grade ≥3 laboratory abnormalities nor serious adverse events related to the study drugs were observed.

Conclusion: Our results do not support the hypothesis that treatment modification improves NC function in patient under stable treatment with EFV.

Table 1: Total and domain-specific Z-scores and symptom scores across 24 weeks of observation, grouped by randomization arm.

	Treatment arm	Baseline mean(sd)	Week 12 mean(sd)	Week 24 mean(sd)	Change week 24 – baseline (95% CI)	P *A vs. B*
Neurocognitive test results (z-scores)						
Memory	A (Switch)	-0.64 (0.92)	-0.48 (1.2)	0.06 (1.07)	0.68 (0.44;0.92)	0.738
	B (Continuation)	-0.69 (0.86)	-0.56 (1.07)	0 (1.05)	0.74 (0.46;1.03)	
Language	A (Switch)	0.62 (1.12)	1.05 (1.13)	1.02 (1.39)	0.38 (0;0.75)	0.653
	B (Continuation)	0.69 (1.27)	0.93 (1.21)	0.86 (1.25)	0.26 (-0.06;0.59)	
Attention	A (Switch)	-0.05 (0.9)	-0.1 (0.8)	0.05 (0.79)	0.03 (-0.2;0.26)	0.202
	B (Continuation)	0.12 (0.88)	0.17 (1.01)	0.34 (0.65)	0.23 (0.01;0.45)	
Motor	A (Switch)	-0.62 (1.99)	-0.35 (1.57)	-0.18 (1.52)	0.46 (0;0.92)	0.335
	B (Continuation)	-0.89 (1.71)	-0.92 (1.53)	-0.77 (1.8)	0.15 (-0.31;0.61)	
Speed	A (Switch)	0.96 (0.36)	0.96 (0.56)	1.08 (0.4)	0.12 (-0.01;0.25)	0.806
	B (Continuation)	0.76 (0.6)	0.89 (0.53)	0.89 (0.51)	0.15 (-0.04;0.33)	
Executive	A (Switch)	0.26 (1.08)	0.48 (1.09)	0.55 (0.8)	0.31 (0.02;0.61)	0.322
	B (Continuation)	0.23 (1.06)	0.08 (2)	0.27 (1.59)	0.09 (-0.27;0.44)	
Global	A (Switch)	0.01 (0.84)	0.22 (0.78)	0.39 (0.70)	0.38 (0.2;0.56)	0.458
	B (Continuation)	-0.04 (0.73)	0.01 (0.86)	0.17 (0.83)	0.28 (0.08;0.49)	
Symptom scores						
PSQI	A (Switch)	6.03 (3.24)	4.91 (2.49)	4.29 (2.45)	-1.58 (-2.49;-0.67)	0.011
	B (Continuation)	4.71 (3.68)	4.5 (3.78)	4.61 (3.5)	-0.08 (-0.8;0.64)	
CNS score	A (Switch)	12.69 (8.31)	8.11 (6.3)	7.09 (4.63)	-5.8 (-8.22;-3.38)	0.002
	B (Continuation)	10.74 (10.78)	7.69 (9.08)	9.35 (10.31)	-0.81 (-2.82;1.2)	
CFQ	A (Switch)	16.86 (11.11)	11.11 (7.34)	8.11 (5.74)	-9.03 (-12.09;-5.97)	0.001
	B (Continuation)	14.47 (14.85)	13.83 (14.46)	10.92 (12.18)	-2.78 (-4.91;-0.66)	

List of abbreviations: CFQ, cognitive failure questionnaire; CNS, central nervous system; PSQI, Pittsburgh Sleep Quality Index

419 BENEFICIAL EFFECT OF 6 MONTHS OF PROBIOTICS ON ASYMPTOMATIC NEUROCOGNITIVE IMPAIRMENT

Luigi Celani, Eugenio Nelson Cavallari, Mariangela Fratino, Claudia Pinacchio, Giuseppe Corano Scheri, Gabriella De Girolamo, Giancarlo Ceccarelli, Claudio M. Mastroianni, Carolina Scagnolari, Vincenzo Vullo, Gabriella d'Ettorre
Sapienza University of Rome, Rome, Italy

Background: HIV infected subjects show high prevalence of mild neurocognitive symptoms; individuals with Asymptomatic Neurocognitive Impairment (ANI) show increased risk of future symptomatic decline but to date interventional strategies to prevent the onset of symptomatic conditions have not been defined.

Methods: 35 HIV infected individuals successfully treated with HAART were enrolled in this unblinded, non-randomized study. At baseline (T0) a battery of 20 neurocognitive tests was administered to evaluate patients' cognitive function and a lumbar puncture was performed to determine neopterin concentration in cerebrospinal fluid (CSF). Subsequently, 9 participants underwent a 6 months course of antiretroviral therapy supplementation with a commercially available oral probiotic (2 sachets, each containing 450 billion bacteria, twice a day; composition: *Lactobacillus plantarum*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus paracasei*, *Lactobacillus delbrueckii subsp. bulgaricus*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, *Bifidobacterium infantis*); after supplementation, participants included in the interventional group were evaluated with a second lumbar puncture and with a second neurocognitive tests assay, whereas controls, for ethical reasons, underwent a second battery of neurocognitive tests after 12 months (T12).

Results: At T0, demographics, variables related to infection and neurocognitive tests results were similar between the two groups; all participants showed an abnormal result in at least one test exploring the executive functions and most individuals presented a pathological impairment in at least two different domains; neopterin concentration in CSF was elevated in 33 out of 35 patients and an higher neopterin level was correlated with a poorer result in several neurocognitive tests. After supplementation with probiotics (T6), participants in the interventional group presented a significant decrease of neopterin concentration ($p < 0.005$) and a significant improvement in many neurocognitive tests, while no significant modifications were observed between T0 and T12 in controls (data showed in Table 1).

Conclusion: Supplementation with this specific probiotic could represent a useful strategy to ameliorate cognitive function in HIV infected individuals with ANI. Further investigations are needed to define the long term benefits of supplementation with this product.

Neurocognitive tests	Probiotics supplementation group vs. Control group (T6 vs.T12)	Probiotics supplementation group (T0 vs. T6)	Control group (T0 vs. T12)
Rey-Osterrieth Complex Figure immediate recall *(more is better)*	22.0 (19.0-23.7) vs. 14.7 (8.8-20.3) (p 0.011)	16.6 vs. 22.0 (p 0.007)	13.1 vs. 14.7 (p 0.603)
Rey-Osterrieth Complex Figure delayed recall *(more is better)*	22.4 (22.0-25.5) vs. 12.6 (5.7-19.1) (p 0.011)	15.5 vs. 22.4 (p 0.008)	11.6 vs. 12.6 (p 0.369)
Rey Auditory Verbal Learning Test immediate recall *(more is better)*	53.0 (49.3-55.6) vs. 32.5 (28.7-37.5) (p 0.008)	46.0 vs. 53.0 (p 0.028)	30.6 vs. 32.5 (p 0.619)
Rey Auditory Verbal Learning Test delayed recall *(more is better)*	12 .0 (10.7-13.8) vs. 5.3 (4.3-8.0) (p 0.008)	9.2 vs. 12.0 (p 0.034)	5.2 vs. 5.3 (p 0.241)
Rey Auditory Verbal Learning Test recognition *(more is better)*	99.0 (97.0-100.0) vs. 96.0 (92.0-98.0) (p 0.013)	98.0 vs. 99.0 (p 0.176)	96.0 vs. 96.0 (p 0.575)
Verbal Fluency *(more is better)*	15.9 (14.1-18.0) vs. 15.3 (13.7-16.8) (p 0.594)	15.0 vs. 15.9 (p 0.233)	15.9 vs. 15.3 (p 0.152)
Phonological Verbal Fluency *(more is better)*	44.0 (42.5-45.0) vs. 25.9 (21.6-36.1) (p 0.021)	30.0 vs. 44.0 (p 0.028)	26.7 vs. 25.9 (p 0.271)
Semantic Verbal Fluency *(more is better)*	49.0 (46.0-49.0) vs. 38.0 (33.5-43.5) (p 0.123)	47.0 vs. 49.0 (p 0.373)	39 vs. 38.0 (p 0.396)
Visual Search Test *(more is better)*	49.0 (45.6-50.0) vs. 46.7 (40.2-50.6) (p 0.722)	46.2 vs. 49.0 (p 0.859)	46.7 vs. 46.7 (p 1.000)
Test of Weights and Measures Estimation – Time *(more is better)*	23.0 (21.0-23.5) vs. 22.0 (18.0-25.0) (p 0.512)	19.0 vs. 23.0 (p 0.038)	22.0 vs. 22.0 (p 0.776)
Test of Weights and Measures Estimation – Weight *(more is better)*	21.0 (20.5-23.5) vs. 20.0 (15.5-21.5) (p 0.08)	19.0 vs. 21.0 (p 0.027)	19 vs. 20.0 (p 0.843)
Test of Weights and Measures Estimation – Total *(more is better)*	45.0 (41.5-46.0) vs. 40.0 (35.5-44.0) (p 0.02)	38.0 vs. 45.0 (p 0.138)	40.0 vs. 40.0 (p 0.776)
Raven's Standard Progressive Matrices *(more is better)*	30.0 (28.5-33.5) vs. 28.3 (25.2-31.6) (p 0.374)	25.7 vs. 30.0 (p 0.208)	28.3 vs. 28.3 (p 0.939)
Verbal Span forward *(more is better)*	5.0 (5.0-6.0) vs. 5.2 (4.6-6.0) (p 0.551)	5.0 vs. 5.0 (p 0.121)	5.2 vs. 5.2 (p 0.632)
Verbal Span backward *(more is better)*	5.0 (4.0-5.0) vs. 4.0 (3.75-5.0) (p 0.206)	5.0 vs. 5.0 (p 1.000)	4.0 vs. 4.0 (p 0.344)
Corsi Block Tapping Test forward *(more is better)*	5.2 (5.0-5.5) vs. 5.2 (5.0-6.0) (p 0.888)	4.7 vs. 5.2 (p 0.049)	5.5 vs. 5.2 (p 0.980)
Corsi Block Tapping Test backward *(more is better)*	4.0 (4.0-4.5) vs. 5.0 (4.0-5.0) (p 0.102)	4.0 vs. 4.0 (p 0.180)	5.0 vs. 5.0 (p 0.317)
Aachener Aphasia Test *(more is better)*	9.0 (9.0-9.0) vs. 9.0 (9.0-9.0) (p 1.000)	9.0 vs. 9.0 (p 1.000)	9.0 vs. 9.0 (p 1.000)
Trail Making Test A (sec.) *(less is better)*	43.0 (39.0-53.0) vs. 51.0 (40.5-65.5) (p 0.674)	50.0 vs. 43.0 (p 0.041)	50.0 vs. 51.0 (p 0.747)
Trail Making Test B (sec.) *(less is better)*	120.0 (76.0-138.0) vs. 98.0 (78.5-146.0) (p 0.138)	115.0 vs. 120.0 (p 0.726)	97.0 vs. 98.0 (p 0.279)

420 LOW DOSE HYDROCORTISONE ENCHANCES COGNITIVE FUNCTIONING IN HIV-INFECTED WOMEN

Leah H. Rubin, Luan Phan, Pauline M. Maki
University of Illinois at Chicago, Chicago, IL, USA

Background: Low dose hydrocortisone (LDH) administration enhances aspects of learning and memory in some populations including PTSD. HIV-infected men demonstrate only acute enhancing effects of LDH on verbal learning; however, the cognitive effects of LDH in HIV-infected women remain unknown. Understanding these effects in HIV-infected women are particularly important given findings from large-scale studies showing stress-related learning and memory impairment in the context of HIV.

Methods: In a double-blind, placebo-controlled, cross-over study we examined the time-dependent effects of a single low dose administration of hydrocortisone (10mg oral; LDH) on cognition in 36 HIV-infected women. Participants were randomized to LDH or placebo and the opposite treatment was given one month later. After pill administration, cognition was assessed 30-minutes (assessing nongenomic effects) and 4-hours later (assessing genomic effects). Self-reported stress/anxiety and salivary cortisol were assessed throughout sessions.

Results: LDH significantly increased salivary cortisol levels versus placebo; levels returned to baseline 4-hours post-administration. At the 30-minute assessment, LDH enhanced verbal learning and memory, working memory, behavioral inhibition, and visuospatial abilities. At the 4-hour assessment, LDH enhanced verbal learning and memory compared to placebo. LDH did not affect subjective stress/anxiety or any other cognitive domain at either time point.

Conclusion: The enduring effects of LDH on learning and memory suggest potential clinical utility in HIV-infected women. These findings are in contrast to our findings in HIV-infected men who did not show any cognitive benefits at the 4-hour time point. Larger, longer-term studies are under way to verify possible sex-specific cognitive enhancing effects of LDH and the clinical significance of these effects in HIV.

421 ORAL MGBG WITH cART BLOCKS AIDS AND SIVE, AND REDUCES CNS INFECTION AND CAROTID IMT

Jaclyn Mallard[1], Jamie Schafer[1], Kevin White[1], Arianna Noggle[1], Joseph Enders[1], Cecily Midkiff[2], Xavier Alvarez[2], Tricia H. Burdo[3], Kenneth C. Williams[1]
[1]Boston College, Chestnut Hill, MA, USA, [2]Tulane National Primate Research Center, Covington, LA, USA, [3]Temple University, Philadelphia, PA, USA

Background: HIV-associated neurocognitive disorders (HAND) and cardiovascular disease persist despite stable viral suppression with combined antiretroviral therapy (cART). Activated monocytes, and brain and cardiovascular macrophages remain despite cART. In this study, we use oral administration of methylglyoxal-Bis-Guanylhydrazone (MGBG), a polyamine biosynthesis inhibitor targeting myeloid cells, with cART, as an adjunctive therapy targeting activated Mo/MΦ.

Methods: Three cohorts of CD8-depleted, SIVmac251-infected Rhesus macaques were used: untreated animals (n = 4), animals that received daily cART (n = 6) at 21 days post infection (dpi) and animals that received daily MGBG+cART (n = 5) at 21 dpi. Treated animals were time-sacrificed at 120 dpi and untreated animals were sacrificed with development of AIDS.

Results: None of the cART or MGBG+cART animals developed AIDS or SIV-associated encephalitis (SIVE), but 3/6 cART alone animals had meningitis, compared to 0/6 MGBG+cART animals. MGBG+cART animals had a significant decrease in MFI of CX3CR1 (p<.01) and CD163 (p<.01) on CD14+CD16+ monocytes compared to controls. At necropsy, percentages of BrdU+ CD14+CD16+ monocytes were significantly lower in MGBG+cART animals (0.4%) compared to cART alone (3.6%) and control animals (23.2%) (p<.05). MGBG+cART resulted in an additive 1.5 fold decrease in the percentage of CD14+CD16+ monocytes compared to control animals vs cART alone (p<.01). MGBG+cART resulted in a 2.5-fold decrease in MFI of CD169 on CD14+CD16+ monocytes compared to cART alone (p<.0001). Plasma viral load of cART vs MGBG+cART was equivalent, and at least 4.5 log less than controls. There was a 10-fold decrease in the number of SIVp28+ cells in the CNS of MGBG+cART animals vs cART alone (p <.05). There was a trend of lower numbers of macrophages in the brains of MGBG+cART animals (23.6+5.5 cells/mm2) compared to cART animals (31.0+4.9 cells/mm2). There were no significant differences between the number of macrophages in left ventricles with MGBG+cART vs cART alone. There was a significant difference between control cIMT vs MGBG+cART (p<.05) and control cIMT vs cART alone (p<.05).

Conclusion: These results demonstrate an additive effect of MGBG+cART targeting activated monocytes and activated, infected CNS macrophages, in addition to blocking AIDS and SIVE and decreasing cIMT. These results point to MGBG that can be used in addition to cART that can function as an adjunctive therapy targeting HIV associated co-morbidities.

422 DEPRESSION IS COMMON AND ASSOCIATED WITH COGNITIVE FUNCTION IN WELL-TREATED HIV

Åsa Mellgren[1], Maria Jivegård[1], Magnus Gisslén[2]
[1]South Älvsborgs Hospital, Boras, Sweden, [2]Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Background: Depression and depressive symptoms are common persons with HIV (PWH) and is often underdiagnosed. Neuroinflammation has been suggested to contribute to the high prevalence of depression but there is very limited data on CSF biomarkers and its relation to depressive symptoms in HIV. We wanted to investigate the association between CSF immune activation, depressive symptoms and neurocognitive function.

Methods: We have prospectively included PWH in a longitudinal study of CSF biomarkers, depressive symptoms and neurocognitive performance. Depressive symptoms were assessed by Montgomery Åsberg Depression Rating Scale (MADRS) where a score >12 was used as cut-off for depression. CSF was analyzed for HIV RNA, white blood cell count, neurofilament light protein (NFL) β2-microglobulin, neopterin, IgG and albumin. Serum and plasma was sampled for HIV RNA, CD4 cell count, albumin, IgG, neopterin and β2-microglobulin. Neurocognitive function was assessed in five cognitive domains by CogState Brief Battery and Groton Maze Learning Test. Patients responded to screening questions regarding cognitive function recommended by EACS. All subjects had been on ART for >6 months (mean 9.7 years +/- 6.7). 51 male and 26 female were included. Mean age was 50 (+/-11.6) years. Statistical method The association between MADRS ≤12 vs >12, and selected patient characteristics, laboratory data and CogState variables were performed by using generalized estimating equation (GEE) models for binary outcome, with log-link function, allowing for repeated measures and adjustment for within-patient correlations. All tests were two-tailed and conducted at 0.05 significance level.

Results: 20 % of individuals scored >12 on MADRS depression score. Depressive symptoms were significantly associated with impaired neurocognitive functioning (Combined CogState score of five tests) (RR=1.8, p<0.001), and to responding "yes" on all three screening questions (RR from 5.1-22.0, p<0.01). No significant association was found between depressive symptoms and plasma or CSF inflammatory markers, CSF NFL, HIV RNA or CD4 cell count (nadir or current).

Conclusion: We found no association between CSF immune-activation and depressive symptoms in well-treated PWH. Instead, a there was significant association between depression and neurocognitive impairment both by subjective measures and CogState neurocognitive testing of five cognitive domains. It is important to screen for depression in patients with neurocognitive symptoms.

423 DEPRESSION SYMPTOM CHANGES OF HIV POSITIVE INDIVIDUALS IN THE RAKAI COHORT

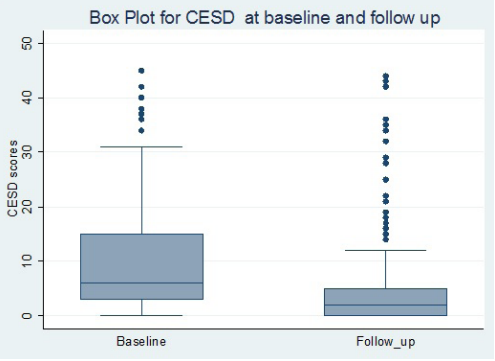
Noeline Nakasujja[1], Gertrude Nakigozi[2], Deanna Saylor[3], Kevin Robertson[4], Ronald H. Gray[3], Maria Wawer[3], Ned Sacktor[3]
[1]Makerere University College of Health Sciences, Kampala, Uganda, [2]Rakai Health Sciences Program, Kalisizo, Uganda, [3]Johns Hopkins University, Baltimore, MD, USA, [4]University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: Immunological function can impact the expression of depression symptoms but has not been well studied, especially in Sub Saharan Africa which has two thirds of the global burden of HIV infection. In this setting only half of HIV+ have access to antiretroviral therapy. Depression, the most common neuropsychiatric disorder in the HIV population is associated with initial HIV diagnosis, the effect of a chronic illness and stigma. We evaluated the effect of baseline immunological status(CD4 and viral load) on the expression of depressive symptoms in a cohort of HIV positive individuals followed up for 2 years

Methods: We evaluated 333 antiretroviral naïve HIV+ (150 with CD4 count < 200cells/µL; 183 with CD4 351-500 cells/µL) at baseline and 2 years after initiation of antiretroviral therapy (ART). Significant depressive symptoms were assessed using the Center for Epidemiologic Studies Depression scale (CESD) with a cut off score of >16. Viral load was measured using Abbot Realtime assay. Odds ratios with 95% CI were estimated using logistic regression.

Results: The mean (SD) age was 35.3 (8.6) years. There were more females 102 (56%) within the CD4 range 350-500 µL. Viral load was >1000 copies in 311 (93.9%) of ART naive participants at baseline and 35 (10.5%) at follow up. By the time of follow up, 312(93%) of the participants had initiated ART. The CESD mean (SD) score was higher at baseline 9.6 (9.3) than at the 2 year follow up 4.4 (7.4) p<0.01, see figure 1. There were 73(22%) individuals with CESD >16 at baseline and 28(8.4%) at follow up. Women had a higher mean CESD score than men both at baseline (10.8 vs 8.4) p<0.01 and follow up (5.2 vs 3.6) p<0.01. Adjusted odds for having significant depressive symptoms (CESD >16) were lower at follow up OR =0.3, 95%CI 0.2-0.5; p<0.01, and if baseline CD4 was 350-500 cells/µL, OR = 0.6, 95%CI 0.3-0.9;p= 0.03. Depression risk was higher for women than men OR = 1.6, 95%CI ;1.1-2.5; p=0.02, and increasing age OR =0.1, 95%CI 1.00-1.05; p=0.01. Viral load was not associated with depression symptoms at baseline and follow up.

Conclusion: Depressive symptoms lessen but persist even when the immunological function improves in HIV patients after initiation of ART. Females have more depressive symptoms than males. Managing depression in HIV infected patients should form part of routine HIV care.



424 CNS TOXICITY OF DTG IS NOT ASSOCIATED WITH PSYCHIATRIC CONDITIONS OR PLASMA EXPOSURE

Christian Hoffmann[1], Eva Wolf[2], Knud Schewe[1], Michael Sabranski[1], Hans-Jurgen Stellbrink[3], Axel Adam[1], Thomas Buhk[1], Stefan Hansen[1], Stefan Fenske[1], Thomas Brinkmann[4], Harald Ertl[4], Jürgen Hartleb[4], Gerrit Mohrmann[4], Christian Noah[4]

[1]ICH Study Center, Hamburg, Germany, [2]MUC Research, Munich, Germany, [3]Infectiologisches Centrum, Hamburg, Germany, [4]Labor Lademannbogen, Hamburg, Germany

Background: Reported rates of neuropsychiatric adverse events (NPAEs) leading to Dolutegravir (DTG) discontinuation in clinical routine have been markedly higher than seen in randomized trials (RCTs), in particular in female and in older pts. It has been speculated that this may be due to higher background rates of psychiatric conditions in HIV+ pts and/or elevated plasma drug levels in specific populations.

Methods: In this single center study, charts of all HIV+ pts who had initiated DTG outside RCTs were evaluated for depressive disorders or other neuropsychiatric diagnoses (ICD-10-CM, Diagnosis Codes F01-F99). In addition, DTG plasma levels from frozen samples collected at various time points after drug intake of pts discontinuing DTG due to NPAEs were measured by liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS). Levels were compared with levels of a control group of pts with a comparable age and gender distribution who had continued DTG containing regimens for at least one year without reported neuropsychiatric problems.

Results: In total, 861 pts (768 males, median age 47.1 years) had initiated DTG outside RCTs since 2014, among them 151 treatment-naïve and 710 treatment-experienced pts. There were 155 pts (18.0%) with depressive disorders and 55 pts (6.4%) with other neuropsychiatric diagnoses. After a median follow-up of 19.6 months, 54/861 pts (6.3%) had discontinued DTG due to NPAEs, mainly sleep disorders (74%), dizzyness (52%), and paraesthesia (33%). NPAEs leading to discontinuation were observed more frequently in women (hazard ratio [HR] 2.31; 95% confidence interval [CI] 1.12-4.74, p=0.03), in patients older than 60 years (HR 2.14; 95% CI 1.10-4.18, p=0.025), but not in patients with depressive disorders (HR 1.00; 95% CI 0.54-1.88, p=0.952) or other neuropsychiatric diagnoses (HR 0.93; 95% CI 0.29-3.00, p=0.896). In 37 patients who had discontinued DTG due to NPAEs of whom stored samples were available, population plasma drug levels of DTG including peak levels did not differ substantially from control pts who did not discontinue DTG due to NPAEs.

Conclusion: In this large cohort of HIV+ patients exposed to DTG in clinical routine, discontinuation due to NPAEs was around 6 %. Drug discontinuation was not associated with a pre-existing or prevalent depression or with other neuropsychiatric diagnoses, but with female sex and older age. The effect of DTG plasma exposure on the occurrence of NPAEs appears to be limited.

425 BRAIN VOLUMES CHANGES AFTER ABC/3TC + EFV OR TDF/FTC + ATV/R AS FIRST-LINE ART

Ignacio Pérez-Valero[1], Lucia Bailon[1], Alicia Gonzalez[1], Belen Alejos[1], Helena Melero[2], Norberto Malpica[2], Jose I. Bernardino[1], Juan González-García[1], Jose R. Arribas[1]

[1]Hospital La Paz Institute for Health Research, Madrid, Spain, [2]Universidad Rey Juan Carlos, Madrid, Spain

Background: Volumetric MRI studies evaluating the effect of ART initiation over cortical and subcortical grey matter (GM) volume changes are scarce, non-randomized and don't compare the effect of ART regimens with different CNS penetration (CP) and neurotoxicity (NT) profiles.

Methods: Randomized, open-label, 24-week pilot clinical trial comparing brain structures (3T-MRI) and neurocognitive changes (NC) in 7 domains after ART initiation with arm1: ABC/3TC+EFV (higher CP and in vitro NT) vs. arm 2: TDF/FTC+ATV/r (lower CP and in vitro NT). We compared volume and thickness changes (week 24 – day 0), in patients who completed all study procedures both by intention to treat (ITT: all patients) and per protocol (PP: excluding patients who changed therapy or did not achieve virologic suppression) analysis. Volumes were calculated using Freesurfer software and normalized using the Intracranial Volume and the Mean Thickness. Comparison were performed using the Wilcoxon signed-rank test and a linear regression estimative model adjusted by significant baseline covariables. Volume changes and NC changes were correlated using Pearson's r.

Results: 25 Caucasian (91.7%) male (100%), mean age: 37.3 years, median CD4+: 480 cells and recent HIV diagnosis (mean time: 0.6 years) were included. 24 of them completed all study procedures (13 allocated to arm 1 and 11 to arm 2). No baseline differences were observed between study groups. During the study, 1 patient (arm 1) discontinued due to a non-related SAE (pneumonia) and 2 had to change therapy (EFV and ATV-related toxicities). By week 24, 10 of 12 patients on arm 1 and 9 of 10 on arm 2 achieved virologic suppression on randomized ART. At week 24, changes in total GM and cortical volumes were different between study arms, by ITT and PP (table). These volumes tended to increase in arm 2 and to decrease in arm 1. No differences were detected in subcortical GM or in cortical white matter volumes. Decrease in total cortical volume correlated (p<0.05) with lower scores in processing speed (WAIS III - Symbols Search: r=0.41), motor functioning (Grooved - Dominant Hand: r=0.48) and verbal fluency (COWAT - PMR: r=0.43).

Conclusion: Our results suggest that the type of ART selected as initial therapy might have a role preserving the grey matter and the cortical integrity. The regimen with lower CP including drugs with lower in-vitro NT tended to preserve grey matter cortical integrity than the comparator with higher CP and higher in vitro NT. Confirmatory studies are needed.

Table: Volumes comparisons by therapy group

Brain volume		Baseline volumes (mm^3) Mean (SD)		Volume changes (mm^3) mean (95%CI)		p value*	p value**
		ABC/3TC+EFV	TDF/FTC+ATV/r	ABC/3TC+EFV	TDF/FTC+ATV/r		
Total Grey Matter	ITT	670687 (29236)	664104 (63874)	-3431 (-9567 to 2705)	14843 (1417 to 28270)	0.0084	0.03
	PP	677977 (29720)	642403 (46486)	-6649 (-11262 to -2036)	16614 (303 to 32925)	0.0043	0.036
Total Subcortical Grey Matter	ITT	61475 (4083)	59158 (4343)	-349 (-846 to 148)	992 (-23 to 2007)	0.0138	0.083
	PP	62292 (3362)	57700 (3224)	-400 (-1010 to 211)	1044 (-238 to 2326)	0.0338	0.123
Cortex	ITT	500607 (23288)	496651 (47792)	-4163 (-9154 to 827)	11175 (-116 to 22466)	0.0084	0.017
	PP	505750 (24084)	482193 (39486)	-7010 (-10562 to -3458)	11826 (-1836 to 25488)	0.0043	0.037
Left Cortex	ITT	249443 (11592)	246592 (22953)	-1717 (-4456 to 1023)	5616 (-151 to 11384)	0.0257	0.047
	PP	252077 (11955)	239904 (19391)	-3130 (-5486 to -774)	6164 (-889 to 13217)	0.0143	0.056
Right Cortex	ITT	251164 (11772)	250059 (25030)	-2447 (-4983 to 90)	5559 (-241 to 11358)	0.0162	0.01
	PP	253673 (12216)	242289 (20222)	-3880 (-5653 to -2108)	5663 (-1274 to 12599)	0.0090	0.038
Cortical white Matter	ITT	479318 (44832)	464835 (44367)	1765 (-2770 to 6300)	4433 (-721 to 9586)	0.4009	0.203
	PP	487918 (43819)	453634 (39617)	1292 (-3547 to 6231)	5256 (-1130 to 11642)	0.2885	0.419
Left cortical White Matter	ITT	238125 (22398)	230436 (21467)	1443 (-906 to 3792)	2566 (167 to 4965)	0.4341	0.329
	PP	242409 (21882)	225082 (1915)	1190 (-1484 to 3864)	3074 (181 to 5967)	0.3691	0.508
Right Cortical White Matter	ITT	241193 (224634)	234400 (22968)	322 (-2022 to 2666)	1867 (-1048 to 4782)	0.4009	0.144
	PP	245509 (21882)	228552 (21144)	102 (-2285 to 2489)	2182 (-1496 to 5860)	0.3691	0.377

* Wilcoxon non-parametric test.

** Linear regression estimative model adjusted by baseline volume, age, current CD4 cell count, history of illicit drugs and/or tabaco use.

426 LONGITUDINAL PET IMAGING OF THE SEROTONERGIC SYSTEM IN SIV-INFECTED NONHUMAN PRIMATES

Swati Shah[1], Sanhita Sinharay[1], Dianne Lee[1], William C. Reid[1], Paul Wakim[1], Kenta Matsuda[2], Avindra Nath[1], Vanessa Hirsch[2], Michele Di Mascio[2], Dima A. Hammoud[1]

[1]NIH, Bethesda, MD, USA, [2]NIAID, Bethesda, MD, USA

Background: Despite known increased depression rates in HIV+ patients compared to controls, there is limited literature evaluating the underlying mechanisms of depression in HIV. A previous ^{11}C-DASB (DASB) PET study (serotonin transporter (SERT) ligand) showed higher binding in depressed compared to non-depressed HIV+ patients, potentially reflecting serotonergic dysfunction as a component of HIV-associated neuropathology. In this study we wanted to assess longitudinal changes in SERT expression in SIV-infected macaques using ^{11}C-DASB PET imaging before and after inoculation, to better understand the pathophysiology of HIV-associated depression.

Methods: Seven Rhesus macaques were infected with a neurovirulent SIV strain (SIVsm804E) known to cause SIV encephalitis in approximately 80% of animals with the Q/Q TRIM5α genotype. Baseline and multiple post inoculation (P.I) follow-up DASB PET scans were obtained using a High Resolution Research Tomograph head-only camera. Correlation of DASB binding potentials (BP_{ND}) with CSF cytokines, CSF and plasma viral loads (VL) as well as duration of infection was performed. Preliminary qPCR was used to assess the expression of SERT mRNA in frontal lobe tissues of 2 infected animals and 2 controls.

Results: Out of the 7 animals, four animals progressed quickly (average 6.5 weeks P.I.) and had to be rescued with treatment. One animal had to be euthanized 12 weeks P.I. Two animals progressed very slowly and did not show symptoms until 90 weeks P.I. Treatment was eventually discontinued in 4 animals and they were allowed to progress to a chronic infectious stage. Six out of 7 macaques showed higher BP_{ND} in the midbrain (range 7-72%, mean=28.31%) at the last time point compared to baseline (fig.1A, B). Neither treatment initiation nor interruption had an effect on BP_{ND}. A repeated-measures mixed model analysis showed that only disease duration was associated with DASB BP_{ND} (p= 0.04). qPCR showed higher SERT mRNA expression in two infected macaques compared to two uninfected animals (fig.1C).

Conclusion: Longitudinal assessment of DASB binding in the SIV infected animals by PET suggests SERT upregulation in these animals. Increased DASB binding positively correlated with the duration of infection but did not correlate with VL or CSF cytokine levels. Upregulated SERT leading to lower synaptic levels of serotonin is a possible mechanism of depression in HIV+ patients and should be further evaluated.

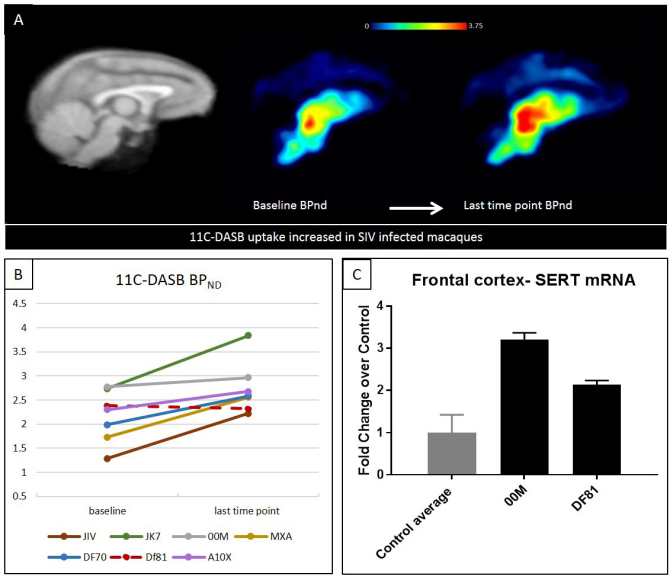


Fig.1: A, parametric BP_{ND} maps at baseline and last time point in an SIV-infected rhesus. B, Graph showing changes between baseline and last time point BP_{ND} in all seven animals. C, Fold change in SERT mRNA expression in the frontal cortex of two infected rhesus macaques compared to controls (n=2).

427 IMMUNOLOGICAL AND NEUROMETABOLITE CHANGES ASSOCIATED WITH SWITCH FROM EFV TO AN INSTI

Nina Lin[1], Yvonne Robles[2], Alan Landay[3], Tyler Starr[2], Jennifer Kinslow[3], Joshua Ladner[2], Rebeca M. Plank[2], Laura F. White[1], Kathy Melbourne[4], Alexander Lin[2], Daniel R. Kuritzkes[2]

[1]Boston University, Boston, MA, USA, [2]Brigham and Women's Hospital, Boston, MA, USA, [3]Rush University Medical Center, Chicago, IL, USA, [4]Gilead Sciences, Inc, Foster City, CA, USA

Background: The mechanisms by which efavirenz (EFV) causes central nervous system (CNS) adverse effects are unclear, but clinically pertinent given the persistent widespread use of EFV globally. We conducted an EFV switch study using magnetic resonance spectroscopy (MRS) to assess changes in specific neurometabolites on brain function, inflammation and oxidative stress.

Methods: 20 HIV-infected adults on EFV+FTC/TDF without overt CNS adverse effects were enrolled into two parallel single-arm switch studies. Participants were switched to either EVG/COBI/FTC/TDF or RAL+FTC/TDF for 8 weeks. Neurometabolites were measured by MRS using single voxel spin echo and spectroscopy. Neuropsychological (NP) assessments were performed: 1) affective symptoms (HAMD, DASS-21, STAI), 2) global brain function (WAIS-R and FRSBE), and 3) sleep quality (PSQI). Cellular (HLA-DR and CD38) and peripheral immunological markers (sCD14, IP-10, sCD163, MCP-1, IL-6, IFABP) were correlated with MRS changes. Pre- and post-EFV measures were evaluated using Wilcoxon matched-paired test.

Results: In paired analyses glutathione (GSH) was decreased (p=0.03), suggesting reduced CNS oxidative stress, while gamma-aminobutyric acid (GABA) levels was increased (p=0.03) following EFV switch. Levels of glutamate (Glu) and aspartate (Asp), neurotransmitters associated with neuronal excitability, were significantly decreased (p=0.04, 0.001) and indicates reduced neurotoxicity. CNS function (attention, memory, spatial skills) tested by WAIS-R (p=0.0002) improved. FRSBE index decreased, suggesting improved executive function and processing (p=.0037). Measures of depression, anxiety and stress (HAMD, DASS and STAI) (p=0.002, =0.01, =0.003, respectively), and sleep quality (PSQI) all improved (p=0.0005). Switch from EFV was associated with a decrease in sCD14 (p=0.008), and increases in IFABP and TNF-RI levels (p=0.05, 0.03). Cellular flow markers showed increase in naïve CD4 and CD8 T cells (HLA-DR-CD38+), suggesting active T cell proliferation (p=0.02, 0.05).

Conclusion: This switch study observed a decrease in CNS oxidative stress with lowering of GSH levels, and changes in GABA, Asp, Glu consistent with improved neuronal function. These CNS changes were associated with less systemic inflammation. Together these data suggest EFV exert CNS toxicity partially through oxidative and inflammatory pathways. The correlation of improved NP performances with neurometabolite changes provides insight into possible cellular mechanisms of EFV neurotoxicity.

Significant mean changes with switch off EFV

	pre-	post-	Difference	P-value
MRS neurometablites				
GSH	4.17	3.37	-0.81	0.028
GABA	0.27	0.31	0.04	0.026
Glu	1.38	1.29	-0.10	0.038
Asp	4.27	3.50	-0.77	0.001
Cellular and soluble immunological markers				
sCD14	3.30E+06	2.78E+06	-5.20E+05	0.008
IFABP	673.20	1032.40	359.19	0.050
TNFRI	786.49	821.41	34.92	0.035
CD4 +HLA-DR-CD38+	49.05	50.85	1.80	0.047
CD8+HLA-DR-CD38+	39.35	44.95	5.60	0.023

428 CHANGES IN BRAIN VOLUME AND COGNITION IN MICE EXPOSED IN UTERO TO ABC/ 3TC-ATV/ RTV

Kayode Balogun[1], Monica Guzman Lenis[1], Lindsay Cahill[2], Howard Mount[3], John Sled[3], Lena Serghides[1]

[1]University Health Network, Toronto, ON, Canada, [2]The Hospital for Sick Children, Toronto, ON, Canada, [3]University of Toronto, Toronto, ON, Canada

Background: Combination antiretroviral therapy (cART) has facilitated the radical reduction of perinatal transmission of HIV. However, there are concerns about the effects of cART on fetal development and long-term health outcomes of the offspring. Studies have reported several adverse neurological outcomes in HIV-exposed uninfected children. Our objective was to investigate the impact of in utero exposure to cART on infant brain development and cognitive behavior using advanced imaging techniques and well-validated behavioral testing methods in a mouse pregnancy model.

Methods: Gravid C57BL/6 mice were exposed to human-relevant plasma concentration of Abacavir (ABC)/Lamivudine (3TC)-atazanavir (ATV)/ritonavir (RTV) or water (control) starting from gestational day (GD) 1 to delivery. At GD 16, mice were euthanized; fetal weights were recorded and fetal morphology was assessed using micro-CT. A subset of the pregnant mice was allowed to carry to term and pups were accessed for developmental milestones (motor, tactile, auditory, and olfactory reflexes) from postnatal day 1-21. Postweaning, all mice were subjected to the novel object recognition test to assess non-spatial learning and memory. Alterations in brain regional volumes were assessed by magnetic resonance imaging.

Results: Fetuses exposed to cART were smaller than the controls [mean (SD); 0.32g (0.09) vs. 0.41g (0.06); P=0.007] and continued to remain smaller until sacrifice at 8 months after birth [mean (SD); 27.95g (1.78) vs. 30.95g (1.87) P=0.00025]. Micro-CT imaging showed significant volumetric changes in different regions of the fetal brains including a significant 7% decrease in the volume of the neocortex and amygdala (P<0.05) and a 7% increase in the hypothalamus in the cART-exposed group compared to controls (P<0.05); similar changes were observed in the adult brains by MRI at 8 months. The development of motor skills, tactile and olfactory reflexes were delayed in the cART-exposed offspring compared to controls (P<0.01). The cART-exposed mice had lower memory indices (MI) compared to controls (P<0.0001), and there was a positive correlation between MI vs. hippocampus CA1 and CA2 (r=0.68, P<0.0001), and MI vs. cingulate cortex (r=0.4, P=0.024).

Conclusion: Our data suggest that the in utero exposure to ABC/ 3TC-ATV/ RTV is associated with volumetric changes in key regions of the brain, developmental delays and cognitive deficits in a mouse model of pregnancy.

429 BRAIN 18F-FDG PET OF SIV-INFECTED MACAQUES AFTER TREATMENT INTERRUPTION OR INITIATION

William T. Schreiber-Stainthorp[1], Sharat Srinivasula[2], Sanhita Sinharay[1], Swati Shah[1], Jing Wang[2], Lori E. Dodd[3], H. Clifford Lane[3], Michele Di Mascio[3], Dima A. Hammoud[1]
[1]NIH, Bethesda, MD, USA, [2]Leidos Biomedical Research, Inc, Frederick, MD, USA, [3]NIAID, Bethesda, MD, USA

Background: Subtle neurocognitive dysfunction has become more prevalent in the post-antiretroviral (ART) era suggesting continuing neurological damage despite treatment. On the other hand, HIV+ patients often fail to adhere to their treatment due to financial, social, and psychological factors. Our study investigates the effects of treatment initiation and interruption on brain inflammation/immune activation using 18F-FDG (FDG) metabolism in SIV-infected macaques, in correlation with clinical and laboratory markers of disease.
Methods: Seven rhesus macaques were infected with SIV and underwent ART-interruption (n=5) and/or initiation (n=5). FDG-PET imaging was performed at baseline and at multiple time points up to 9 months after treatment modification. Mean and maximum Standardized Uptake Values (SUV) for the whole-brain were calculated. Plasma/CSF viral load (VL) and cytokine levels were measured. We evaluated changes in SUV from baseline to one month using a paired t-test. Mixed-effect linear regression models evaluated changes over multiple time-points and the association of SUV with disease markers.
Results: Treatment interruption was associated with increased whole-brain SUVmean and max after 1 month (p=0.038; p=0.041) (Fig.1). The change was most pronounced during this early period however time was not statistically significant when evaluated in mixed effect linear regression models over the rest of the follow-up period. Decreased CD4+ and CD8+ cell counts and increased CSF VL were associated with increased SUVmean and max. Similarly increased CSF IL-15 was associated with increased SUVmean. The pattern within the treatment initiation group was far more variable and statistically significant associations were not observed (Fig.1), despite decreased plasma/CSF VL, increased CD4+ and CD8+ counts and decreased plasma/CSF cytokines.
Conclusion: In this study, ART interruption was associated with increased brain metabolism, which may reflect neuroinflammation in the setting of viral rebound. These effects were observed within one month of interruption. Although we cannot document permanent neurologic damage in association with increased glucose metabolism, this raises concerns about the potential damage of even brief periods of non-adherence to ART. Treatment initiation, however, did not result in significant changes in brain metabolism. This could be due to the long time needed for neuroinflammation to abate under the effects of viral control, beyond our follow-up period.

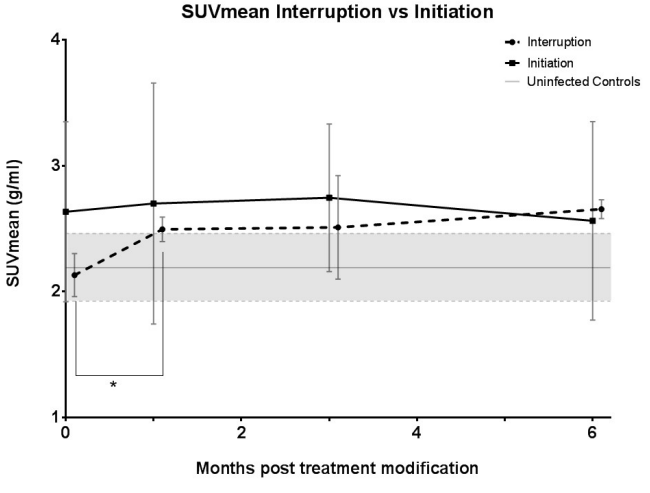


Fig.1: Average SUVmean values in the interruption and initiation groups. Control values (mean +/- SD) are highlighted.

430 INTACT STRUCTURAL AND FUNCTIONAL BRAIN IMAGING IN ACUTE HIV

Vishal Samboju[1], Carissa Philippi[2], Phillip Chan[3], Yann Cobigo[1], James L. Fletcher[3], Merlin L. Robb[4], Joanna Hellmuth[1], Khunthalee Benjapornpong[3], Netsiri Dumrongpisutikul[5], Mantana Pothisri[5], Robert Paul[2], Jintanat Ananworanich[4], Serena S. Spudich[6], Victor Valcour[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]University of Missouri St Louis, St Louis, MO, USA, [3]SEARCH, Bangkok, Thailand, [4]US Military HIV Research Program, Silver Spring, MD, USA, [5]Chulalongkorn University, Bangkok, Thailand, [6]Yale University, New Haven, CT, USA

Background: HIV is identified in cerebrospinal fluid within 8 days of estimated viral exposure. Neurological findings and impaired neuropsychological testing performance are documented in a subset of individuals with acute HIV infection (AHI). The purpose of this study was to determine whether microstructural white matter and resting-state functional connectivity (rsFC) are disrupted during AHI.
Methods: We examined 49 AHI (100% male; mean age=30±SD 9.9) and 23 HIV-uninfected (HIV-C0) Thai participants (78% male; age=30±5.5) with diffusion tensor imaging (DTI) and rsFC acquired at 3 Tesla, and four neuropsychological tests (summarized as NPZ4). MRI for the AHI group was performed prior to antiretroviral treatment (ART) in 26 participants and 2 (±1.1) days after ART in 23 participants. Fractional anisotropy (FA), mean (MD), axial (AD), and radial diffusivity (RD) were quantified for DTI. Seed-based voxelwise rsFC analyses were completed for the default mode (DMN), fronto-parietal, and salience and 6 subcortical networks. rsFC and DTI analyses were corrected for family-wise error, with voxelwise comparisons completed using t-tests. Group-specific voxelwise regressions were conducted to examine relationships between imaging indices, clinical variables, and treatment status.
Results: The AHI group had a mean (SD) CD4 count of 421 (±234) cells/uL, 6.07(±1.1) $\log_{10}$ copies HIV RNA and estimated duration of infection of 20 (±5.5) days. There were no differences between AHI and HIV-C0 groups for DTI metrics. Within the AHI group, voxelwise analyses revealed associations between brief exposure to ART and higher FA and lower RD and MD bilaterally in the corpus callosum, corona radiata, and superior longitudinal fasciculus ($p < 0.05$). Diffusion indices were unrelated to clinical variables or NPZ-4. The AHI group had reduced rsFC between left parahippocampal cortex (PHC) of the DMN and left middle frontal gyrus compared to HIV-C0 ($p < 0.002$). Within AHI, ART status was unrelated to rsFC. However, higher CD4 count correlated to increased rsFC in the right lateral parietal and PHC seeds in the DMN. NPZ-4 was correlated positively with rsFC in the bilateral caudate seed ($p < 0.002$).
Conclusion: Study findings reveal limited disruption to structural and functional brain integrity in the earliest stages of HIV. Longitudinal studies are needed to determine if treatment with ART during AHI is sufficient to prevent the evolution of progressive brain dysfunction in chronically infected individuals.

431 HIV INFECTION AND AGE HAVE INDEPENDENT EFFECTS ON BRAIN GRAY MATTER VOLUME

Erin O'Connor[1], Thomas Zeffiro[1], Melissa F. Murray[2], Donna Martineck[2], James T. Becker[2]
[1]University of Maryland, Baltimore, MD, USA, [2]University of Pittsburgh, Pittsburgh, PA, USA

Background: Although many studies have documented cortical and subcortical white and gray matter volume (GMv) changes following HIV infection (1,2), GMv is also known to decline with age and illicit drug use. As the HIV infected population is steadily aging, the effects of age and past drug use may confound attempts to identify specific effects of serostatus on regional GMv. The effects of age and drug abuse may also complicate the use of brain structural measures more generally in the diagnosis and treatment assessment of HIV-Associated Neurocognitive Disorders. Here we examined the effects of serostatus, age and past drug use on regional GMv.
Methods: Participants were 113 seropositive and 88 seronegative men, ages 23-73, with 118 reporting past illicit drug use. Seropositive participants were all treated with anti-retroviral therapies. Regional GMv was estimated using tissue segmentation of 1mm^3 T1-weighted 3-D anatomical brain images. Mixed effects linear regression models were used to explore effects of serostatus, race, age, field strength, intracranial volume and drug use on regional GMv using both a priori regions and Voxel-Based Morphometry.
Results: Seropositive participants had bilateral decreases in the volume of the caudate nucleus and putamen, bilaterally ($p<0.05$ FWE-corrected).

Spatially independent effects of age and past drug use were also seen ($p<0.05$ FWE-corrected), with age broadly affecting numerous frontal and temporal cortical regions (Figure 1). There were no significant interactions between HIV serostatus and chronological age on any of the GMv measures.

Conclusion: Regional GMv is subject to additive effects of serostatus, age and drug use. HIV infection is independently associated with basal ganglia volume reductions equivalent to 20-30 years of typical aging. Serostatus effects were regionally specific when age and drug use were controlled, suggesting that basal ganglia GMv measured using computational neuroanatomy methods may be a useful biomarker to follow HIV treatment effects. White matter reductions in treated HIV infection may reflect independent effects of age, age-related comorbidities, and past or current drug use. References (1) O'Connor EE, Jaillard A, Renard F, Zeffiro TA. Reliability of White Matter Microstructural Changes in HIV Infection: Meta-Analysis and Confirmation. AJNR. 2017 (2) O'Connor EE, Zeffiro TA, Zeffiro TA. Brain Structural Changes Following HIV Infection: Meta-analysis. AJNR. (in press)

432 MULTIMODAL BRAIN IMAGING PREDICTS NEUROCOGNITIVE IMPAIRMENT IN CHRONIC HIV

Talia M. Nir[1], Hei Y. Lam[1], Chris R. Ching[1], Neda Jahanshad[1], Jaroslaw Harezlak[2], Kenia Martínez[3], Tong Zhu[4], Giovanni Schifitto[5], Ronald Cohen[6], Paul M. Thompson[1], Bradford A. Navia[7]

[1]University of Southern California, Los Angeles, CA, USA, [2]Indiana University, Bloomington, IN, USA, [3]General University Hospital Gregorio Marañón, Madrid, Spain, [4]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [5]University of Rochester, Rochester, NY, USA, [6]University of Florida, Gainesville, FL, USA, [7]Tufts University, Boston, MA, USA

Background: Neurological injury can persist in individuals with chronic HIV infection, despite viral suppression with combined antiretroviral therapy (cART). Brain metabolite disturbances in treated HIV+ individuals, linked to inflammatory processes and neuronal loss, have been shown to predict neurocognitive impairment (NCI). We hypothesized that using multimodal markers of brain injury-diffusion weighted imaging (DWI) measures of white matter (WM) microstructure, in addition to magnetic resonance spectroscopy (MRS)-would better predict NCI and AIDS Dementia Complex (ADC) decline in chronically HIV-infected adults on stable cART.

Methods: 50 adults underwent MRS and DWI brain scans (mean age: 48.1+/-7.6 yrs; sex: 32M/18F). Levels of N-acetylaspartate (NAA), myo-inositol (MI), choline (Cho), glutamate/glutamine (Glx), and creatine (Cr) were measured in frontal gray matter, frontal WM, and the basal ganglia (BG). Using ENIGMA's DTI protocol (http://enigma.usc.edu), fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) measures were extracted from the full WM. Baseline (bl) NCI was defined as an ADC ≥1 (n=8). Logistic regressions tested whether absolute metabolite concentrations, WM measures, and standard plasma measures of disease severity (nadir/current CD4+ count and viral load) individually predicted bl-ADC status or, relative to those that remained stable (n=24), longitudinal decline in ADC (n=8), controlling for sex and age (and time interval in longitudinal analyses). To compare models, McFadden and Nagelkerke pseudo R^2, Akaike information criterion (AIC), and area under the ROC curve (AUC) were obtained for each predictor separately, and the model including all significant predictors.

Results: Compared to neuroasymptomatic individuals and those that remained stable, individuals with bl-ADC and those that declined showed significantly lower BG NAA, a neuronal integrity marker, and higher WM diffusivity (Table 1). Only bl-ADC was associated with lower current CD4+ count. Of the DWI measures, AD, which may reflect axonal injury, best predicted bl-ADC and decline. Inclusion of BG NAA, CD4+ count, and AD measures in the model improved bl-ADC prediction, while further inclusion of MD and RD improved prediction of decline.

Conclusion: Chronically HIV-infected individuals on cART are at risk for brain injury and progressive NCI. Multimodal approaches may help us better understand HIV-associated neuropathology and help identify those at risk for NCI.

Table 1. For DWI, MRS, and plasma measures significantly associated with baseline ADC or ADC decline, the McFadden and Nagelkerke pseudo R^2 (mR^2 and nR^2), AUC, and AIC are reported for single and multi-modal models.

Category	Subset Linked w/ bl-ADC	p-value	z-stat	mR^2	nR^2	AIC	AUC
MRS	BG NAA	0.011	-2.55	0.29	0.39	39.14	0.85
DWI	MD	0.013	2.48	0.23	0.32	41.66	0.78
	RD	0.023	2.28	0.20	0.28	42.96	0.78
	AD	**0.007**	**2.72**	**0.27**	**0.36**	**40.08**	**0.80**
Plasma	Current CD4+	0.039	-2.06	0.19	0.26	43.63	0.76
Model Predicting bl-ADC				**mR^2**	**nR^2**	**AIC**	**AUC**
BG NAA + CD4				0.34	0.44	39.04	0.87
CD4 + AD				0.36	0.46	38.14	0.85
BG NAA + AD				0.36	0.46	38.17	0.87
BG NAA + CD4 + AD				**0.41**	**0.52**	**37.80**	**0.91**
BG NAA + CD4 + MD				0.40	0.51	38.21	0.89
BG NAA + CD4 + RD				0.39	0.50	38.57	0.88
BG NAA + CD4 + RD + AD + MD				0.44	0.55	40.51	0.91
Category	**Subset Linked w/ ADC Decline**	**p-value**	**z-stat**	**mR^2**	**nR^2**	**AIC**	**AUC**
MRS	BG NAA	0.019	-2.34	0.46	0.60	29.32	0.89
DWI	MD	0.012	2.49	0.45	0.59	29.75	0.91
	RD	0.020	2.32	0.40	0.53	31.67	0.90
	AD	**0.016**	**2.40**	**0.53**	**0.67**	**26.76**	**0.93**
Plasma	NA	--	--	--	--	--	--
Model Predicting ADC Decline				**mR^2**	**nR^2**	**AIC**	**AUC**
BG NAA + AD				0.54	0.67	28.62	0.92
BG NAA + MD				0.49	0.62	30.46	0.92
BG NAA + RD				0.47	0.61	31.04	0.90
BG NAA + AD + MD + RD				**0.64**	**0.76**	**28.85**	**0.95**

433 LESION LOAD IS ASSOCIATED WITH NEUROCOGNITIVE DEFICITS IN HIV-INFECTED INDIVIDUALS

Manori De Alwis[1], Matthew K. Schindler[1], Anuradha Ganesan[2], Seung Hyun Won[3], Robert Deiss[4], Xiuping Chu[3], Daniel B. Hawley[4], Brian K. Agan[3], Stanley Rapoport[1], Daniel S. Reich[1], Joseph Snow[1], Edmund C. Tramont[1], Bryan Smith[1], **Govind Nair**[1], Avindra Nath[1]

[1]NIH, Bethesda, MD, USA, [2]Walter Reed National Military Medical Center, Bethesda, MD, USA, [3]Uniformed Services University of the Health Sciences, Bethesda, MD, USA, [4]Naval Medical Center San Diego, San Diego, CA, USA

Background: Comorbid infections and use of illicit drugs so often accompany HIV infection and confound radiological interpretation. These confounders could be addressed by using suitable control groups, thereby parsing out any effects of HIV infection.

Methods: Three cohorts were used: (i) subjects with HIV recruited at the National Institutes of Health (NIH+, n=115, 34% male, mean and SD of age 51±8 years), (ii) subjects with HIV from the Department of Defense with fewer comorbidities and less drug use (DOD+, n=83, 99% m, 43±11 yrs), and (iii) control subjects without HIV matched to the NIH+ group for socioeconomic and demographic factors (NIH-, n=44, 45% m, 49±9 yrs). Assessment by 3T MRI was done on 1mm isotropic 3D-FLAIR VISTA sequence. MD and MKS rated subjects as having mild, moderate, or severe lesion number, lesion volume, amount of confluent lesions, diffuse white matter (WM) abnormality, and ventricular enlargement. Chi-square and t-tests were used.

Results: NIH+ and NIH- did not differ in socioeconomic and demographic factors other than in prevalence of drug use (38% in NIH- and 86% in NIH+, $p<0.05$). NIH+ subjects had more lesions ($p=0.005$, Fig 1A), more confluent lesions ($p=0.003$), and larger ventricles ($p=0.02$, Fig 1B) than NIH- subjects. DOD+ group was younger ($p<0.001$) and had lower drug use (4%, $p<0.0001$) than both NIH groups. DOD+ also had lower lesion numbers, lesion volumes, confluent lesions, and WM abnormality than NIH- and NIH+ groups ($p=0.016$ and $p<0.01$, respectively). In addition, DOD+ had lesser ventricular enlargement than NIH+ ($p=0.0062$), but not the NIH- ($p=0.97$). Within the NIH+ group, those with more lesions were more likely to have HIV Associated Neurocognitive Disorder (HAND, $p=0.04$), and those with larger ventricles had lower neurocognitive T-scores, a measure indicating lower cognitive performance ($p=0.027$). In the DOD+ group, too, higher lesion number was associated with lower T-scores ($p<0.04$).

Conclusion: Both DOD+ and NIH- groups had less WM lesions and WM abnormality than NIH+, with DOD+ exhibiting the lowest lesion burden.

Increased lesion loads were associated with decreased neurocognition in the HIV+ groups. Ventricular enlargement, a measure of brain atrophy, was associated with HIV infection within the two well-matched NIH cohorts and may highlight the role HIV plays in brain volume loss. Use of illicit drugs seems to compound effects of HIV in producing both WM lesions and brain atrophy. Ongoing analyses will further explore these trends.

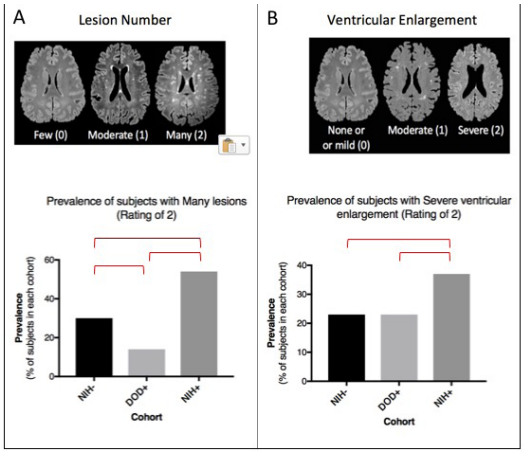


Figure 1.
(A) NIH+ subjects had higher amounts of lesions than both the other cohorts, and the NIH- subjects had more lesions than the DOD+ subjects.

(B) The NIH+ also had more ventricular enlargement than both the other cohorts, but the NIH- subjects did not differ in ventricular enlargement from the DOD+ subjects.

Brackets indicate $p<0.05$ between groups.

434 ANALYSIS OF THE EFFECTS OF HIV DISEASE ON FUNCTIONAL NEUROMAGNETIC CONNECTIVITY

Mark D. Kelley[1], Melissa F. Murray[1], Donna Martineck[1], Ricardo Bruna[2], Anto Bagic[1], James T. Becker[1]
[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]Technical University of Madrid, Madrid, Spain

Background: There is no generally accepted biomarker linking expression of cognitive impairment to HIV disease. Magnetoencephalography (MEG) is a noninvasive test that measures magnetic fields induced by synchronous activity of neuron groups. This study investigated the merits of MEG to identify alterations in functional connectivity (FC) apparent before onset of HIV-associated dementia.

Methods: 54 individuals (31 HIV+) participated in this study. Subjects were 37-64 years old, right handed, and native English speakers; 36 were men, and 28 had more than 14 years of education. None had histories of ADD/ADHD, active drug abuse, current Axis I psychiatric disorder, or neurological disease. An Elekta NeuroMag scanner with 102 triplet sensors (2 gradiometers; 1 magnetometer) was used to examine all participants. Five minutes each of "eyes open" and "eyes closed" task-free data were collected and divided into approximately 100 three-second epochs per condition. The eyes open gradiometer MEG data underwent power and sensor-space connectivity analyses using HERMES software (hermes.ctb.upm.es). Brain structural integrity was analyzed using Voxel-Based Morphometry and SPM Anatomy. Phase-Locking Values (PLV) were calculated between all pairs of sensors (20,706) and quantitative volumetric data were measured for 84 anatomically defined regions.

Results: Relative power in the left temporal lobe was lower in HIV+ participants (delta frequency) and higher in the left and right parietal ROIs (gamma frequency). The theta:gamma ratio in the right parietal region was higher in HIV+ participants. No measures of PLV were significantly associated with HIV infection (0.5 PLV threshold). Among infected persons only, longer duration of infection was associated with higher PLVs within bilateral temporal, right parietal, and right frontal ROIs. Strength of connection between the posterior cingulate cortex and both temporal ROIs (gamma frequency) was higher in seropositive individuals, and had a negative correlation with local gray matter volume.

Conclusion: There is increasing evidence that MEG may be a useful imaging method to detect alterations in brain function prior to onset of clinical symptoms. Relative power decreases in HIV+ individuals is consistent across studies; we show here that changes in FC in a circuit linked to cognition is affected both by HIV infection and brain structural integrity suggesting the possibility of both an ongoing process due to infection, and a legacy effect from prior structural damage.

435 BRAIN WHITE MATTER HYPERINTENSITIES, HIV DISEASE, COGNITION AND DIABETES

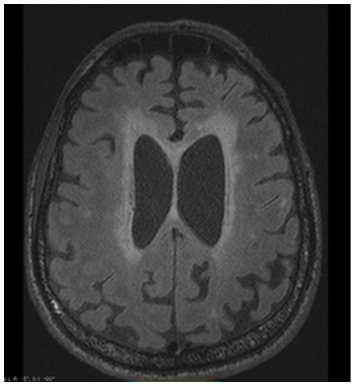
Minjie Wu[1], Omalara Fatukasi[1], Shaolin Yang[2], Jeffry Alger[3], Peter B. Barker[4], Tae Kim[1], Andrew Levine[3], Eileen Martin[5], Cynthia Munro[4], Todd B. Parrish[6], Ann B. Ragin[6], Ned Sacktor[4], Eric C. Seaberg[4], James T. Becker[1]
[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]University of Illinois at Chicago, Chicago, IL, USA, [3]University of California Los Angeles, Los Angeles, CA, USA, [4]Johns Hopkins Hospital, Baltimore, MD, USA, [5]Rush University Medical Center, Chicago, IL, USA, [6]Northwestern University, Chicago, IL, USA

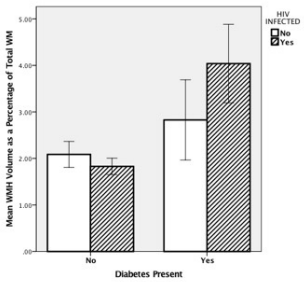
Background: HIV encephalitis includes the presence of white matter pallor and multinucleated giant cells at neuropathology. Since the onset of CART use, the incidence of HIV-Associated dementia and of encephalitis have fallen dramatically. The present study investigates the extent of white matter hyperintensities (WMHs) among individuals with HIV Disease, their impact on psychomotor speed, and factors that predict their presence (see left-hand panel of figure for example of peri-ventricular WMHs). As HIV Disease is associated with increased risk of cerebrovascular disease and stroke, we focused on factors such as diabetes and hypertension as risk modifiers.

Methods: 322 men participating in the Multicenter AIDS Cohort Study (MACS) (185 HIV-infected, age: 57.5 (+6.0)) underwent MRI scans of the brain on Siemens 3T systems. T1-weighted MP-RAGE and Fluid Attenuated Inversion Recovery (FLAIR) images were obtained and processed using a semi-automated method for identifying and measuring WMHs. To segment WMHs, the algorithm uses the image intensity histogram to automatically select "seeds" of possible WMH and then iteratively clusters voxels based on their adjacency and affinity (i.e., fuzzy connectedness) to the seeds. WMH burden was expressed as the percentage of total white matter that was abnormal.

Results: There were no statistically significant associations between WMHs and HIV Disease. However, in an adjusted model the extent of WMH was greater in men age > 60 (β=.21), of Non-Caucasian Race (β=.14), with a lower glomerular filtration rate (β= -.12) and with Diabetes (β=.14)(See right-hand panel of figure). There was no interaction between HIV status and age, although the interaction between age and diabetes was significant (β=.14). Race had a direct impact on WMH volume, and GFR was also predicted by Race (β=.15) and Hypertension (β= -.19). The extent of WMHs was significantly associated with performance on neuropsychological measures of psychomotor speed (β=.24), even after adjusting for age, education, and race.

Conclusion: WMHs were a hallmark of HIV-Associated Dementia and Encephalitis prior to the use of CART. In today's therapeutic environment, factors that affect the vasculature (e.g., hypertension and vascular disease) are the best predictors of WMHs and brain vascular disease. Early treatment and prevention could result in better brain health and better cognitive functions among infected individuals. Extra attention should be paid in African-Americans who have an increased risk of CVD.





436 MULTIVARIATE PATTERN ANALYSIS OF VOLUMETRIC NEUROIMAGING DATA IN TREATED HIV-DISEASE

Jonathan Underwood, James H. Cole, Robert Leech, Alan Winston
Imperial College London, London, UK

Background: Accurate prediction of longitudinal changes in cognitive function in treated HIV-disease would potentially allow targeted intervention in those at greatest risk of cognitive decline. High resolution neuroimaging and machine learning techniques have shown promise in other disease areas but there are

little data in treated HIV-disease. We sought to build a multivariate model using volumetric neuroimaging data only to accurately predict cognitive function.
Methods: T1-weighted neuroimaging data from virally suppressed people living with HIV (PLWH) from the CHARTER cohort (n=139) were segmented into grey and white matter and spatially normalised before entered into machine learning models. Cognitive function was tested across seven cognitive domains with longitudinal decline determined using regression based change scores as previously described. Predictive ability to assess cognitive function was determined using leave-one-out cross validation. Additionally, a multivariate model of brain ageing (training set n=2001, age range 18-90, model R^2=0.88) was used to measure the deviation of apparent brain age from chronological age and assess its relationship with cognitive function.
Results: Cognitive impairment, defined using the global deficit score (GDS), was present in 37.4%. However, it was generally mild, with only 4.3% meeting the criteria for HIV-associated dementia, and occurred more commonly in PLWH with confounding comorbidities (p<0.001). Longitudinal cognitive decline was present in 14.5%. Although multivariate prediction of cognitive impairment as a dichotomous variable at baseline was poor (table), prediction of the global T-score was better than a comparable linear model (adjusted R2=0.08, p<0.01 vs adjusted R2=0.01, p=0.14). Accurate prediction of longitudinal changes in cognitive function was not possible (p=0.82). Brain-predicted age exceeded chronological age by 1.17 (-0.14-2.53) years, but was greatest in those with confounding comorbidities (5.87 [1.74-9.99] years) and prior AIDS (3.03 [0.00-6.06] years). The relationship between this deviation and cognitive function was attenuated when covarying for comorbidity status.
Conclusion: Although cognitive impairment was present in about a third of virally suppressed patients it was confounded by comorbid conditions. Accurate prediction of cognitive function using multivariate models of T1-weighted MRI data was not achievable, which may reflect the small sample size, heterogeneity of the data or that impairment was usually mild.

Table. Prediction performance by model for cognitive impairment at baseline and longitudinally.

Model	Class accuracy (%)	*p*-value	PPV (%)	Class accuracy (%)	*p*-value	PPV (%)	Balanced accuracy (%)	AUC	*p*-value
	Not impaired (n=87)			Impaired (n=52)			Overall		
SVM	72.4	0.33	65.0	34.6	0.25	42.9	53.5	0.56	0.22
GPC	77.0	0.56	65.7	32.7	0.10	46.0	60.4	0.59	0.14
	Non-decliners (n=93)			Decliners (n=17)			Overall		
SVM	97.9	0.48	84.3	0.0	1.00	0.00	48.9	0.42	0.63
GPC	98.9	0.86	84.4	0.0	1.00	0.00	49.5	0.42	0.87

P-values calculated with permutation testing (1,000 repetitions).

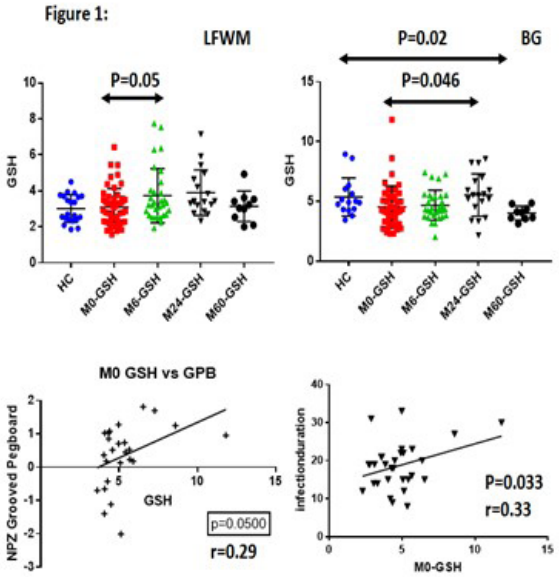
Abbreviations: AUC: area under the receiver operator curve; GPC: Gaussian process classification; PPV: positive predictive value; SVM: support vector machine.

437 CEREBRAL GLUTATHIONE METABOLISM IN ACUTE HIV INFECTION AND RESPONSE TO ART

Napapon Sailasuta[1], Jennifer Daniels[2], Phillip Chan[3], Carlo Sacdalan[3], Merlin L. Robb[4], Somporn Tipsuk[3], Jintanat Ananworanich[4], Duanghathai Suttichom[3], Robert Paul[5], Nisakorn Ratnaratorn[3], Mantana Pothisri[6], Netsiri Dumrongpisutikul[6], Serena S. Spudich[7], Victor Valcour[2]
[1]University of Hawaii at Manoa, Honolulu, HI, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]SEARCH, Bangkok, Thailand, [4]US Military HIV Research Program, Silver Spring, MD, USA, [5]University of Missouri St Louis, St Louis, MO, USA, [6]Chulalongkorn University, Bangkok, Thailand, [7]Yale University, New Haven, CT, USA

Background: Oxidative stress, an imbalance between the generation of free reactive oxygen or nitrogen species and body's ability to neutralize their harmful effects via antioxidants including glutathione (GSH), has been implicated in HIV pathogenesis. Prior studies have reported alteration of blood GSH levels during HIV, but brain GSH levels have never been reported. We measured cerebral total GSH in pre-antiretroviral therapy (ART) acute HIV infection (AHI) and after ART using magnetic resonance spectroscopy (MRS).
Methods: 98 Thai AHI participants had single voxel proton brain MRS via a 3T Phillips scanner using standard single voxel double spin echo data acquisition with an echo time of 35ms. Scans were obtained prior to ART at a mean 20 days estimated duration of infection (baseline, M0, n=53), or after six (M6, n=31), 24 (M24, n=18) and 60 (M60, n=9) months of ART started in AHI. 13 participants had scans both at M0 and M6. HIV negative participants were studied as healthy controls (HC, n=13). Single voxel MRS was acquired from the basal ganglia (BG) and the left frontal white matter (LFWM). LCModel was used to quantitate brain metabolites using GAMMA simulated reference basis sets. A 4-test neuropsychological battery was performed at all visits. Non-parametric statistical methods were used.
Results: At baseline, median age was 29.4 years, mean (Q1, Q3) CD4+ count was 423 (137, 773) cells/mm^3 and log plasma HIV RNA was 6.0. BG GSH was reduced in M60 compared to HC (mean (SD)=4.02(0.19) vs. 5.37(0.41), p=0.02), and reduced in M0 compared to M24 (4.54(0.02) vs 5.53(0.41), p=0.046). In the LFWM, reduced GSH was observed in M0 compared to M6 (3.08 (1.03) vs 3.73(1.5), p=0.05). Pearson correlation was significant between GSH levels at M0 and both a) estimated duration of infection (p=0.033, r=0.33) and b) grooved pegboard performance(p=0.05, r=0.29 (Figure 1)).
Conclusion: We report a reduction of cerebral GSH in naïve and treated HIV-infected participants supporting the idea of glutathione metabolism dysfunction and persistent oxidative stress in HIV brain even after early ART. We noted, under our MRS scanning protocol, the two forms of glutathione, the reduced GSH and the oxidized glutathione (GSSG), exhibit very similar proton MRS spectra, therefore glutathione in this study represents total GSH levels. Further study is underway using the novel J-editing method to measure alterations in GSH without GSSG contamination.

Figure 1:



438 AMYLOID UPTAKE BY PET IMAGING SUGGEST PREMATURE AGING IN OLDER HIV+ INDIVIDUALS

Ned Sacktor, Richard Skolasky, Heidi Roosa, Cornelia Demsky, Yun Zhou, Weiguo Ye, Noble George, Peter B. Barker, Dean Wong, Mona Mohamed
Johns Hopkins Hospital, Baltimore, MD, USA

Background: HIV+ infection leads to pre-mature aging in multiple organ systems. Amyloid deposition, a hallmark of Alzheimer's disease, can be detected by brain position emission tomography (PET) imaging. The objectives of this study were to determine if amyloid uptake measured by PET [18F] AV-45 (Florbetapir) is increased in older individuals greater than age 50 years: 1) stratified by HIV-associated neurocognitive disorder (HAND) stage among HIV+ individuals, 2) stratified by serostatus, and 3) is increased at an earlier age in HIV+ individuals compared to HIV- individuals.
Methods: 43 HIV+ and 23 HIV- individuals received neurological evaluations including neuropsychological testing, functional assessments and high resolution research tomography (HRRT) PET [18F] AV-45 imaging. AV-45 uptake was measured by cerebellum standardized uptake value ratios (SUVR) in 17 cortical and subcortical regions. Global and regional cortical uptake were compared 1) by HAND stage (among HIV+'s only), 2) by serostatus (entire cohort), and 3) stratified by age decade comparing individuals in their 50's, 60's and 70's by serostatus.
Results: Age decade for HIV+ individuals were 50's (n =22), 60's (n=20), and 70's (n=1), and for HIV-'s: 50's (n=6), 60's (n=10), and 70's (n=7). HAND stage

for HIV+ individuals was as follows: normal cognition- (n= 11), asymptomatic neurocognitive impairment (ANI)- (n= 12), mild neurocognitive disorder (MND)- (n= 10) , HIV dementia- (n= 10). There were no differences in median global cortical uptake stratified by HAND stage or HIV serostatus. However, the median global cortical SUVR uptake for HIV+ individuals in their 50's, 60's, and 70's were 1.47, 1.31, and 1.26 respectively, whereas for HIV- individuals, they were 1.37, 1.41, and 1.58, respectively (non-significant), suggesting a trend for increased global cortical amyloid uptake at an earlier decade of life among HIV+ individuals. For 50 year olds, HIV+ individuals had increased uptake in the posterior cingulate cortex [median (IQR) = 1.59 (1.44-1.80)] compared to HIV- individuals [median (IQR) = 1.43 (1.25-1.45)], (p =0.038).
Conclusion: Amyloid deposition as measured by PET imaging may occur at an earlier age in HIV+ individuals > age 50 compared to age matched HIV- individuals suggestive of premature aging in the brain. However, amyloid deposition did not correlate with cognitive impairment. Further longitudinal studies of PET amyloid imaging and cognition in older HIV+ individuals are warranted.

439 NEUROIMAGING CORRELATES OF FRAILTY, COGNITION, AND HIV

Jeremy Strain, Robert S. Smith, Sarah Cooley, Beau M. Ances
Washington University St Louis, St Louis, MO, USA

Background: Chronically infected HIV+ patients are afflicted with a variety of age-related comorbities that can manifest as cognitive sequelae. Frailty is a phenotypic assessment that examines different physical attributes as a generic metric for secondary anatomical etiologies. In a data driven approach we assessed the relationship between brain integrity (neuroimaging [functional and structural] and neuropsychological performance) and frailty in an HIV+ population.
Methods: 89 HIV+ patients, ranging in age from 50 to 85 (M=57.4; SD=6.43), were dichotomized as either frail (≥3)(n=11) or non-frail (<3)(n=78) using the Fried criteria. Global deficit scores (GDS) and domain specific scores (executive, psychomotor speed, and memory) were derived from a NP battery of tests. Voxel-wise comparisons with a cluster-based technique were performed on resting cerebral blood flow (rCBF) comparing non-frail and frail HIV+ participants. The CBF cluster analysis yielded 8 regions of interest (ROIs) that showed significantly lower CBF in frail compared to non-frail HIV+ individuals. These CBF ROI clusters served as seeds for probabilistic white matter tractography.
Results: A significant association was seen for average fractional anisotropy (FA) and CBF for the four (bilateral frontal poles, anterior cingulate and posterior cingulate) structurally connected regions (p<0.001). Average FA, for white matter connecting the four regions, was significantly decreased in frail compared to non-frail HIV+ individuals (p=0.017). Lower FA values were also associated with worse cognition (both global (p=0.001) and executive domain (p=0.022)). Both CBF and FA significantly predicted GDS outcome (p=0.009) but only CBF significantly improved the model (p=0.034).
Conclusion: We conclude that HIV+ frail individuals have reductions in rCBF and associated reductions in structural connections between these areas. Both lower CBF and reduced FA in these ROIs predicted poorer cognitive performance suggesting a possible etiology to the behavioral changes associated with the frailty index. This multi-modality approach suggests that the frailty index is capable at identifying secondary pathologies that reflects accentuated functional and structural damage in HIV+ individuals.

440 SUBCLINICAL GLOBAL AND THALAMIC HYPOMETABOLISM ON FDG-PET IN TREATED HIV+ SUBJECTS

Dima A. Hammoud, Sanhita Sinharay, Sally Steinbach, Paul Wakim, Katrina Geannopoulos, Katherine Traino, Amit Dey, Stanley Rapoport, Edmund C. Tramont, Joseph Snow, Nehal N. Mehta, Bryan Smith, Avindra Nath
NIH, Bethesda, MD, USA

Background: Despite improved life expectancy in HIV seropositive (HIV+) individuals, HIV-associated neurological disorders (HAND) remain a major morbidity. The specific neuronal populations that contribute to HAND however are unknown. 18F-Fluoro-Deoxyglucose Positron Emission Tomography (FDG-PET) quantitatively measures glucose metabolism in the brain and can identify regional differences in neuronal function.
Methods: We used brain FDG-PET imaging to evaluate optimally-treated, virologically-suppressed HIV+ individuals (n=47), compared to age-matched healthy controls (HCs; n=19) and to a group of HIV seronegative (HIV-; n=11) age-matched subjects from the same socio-economic background, sharing many of the comorbidities seen in the HIV+ group. We compared global and regional FDG standardized uptake values (SUV) (subcortical/central structures) amongst the groups and correlated them to various clinical variables and to neuropsychological assessments at the time of the scanning. Whole brain SUVmean and SUVmax were measured for all subjects and compared. Regional uptake values (SUVmean, SUVmax and relative SUVmean = regional SUVmean/Whole brain SUVmean) were also assessed in the caudate, putamen, thalamus, and cerebellum.
Results: We found statistically significant lower whole brain SUVmax in HIV+ compared to HC but not to HIV-. Among subregions, only thalamic relative SUVmean values were significantly lower in HIV+ compared to HC and to HIV- subjects (Figure.1). Using a mixed-effect statistical model, the most predictive clinical variables for reduced thalamic relative SUVmean was group (HIV status) and prior drug use. Considering the HIV+ group separately, cardiovascular disease risk (measured as the 10-year Atherosclerotic Cardiovascular Disease (ASCVD) risk) correlated with most of the other SUV values.
Conclusion: HIV+ and HIV- subjects with similar co-morbidities showed global hypometabolism compared to HC suggesting an important role for those co-morbidities, especially cardiovascular disease, in neuronal loss/dysfunction. Of the four regions measured, only the thalamus showed significantly lower relative SUVmean values in HIV+ compared to HIV-, possibly reflecting a specific effect of the virus, and potentially explaining memory, executive functioning and attention deficits in this patient population.

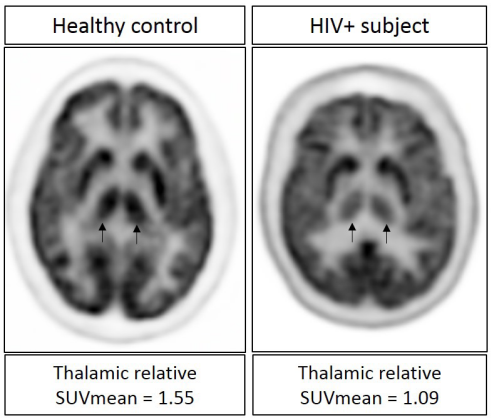


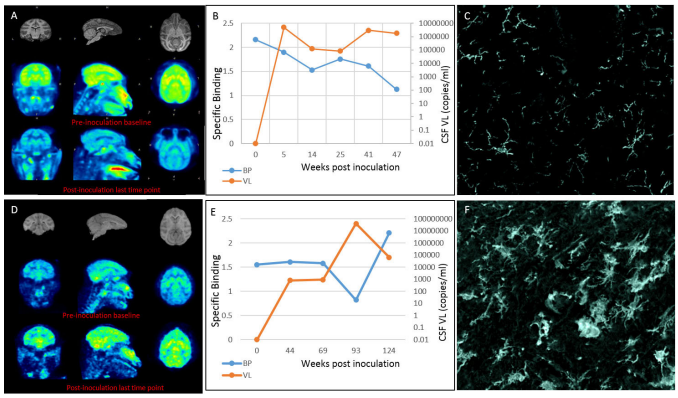
Figure 1: Qualitative comparison of thalamic FDG uptake (black arrows in both panels) compared to caudate and putamen uptake in a healthy control versus an age-matched HIV+ subject.

441LB BRAIN PET IMAGING OF MICROGLIA IN MACAQUES WITH SIV ENCEPHALITIS

Dima A. Hammoud, Sanhita Sinharay, Kenta Matsuda, Dianne Lee, Swati Shah, William Reid, Paul Wakim, Vanessa Hirsch, Avindra Nath, Michele Di Mascio
NIH, Bethesda, MD, USA

Background: Microglial activation (neuroinflammation) is hypothesized to play a central role in neuronal damage associated with HIV. In this study we wanted to image the translocator protein (TSPO), a mitochondrial membrane receptor overexpressed in activated microglia in macaques infected with a neuro-tropic SIV strain (SIVsm804E), before and after inoculation, using [18F]-DPA714 PET.
Methods: Dynamic PET imaging with [18F]-DPA714 followed by displacement with cold PK11195 (TSPO antagonist) was performed in 5 SIV-infected macaques at baseline as well as different time points following inoculation. Regional and whole brain volumes of interest were drawn on the respective MR images and specific/total binding was calculated as standardized uptake values (SUV) at equilibrium using PMOD 3.7. Multiplex post-mortem immunofluorescent (IF) staining for microglia/macrophages (iba1), neurons (NeuN), and apoptosis (cleaved caspase-3/PARP) was performed in all animals and compared to 3 normal monkey brains. Correlation of SUV values with cerebrospinal fluid (CSF) and plasma viral load (VL) was also performed.

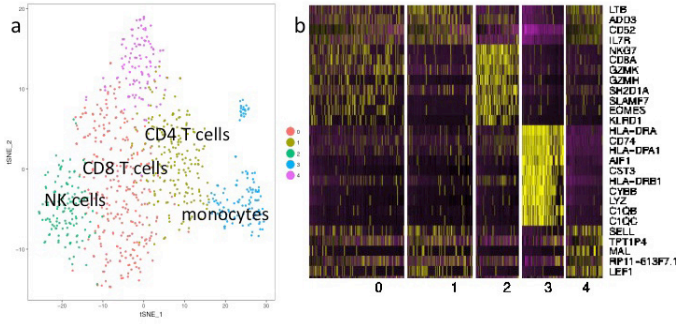
Results: When the last time point (pre-euthanasia) was compared to pre-inoculation baseline, [18F]-DPA714 total binding was decreased in 4 animals (Fig. 1A) and increased in one (Fig.1D). We found an inverse relationship between binding and CSF VL: binding decreased when VL increased and vice versa (Fig. 1B and E). Pathology results in 4 of the animals compared to 3 uninfected monkey brains showed unchanged or mildly decreased Iba1 staining in the background compared to controls (Fig.1C) but with increased diffuse CC3/PARP staining. There was however evidence of multiple microglial nodule with increased Iba1 and CC3/PARP staining. The only animal showing increased binding on PET at the last time point (Fig.1D and F) showed a combination of diffuse and focal microglial activation on IF staining.
Conclusion: In SIV encephalitis macaques, we found an inverse relationship between CSF VL and microglial activation by imaging and IF staining with microglial loss/apoptosis associated with very high CSF VL and microglial activation associated with lower CSF VL. Apoptosis staining co-localized with microglial and neuronal stains suggesting cellular death/loss in association with high VL. Our results provide a new insight into the role/status of microglia/macrophages in early stages of the disease when very high CSF viral loads are observed (Feibig stages II-IV).



442 SINGLE-CELL RNA SEQUENCING TO CHARACTERIZE CSF IN VIROLOGICALLY SUPPRESSED HIV

Shelli Farhadian[1], Chryssa Zografu[1], Sameet Mehta[1], Jennifer Chiarella[1], Kevin Robertson[2], Sarah Yosief[2], Jenna Pappalardo[1], David Hafler[1], Serena S. Spudich[1]
[1]Yale University, New Haven, CT, USA, [2]University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: The cellular mechanisms underlying persistent central nervous system (CNS) immune activation in HIV during antiretroviral therapy (ART) are incompletely understood. Advances in single-cell RNA sequencing (scRNA-seq) permit simultaneous examination of thousands cellular transcriptomes, allowing for a previously unrealized level of cellular resolution. Here we develop the first successful application of massively parallel scRNA-seq to cerebrospinal fluid (CSF) to profile thousands of single cell transcripts from CNS tissue.
Methods: CSF and blood sampling and neuropsychological testing (total Z scores) were performed in a pilot study of HIV+ (n=4) individuals on ART with plasma viral load <20 cps/mL for >1 yr, and HIV- controls (n=3). Fresh cells were isolated from 25cc CSF on the day of collection, then ~10,000 cells were applied to nanowell arrays designed for single isolation and preloaded with uniquely barcoded beads. Cells were lysed, mRNAs were reverse transcribed, and single cell libraries prepared with NexteraXT. ~5000 cells/sample were sequenced (Illumina; average depth 60,000 reads/cell). Single-cell transcripts were analyzed with Seurat R package for identification of highly variable genes, dimensionality reduction, and unsupervised clustering.
Results: The mean age in HIV+ and controls was 49 years, with total Z scores -0.87 and -0.96, and CD4 594 cells/ul and 860 cells/ul, respectively. 2 participants had HIV detected in CSF (38 and 99 cps/mL). For all samples, we successfully produced single cell libraries with average cDNA size 400-700bp. 2,000 cells per sample were randomly selected for further computational analysis, and filtered for high quality cells (>200 and <2500 unique transcripts and <10% mitochondrial RNA). This yielded a mean 802 cells per sample for further analysis, and 3-5 clusters per sample. A representative analysis of CSF from one HIV+ participant is shown **(Figure).** Cluster analysis **(a)** shows 5 distinct groups of cells, and heat map **(b)** shows differentially expressed genes that identify the clusters as CD8 T cells (34%), CD4 T cells (23%), NK cells (15%), and monocytes (15%).
Conclusion: We successfully employ scRNA-seq to classify CSF immune cells. The depth and breadth of gene expression profiles obtained with single-cell resolution will allow us to identify unique CNS cell populations associated with persistent CNS immune activation in ART-suppressed HIV.



443 HIV-RNA IN THE OLFACTORY MUCOSA OF HIV-POSITIVE PATIENTS

Mattia Trunfio[1], Tiziano Allice[1], Luca Bertero[1], Daniele Imperiale[2], Sebastiano Catera[2], Veronica Pirriatore[1], Giovanni Di Perri[1], Maria Enrica Amasio[2], Paola Cassoni[1], Valeria Ghisetti[3], Stefano Bonora[1], Andrea Calcagno[1]
[1]University of Torino, Torino, Italy, [2]Maria Vittoria Hospital, Torino, Italy, [3]Amedeo di Savoia Hospital, Torino, Italy

Background: Central nervous system (CNS) HIV infection is assessed on cerebrospinal fluid (CSF) through lumbar puncture (LP), although CSF represents a proxy of brain tissue and LP is a non risk-free procedure. Since olfactory mucosa (OM) is the only CNS tissue that is easily accessible, nasal brushing (NB) may represent an alternative safe diagnostic technique to evaluate CNS viral compartmentalization
Methods: Naive and on cART HIV-positive patients undergoing LP for clinical reasons were included. After informed consent, patients underwent (<72 hours from the LP) a NB; OM swabs were inserted in Copan UTM viral transport medium. CSF and plasma HIV-RNA (pIVL) were quantified with CAP/CTM v.2.0 HIV-1 (Roche Molecular, USA, detection limit 20 copies/mL). OM HIV-RNA was measured with a modified CAP/CTM procedure. Immunovirological data and CSF biomarkers [ELISA: tau, ptau, neopterin, S100β; immunoturbidimetric method: Reiber diagrams] were recorded. Data are reported as medians (interquartile ranges) and analyzed through non-parametric tests
Results: 47 patients were included (74.5% male, 85.1% Caucasian, median age 51 years [47-57]). 19 patients were naïve (pIVL and CSF HIV-RNA 5.2 and 3.3 Log_{10} copies/mL; current CD4 44 cell/uL), while 28 on cART (pIVL and CSF HIV-RNA undetectable and 1.3 Log_{10} copies/mL; current and nadir CD4 456 and 177 cell/uL). CSF escape (CSFE) was observed in 5 patients (10.6%). Mild discomfort, sneezing and lacrimation were the only reported side effects for NB. OM HIV-RNA was detectable in 23 patients (17 naïve: 3.1 Log_{10} copies/mL [2.0-3.7]; 6 on cART: 1.9 Log_{10} copies/mL [1.6-2.1]) and correlated with current CD4 count (ρ -.509, p<.01), Log_{10} pIVL and CSF HIV-RNA (ρ .746, p<.01 and ρ .663, p<.01), PBMC HIV-DNA (ρ .582, p<.01) and CSF neopterin (ρ .671, p<.01). OM HIV-RNA was higher than pIVL in 5 treated patients (4 aviremic including 2 CSFE) and than CSF HIV-RNA in 5 naïve and 4 treated patients (3 aviremic including 1 CSFE). An OM escape (OM HIV-RNA more than 1 Log_{10} above pIVL) was associated with higher risk of CSFE (OR 12.7, p=.01)
Conclusion: Non-invasive monitoring of HIV tissue replication may have major implications; OM HIV-RNA has been safely measured in around half NB samples. The reported association with HIV-DNA and neopterin is promising as a marker of residual viral burden and immune activation. Further studies are required to establish whether OM HIV-RNA may be a reliable surrogate of CSF/brain tissue HIV-RNA

444 DISTINCT HIV POPULATIONS IN CSF AND BLOOD DURING ACTIVE CRYPTOCOCCAL MENINGITIS

Maura Manion[1], **Camille Lange**[2], Kathy Huppler Hullsiek[3], Brandon Keele[4], Helene Highbarger[5], David Meya[6], David R. Boulware[3], Frank Maldarelli[2], Irini Sereti[1]

[1]NIAID, Bethesda, MD, USA, [2]National Cancer Institute, Frederick, MD, USA, [3]University of Minnesota, Minneapolis, MN, USA, [4]AIDS and Cancer Virus Program, Frederick, MD, USA, [5]Leidos Biomedical Research, Inc, Frederick, MD, USA, [6]Makerere University, Kampala, Uganda

Background: Central nervous system (CNS) infections like cryptoccocal meningitis (CM) are postulated to influence the formation and persistence of an HIV CNS reservoir through trafficking of infected and activated cells, but the mechanisms by which compartmentalization may occur are unknown. Viral compartmentalization present at antiretroviral therapy (ART) initiation may affect the establishment of that reservoir. We investigated the role of pre-ART CM co-infection on the HIV reservoir by characterizing HIV-1 populations in plasma, PBMC and cerebrospinal fluid (CSF).

Methods: Patients with HIV and CM infections (N=73) were enrolled in clinical trials of ART initiation (COAT, ASTRO-CM). They had lumbar puncture and phlebotomy prior to anti-fungal therapy and subsequent ART. Plasma and CSF HIV RNA were quantified. A subset of subjects with CSF viral RNA levels > plasma HIV levels (N=9) and subjects with plasma RNA > CSF RNA (N=9) underwent single genome sequencing (SGS) of full length HIV env in plasma and CSF. Cell-associated HIV DNA was recovered for a subset (N=5) of subjects. A total of 786 full length env SGs were obtained from plasma and CSF, and 206 SGs were obtained from cell-associated HIV DNA. SGs were aligned and subjected to phylogenetic analyses (MEGA). Analyses for population shift and R5/X4 tropism predictions (GENO2PHENO) were done. Immunologic and virologic data were analyzed in the context of clinical and demographic data.

Results: Subjects with CSF pleocytosis (WBC>5 cells/μL), had higher levels of HIV in CSF than in plasma ($p<0.05$). In general, the proportions of variants with R5 and X4 CD4 entry phenotype were similar in CSF and plasma, but strong discordance was detected in 4 subjects, reflecting compartmentalization of CD4 phenotypes. Sensitive compartmentalization analysis revealed distinct HIV populations in CSF and plasma in 5 subjects. Additional analysis of cell-associated HIV variants present in PBMC and CSF cells revealed HIV variants in CSF as distinct from HIV in CSF cells, but indistinguishable from PBMC-derived HIV.

Conclusion: Pre-ART compartmentalization of HIV populations in CSF and peripheral blood was detectable in the majority of subjects with CM. Increases in CSF cell numbers were associated with elevated levels of HIV in CSF, but the HIV variants present in these cells were not typically present in the CSF HIV populations, indicating that CSF pleocytosis in CM does not substantially contribute to establishing HIV populations in CNS.

445 NEUROLOGIC STABILITY WITH BRIEF ANALYTIC TREATMENT INTERRUPTION AFTER EARLY ART

Joanna Hellmuth[1], Donn Colby[2], Eugène Kroon[2], Carlo Sacdalan[2], Phillip Chan[2], Jintana Intasan[2], Victor Valcour[1], Trevor Crowell[3], Linda Jagodzinski[3], Khunthalee Benjapornpong[2], Nelson L. Michael[3], Jintanat Ananworanich[3], Robert Paul[4], Serena S. Spudich[5]

[1]University of California San Francisco, San Francisco, CA, USA, [2]SEARCH, Bangkok, Thailand, [3]US Military HIV Research Program, Silver Spring, MD, USA, [4]University of Missouri St Louis, St Louis, MO, USA, [5]Yale University, New Haven, CT, USA

Background: The central nervous system (CNS) is a likely reservoir of HIV and is vulnerable to viral rebound and increased inflammation upon cessation of antiretroviral therapy (ART). Thus, careful evaluations of CNS outcomes are critical for HIV remission studies employing analytic treatment interruption (ATI). This study investigated changes in neurologic measures across three small, closely monitored HIV remission trials involving ATI in participants who previously initiated ART during acute HIV infection (AHI).

Methods: Pre-ATI, participants received either vorinostat/hydroxychloroquine/maraviroc (n=7), or no added intervention (n=9). Eight other participants received the broadly neutralizing VRC01 antibody at and during ATI. Criteria for restarting ART included confirmed plasma HIV RNA >1,000 cps/mL. Pre- and post-ATI (on the day of, or after ART resumption) assessments included standard measures of mood and anxiety; ACTG-derived macroneurological exam; Color Trails 1 and 2; Grooved Pegboard; Trail-making A; and the computerized Flanker Task. Elective tests included cerebrospinal fluid (CSF) sampling (pre-, during ATI at first plasma HIV RNA > 20 cps/mL, and post-ATI) and brain diffusion tensor imaging (DTI; pre- and during ATI). Analyses employed paired t-test and ANOVA.

Results: At ART initiation, 54% of participants were in Fiebig I/II. ATI was preceded by a median of 3.4 years on cART (IQR 2.6-4.8). Median ATI duration was 30 days (IQR 19-37). Comparing pre- vs. post-ATI measures, there was no change in PHQ-9 depression score (3.9 vs. 4.8; p=0.510; n=14), HADS depression score (2.2 vs. 2.2; p>0.999; n=14), HADS anxiety score (3.6 vs. 4.2; p=0.677; n=14), Distress Thermometer rating (2.2 vs. 3.4; p=0.252; n=14), prevalence of neurologic findings (26% vs. 26%) or number of neurologic findings (0.7 vs. 0.6; p=0.516; n=23). The global neuropsychological test z-score modestly improved from pre-ATI to post-ATI (0.7 vs. 1.0; p=0.007 n=12). There were no differences in Flanker performance pre-, during and post-ATI. Two participants had detectable CSF HIV RNA during ATI before cART resumption, one at 29 days (25 cps/mL) and one at 34 days (42 cps/mL). There were no differences in DTI measures pre- vs. during ATI (n=12).

Conclusion: In a small sample, we identified no adverse neurologic outcomes in AHI participants who underwent brief, closely monitored ATI. Further studies are needed to validate the CNS safety of ATI in HIV remission trials for longer ATI durations and in other populations.

446 SPECIFIC CSF VIRAL ESCAPE FINDINGS COMPARED TO PRE-cART HIV ENCEPHALITIS

Valentina De Zan[1], Francesca Ferretti[2], Simonetta Gerevini[1], Laura Passeri[1], Adriano Lazzarin[1], Cinque Paola[1]

[1]San Raffaele Scientific Institute, Milan, Italy, [2]Chelsea and Westminster NHS Foundation Trust, London, UK

Background: Suppressive combined antiretroviral therapy (cART) has drastically reduced the incidence of HIV encephalitis, however CNS breakthrough, or 'cerebrospinal fluid (CSF) viral escape', is an emerging phenomenon resulting in significant neurological debilitation. Although both pre-cART HIV encephalitis (HIVE) and CSF escape encephalitis (esc-HIVE) result from HIV replication in the CNS, they seem to differ in several ways. Aim of this study is to characterize and compare clinical, radiological and CSF aspects of these two conditions.

Methods: We retrospectively examined clinical, radiological and CSF data from patients with either esc-HIVE (defined by occurrence of incident neurological symptoms in patients on ART for >9 months and detectable CSF HIV-RNA while undetectable in plasma, or CSF HIV-RNA >2-fold than plasma levels) or HIVE. We also compared levels of immune activation markers (CCL2, CXCL10, suPAR) measured in cryopreserved CSF samples from 8 esc-HIVE and 17 HIVE patients. Comparisons were made with Mann-Whitney U test or Fisher exact test, as appropriate.

Results: Laboratory and CSF findings at the time of diagnosis of esc-HIVE or HIVE are reported in the Table. Clinical symptoms and signs included memory and cognitive impairment (esc-HIVE=10, HIVE=10), cerebellar signs (esc-HIVE=11, HIVE=3), focal signs (esc-HIVE=8, HIVE=2), alteration of consciousness (esc-HIVE=4, HIVE=3), agitation/psychosis (esc-HIVE=0; HIVE=4). In esc-HIVE, MRI showed areas of white matter hyperintensity either involving the periventricular or other brain or cerebellum regions in 16/19 cases (84%), edema with sulcal effacement in 10/19 cases (53%), and no abnormalities in 3 cases. In patients with HIVE, MRI findings showed cortical and/or subcortical atrophy in 14/16 cases (88%) and diffuse periventricular white matter hyperintensity, most frequently symmetrical involving frontal lobes, in 11/16 cases (69%).

Conclusion: Despite some similarities in clinical presentations between esc-HIVE and pre-cART HIVE, MRI frequently showed an inflammatory pattern in esc-HIVE, with no atrophy, which was in turn common in all pre-cART HIV cases. In addition, CSF cells and proteins were higher and levels of HIV replication and macrophage activation CSF markers were lower in esc-HIVE. These findings suggest different underlying mechanisms between the two entities, with esc-HIVE associated with lower extent of HIV replication and presence of inflammatory response in the CNS.

	esc-HIVE (n=21) Median [IQR]	HIVE (n=17) Median [IQR]	p value
Demographic characteristics			
- Age	49 [44-51.5]	33 [31.5-38]	*< 0.0001*
- Males	14 (67%)	13 (77%)	0.72
Laboratory findings			
- Current CD4+ (cells/μL)	316 [246-533.5]	16 [3-53]	*< 0.0001*
- Plasma HIV RNA (log_{10} copies/mL)	1.63 [1.56-3.02]	5.55 [5.01-5.86]	*< 0.0001*
- CSF HIV RNA (log_{10} copies/mL)	3.02 [2.89-4.12]	5.28 [5.08-5.68]	*< 0.0001*
- CSF WBC (cells/μL)	15 [7.75-43]	2 [1-4.5]	*0.005*
- CSF total proteins (mg/dL)	79 [69-122]	53 [40.5-77]	*0.006*
CSF inflammatory markers			
- CCL2 (pg/mL)	1007 [860.6-1612]	3822 [1046-7481]	0.07
- CXCL10 (pg/mL)	7512 [741.2-18219]	5275 [1239-20387]	0.74
- suPAR (pg/mL)	184.5 [32.75-311.1]	3970 [2560-5880]	*< 0.0001*

447 RISK AND PREDICTORS OF ASYMPTOMATIC AND SYMPTOMATIC CSF VIRAL ESCAPE IN HIV+ PATIENTS

Carmela Pinnetti, Patrizia Lorenzini, Ilaria Mastrorosa, Valentina Fedele, Stefania Carta, Alessandra Vergori, Alberto Giannetti, Massimo Tempestilli, Adriana Ammassari, Susanna Grisetti, Francesco Baldini, Chiara Agrati, Maria R. Capobianchi, Carlo F. Perno, Andrea Antinori
Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy

Background: Symptomatic CSF viral escape (sCVE) has been associated with an independent replication and evolution of resistance in the CNS, whereas asymptomatic CVE (aCVE) could be the result of cells trafficking or it may be an occasional "blip". Aim was to estimate the risk and identify the predictors of aCVE and sCVE in HIV+ patients (pts).

Methods: Single-centre, retrospective study on CSF/plasma pairs from HIV+ pts with and without neurologic signs and symptoms undergoing lumbar puncture (LP) for diagnostic or therapeutic reasons. CVE was defined as: a) detectable CSF HIV-RNA with concurrent plasma <50 cp/mL; b) CSF HIV-RNA >1.0 log_{10} higher than (aCVE) or 2x (sCVE) concomitant plasma. Impaired Blood Brain Barrier (BBB) was defined by CSF/plasma albumin quotient x 103 (Qalb) higher than age-normalized reference threshold. Variables analyzed: gender, age, HIV transmission mode, CDC stage C, duration of HIV infection and of antiretroviral exposure, CD4 at nadir and at LP, HCV coinfection, CPE score, cells and proteins in CSF, CSF neopterin, CSF NFL, CSF sCD14, BEE dysfunction, calendar year of LP. Adjusted ORs of CVE were calculated by fitting a multivariable logistic regression model.

Results: 624 CSF/plasma paired samples from 322 pts, collected between 1999 and 2014, were included. At LP, 82.5% of pts were male, median age 46y (IQR, 40-51), and HIV transmission: 39.7% heterosexual, 22% MSM, 28.8% IDU. Among samples, CD4 nadir was <200/mm^3 in 59.3%, CDC stage C in 87.8%. CSF was collected in 18% in 1999-2004, 33.3% in 2005-2009, and 48.7% in 2010-2014. At LP, 59% of samples had HIV-RNA <50 cp/mL in plasma and a median CD4 of 178/mm^3 (IQR, 79-362). aCVE was observed in 29 samples (4.6%), sCVE in 22 (3.2%). At multivariable analysis, older age, CD4 nadir <200 and less recent calendar period were associated with an increased risk of aCVE. In a subgroup of 153 samples from pts with available Qalb, BBB dysfunction was associated with 5.6 fold higher risk of aCVE. Otherwise, only female gender and increased number of cells in CSF were found associated with higher probability of sCVE (Tab.1).

Conclusion: In this large paired CSF/plasma sample collection, aCVE and sCVE were found with a low prevalence. aCVE, which was less frequent in more recent years, was predicted by immunological status at LP and BBB damage. Conversely, sCVE was associated with higher CSF pleiocytosis, suggesting that an inflammatory response against HIV-1 may be implicated in the pathogenesis of this disorder.

predictors of aCVE	OR	95% CI		p
Age, 10 yrs higher	1.63	1.09	2.43	0.018
Nadir CD4<200 cell/mmc	2.88	1.86	4.46	<0.001
CD4+ cell/mmc at LP				
<200	1.00			
201-350	0.66	0.23	1.89	0.439
350+	0.45	0.12	1.75	0.250
CPE score of current regimen	1.09	0.90	1.31	0.374
Calendar year of LP				
1999-2003	1.00			
2004-2008	0.26	0.07	0.89	0.033
2009-2014	0.18	0.06	0.50	0.001

predictors of sCVE	OR	95% CI		p
Male gender	0.38	0.15	0.96	0.040
>5 cells in CSF	5.88	2.40	14.41	<0.001

Tab. Predictors of aCVE and of sCVE estimated by multivariable logistic regression.

448 CSF AND BLOOD HIV RNA RELATIONSHIP IN ACUTE HIV IS LINKED TO CD4/CD8 RATIO

Phillip Chan[1], Payal Patel[2], Joanna Hellmuth[3], Donn Colby[1], Eugène Kroon[1], Carlo Sacdalan[1], James L. Fletcher[1], Suteeraporn Pinyakorn[4], Linda Jagodzinski[5], Shelly J. Krebs[5], Nelson L. Michael[5], Jintanat Ananworanich[4], Victor Valcour[3], Serena S. Spudich[2]
[1]SEARCH, Bangkok, Thailand, [2]Yale University, New Haven, CT, USA, [3]University of California San Francisco, San Francisco, CA, USA, [4]US Military HIV Research Program, Bethesda, MD, USA, [5]US Military HIV Research Program, Silver Spring, MD, USA

Background: HIV RNA levels in the systemic circulation and cerebrospinal fluid (CSF) are closely linked in chronic infection with a relationship modified by the degree of immunosuppression and presence of central nervous system (CNS) opportunistic infections or HIV encephalitis. Examination of this relationship during acute HIV infection (AHI) offers a unique opportunity to explore determinants of viral entry into the CNS and may be essential in deciphering origins of HIV CNS compartmentalization and the development of neurologic complications.

Methods: We examined pre-antiretroviral therapy baseline data in the RV254/SEARCH010 Thai AHI cohort to identify factors that correlate to CSF HIV RNA level and the degree of CNS invasion relative to blood, quantified by the difference between plasma and CSF HIV RNA level (Log_{10}plasma HIV RNA - Log_{10}CSF HIV RNA = PCdiff). Plasma and CSF HIV RNA levels across the Fiebig stages were explored and CSF immune markers were compared in a subset of participants in relation to their PCdiff status.

Results: From Apr 2009 to Dec 2016, 117/430 enrollees underwent lumbar puncture (97%male, median age 27 (IQR 23-32) years, and median duration of infection 18 (IQR 14-23) days). 43 (37%) presented at Fiebig stage I or II. 27 (23%) had HIV RNA levels below the level of quantification (80 copies/ml). Among those with a quantifiable level (n=90), the median CSF HIV RNA level and PCdiff were 3.76 (IQR 2.81-4.82) and 2.36 (range 0.10-4.40) log_{10}copies respectively. Median HIV RNA level was highest during Fiebig III in plasma (6.49 log_{10}copies) and Fiebig IV in CSF (4.41 log_{10}copies). In a multivariate linear regression model, plasma HIV RNA level and CD4/CD8 ratio correlated with CSF HIV RNA level (p<0.001) with adjusted β coefficient of 0.604 and -0.616, respectively. CD4/CD8 ratio was the only correlating factor of PCdiff (p=0.018, adjusted β coefficient = 0.380). Seven participants had a small PCdiff below 1 log_{10} (Figure). Compared to others with quantifiable CSF HIV RNA, they had statistically higher levels of CSF neopterin (p=0.030), sCD163 (p=0.006), IL-6 (p=0.031) and sCD14 (p=0.011).

Conclusion: In AHI, CSF HIV RNA level correlates with that in plasma and associates with heightened CNS immune activation, and PCdiff is larger in AHI than in chronic infection. Higher CD4/CD8 ratio independently correlates with lower CSF HIV RNA level and higher PCdiff, suggesting a protective role of systemic immune preservation in limiting HIV entry into the CNS.

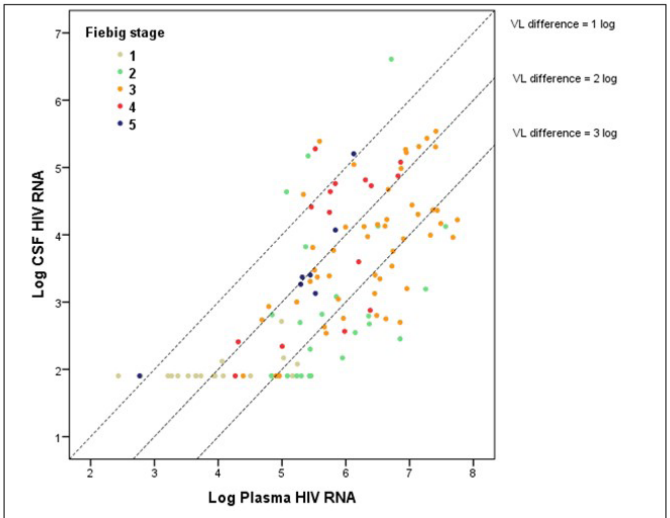


Figure 1. Correlation between CSF and plasma HIV RNA level by Fiebig staging. A level of 80 copies/ml was assigned to the CSF samples with HIV RNA level below quantification.

449 PERIPHERAL AND CSF IMMUNE ACTIVATION AND INFLAMMATION IN HIV+ PATIENTS STARTING cART

Esther Merlini[1], Francesca Iannuzzi[1], Andrea Calcagno[2], Francesca Bai[1], Mattia Trunfio[2], Antonella D'Arminio Monforte[1], Stefano Bonora[2], Giulia Marchetti[1]
[1]University of Milan, Milan, Italy, [2]University of Turin, Turin, Italy

Background: Cerebrospinal Fluid (CSF)/plasma HIV-RNA ratio≥1 has been associated with neurocognitive impairment. We sought to explore whether CSF/plasma HIV-RNA ratio associates with peripheral and CSF inflammation and activation and with neurocognitive screening test performance, in HIV+ patients (pts) before (T0) and after 12 months (T12) of suppressive cART.

Methods: We enrolled 70 HIV+ cART-naive pts. 33/70 were followed for 12 months after cART. At T0 and T12 pts underwent lumbar puncture and blood withdrawal. Pts were stratified according to CSF/Plasma ratio: high CSF/plasma HIV-RNA ≥1 (H-C/P); low CSF/plasma HIV-RNA <1 (L-C/P). Immuno-virological analyses: CD38/CD45RA/CD45R0/HLA-DR/CCR7/Ki67, IL-2/IFN-γ after HIV/CMV exposure on CD4/CD8 (flow cytometry); total HIV-DNA (q-PCR) on PBMCs; IFN-γ /IL-6/sCD14/TNF-α/MCP1/IP10/neopterin/S100Beta (Luminex/ELISA) on plasma and CSF. In 22/33 pts at T0 and T12 we also performed screening neurocognitive assessment: international HIV dementia scale, mini-mental state examination, frontal assessment battery. Cognitive impairment defined as ≥2 tests altered. Statistical analyses: Chi-square, Mann-Whitney, Kruskal-Wallis, Wilcoxon paired tests.

Results: 61/70 pts (87%) were L-C/P; at T0 L-C/P and H-C/P pts showed comparable peripheral and CSF inflammation, peripheral HIV reservoir, T-cell activation/proliferation and maturation, and HIV/CMV-specific response (Fig.1a). At T12, while both H-C/P and L-C/P significantly reduced T-cell activation, only L-C/P pts showed a reduction in CSF sCD14, IL-6 and MCP-1 and in plasma TNF-α (Fig.1b). Besides, L-C/P pts alone showed an increase in naïve CD4+ and CD8+ and central memory CD4+, with a parallel reduction of effector memory CD8+ (Fig.1b). Having shown changes in peripheral and CSF immune parameters, according to CSF/plasma ratio, we next investigated possible associations with cognitive performance. Indeed, we observed that at T0, 9/22 subjects presented altered cognitive impairment: 5/16 (31%) L-C/P, 4/6 (67%) H-C/P (p=.178), with no significant variation at T12 (L-C/P: 4/16; H-C/P: 4/6; p=.137).

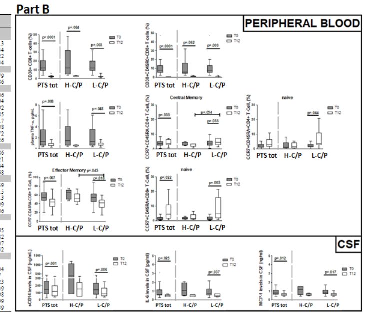
Conclusion: Although showing a slower response in terms of peripheral and CSF pro-inflammatory/effector phenotypes on cART, HIV+ pts with high CSF/plasma HIV-RNA ratio seem to maintain stable cognitive performance, as assessed by screening tests. A longer follow up may be needed in order to assess the time-trends of cognitive functioning in pts presenting with high CSF/plasma HIV RNA ratio.

Figure 1

Part A

	Total (n=70)	L-C/P (n=61)	H-C/P (n=9)	p
Peripheral Blood Markers				
T-cell activation, Median (IQR)				
CD8+38+, %	12,0 (9,00-20,30)	12,00 (9,00-20,00)	12,00 (5,00-32,00)	0.613
CD8+CD38+CD45R0+, %	7,00 (5,00-13,30)	7,00 (5,00-13,00)	6,00 (4,00-16,00)	0.634
HLA-DR+CD38+CD4+, %	2,10 (1,00-5,10)	1,90 (0,95-5,05)	3,30 (1,03-6,85)	0.522
HLA-DR+CD38+CD8+, %	8,35 (4,50-14,50)	8,35 (4,45-13,73)	8,35 (5,58-18,55)	0.734
T-cell proliferation, Median (IQR)				
KI67+CD4+, %	3,10 (1,75-6,60)	3,15 (1,80-6,55)	1,90 (1,60-9,40)	0.579
KI67+CD8+, %	2,90 (1,55-5,75)	2,95 (1,75-5,68)	2,00 (0,80-6,50)	0.386
T-cell maturation, Median (IQR)				
CD4+CCR7+CD45RA+ (naive), %	2,00 (1,05-3)	2,00 (1,20-3,10)	1,25 (0,28-4,20)	0.406
CD4+CCR7+CD45RA- (CM), %	3,80 (2,40-5,10)	3,90 (2,43-5,43)	2,65 (2,35-4,70)	0.494
CD4+CCR7-CD45RA+ (TD), %	36,9 (27,3-46,30)	36,80 (27,53-45,13)	42,30 (14,68-52,68)	0.692
CD4+CCR7-CD45RA- (EM), %	56,3 (45,90-66,7)	56,30 (45,83-66,55)	51,75 (42,15-82,13)	0.885
CD8+CCR7+CD45RA+ (naive), %	1,20 (0,70-2,40)	1,15 (0,70-2,45)	1,50 (0,80-2,40)	0.717
CD8+CCR7+CD45RA- (CM), %	1,50 (1,00-2,10)	1,50 (1,03-2,08)	1,50 (0,80-2,10)	0.908
CD8+CCR7-CD45RA+ (TD), %	42,10 (32,1-47,7)	43,40 (33,83-47,60)	32,10 (26,90-48,70)	0.172
CD8+CCR7-CD45RA- (EM), %	54.10 (47-64,80)	53,95 (44,30-62,50)	64,90 (49,70-70,30)	0.126
Plasma Cytokines, Median (IQR)				
IL-6, pg/ml	2,30 (0,80-4,00)	1,82 (0,68-3,76)	3,50 (1,54-6,27)	0.086
TNFa, pg/ml	1,30 (0,60-3,50)	1,33 (0,60-3,60)	1,49 (0,62-4,08)	0.921
sCD14, ug/ml	3,50 (2,60-5,00)	3,53 (2,64-4,92)	3,86 (2,78-5,36)	0.544
IFN-y, pg/ml	59,1 (41,1-67,70)	52,14(39,72-66,02)	65,85 (57,42-88,58)	0.068
HIV-specific T-cell Response, Median (IQR)				
CD4+IL2+IFN-y+, %	0 (0-0)	0 (0-0,075)	0 (0-0)	0.939
CD4+IL2+IFN-y-, %	0,8 (0,1-1,8)	0,9 (0,4-1,6)	0,75 (0,025-1,898)	0.815
CD4+IL2-IFN-y+, %	0 (0-0,5)	0,2 (0-0,5)	0 (0-0,575)	0.713
CD8+IL2+IFN-y+, %	0 (0-0,1)	0,1 (0-0,2)	0 (0-0,1)	0.099
CD8+IL2-IFN-y+, %	0 (0-0,1)	0,1 (0-0,4)	0 (0-0,113)	0.406
CMV-specific T-cell Response, Median (IQR)				
CD4+IL2+IFN-y+, %	0 (0-0,1)	0 (0-0,15)	0 (0-0,1)	0.8
CD4+IL2+IFN-y-, %	0,9 (0,2-2,3)	2 (1,3-3,3)	0,66 (0,12-2,1)	0.065
CD4+IL2-IFN-y+, %	0,4 (0-0,7)	0,5 (0,08-0,85)	0,4 (0-0,73)	0.782
CD8+IL2+IFN-y+, %	0 (0-0,1)	0 (0-0,1)	0 (0-0,095)	0.907
CD8+IL2-IFN-y+, %	0 (0-0,3)	0,2 (0-0,8)	0 (0-0,235)	0.442
CSF Soluble Markers				
CSF Cytokines, median (IQR)				
sCD14, ng/ml	147 (78-264)	144,2 (72,91-232)	670 (78,44-1195)	0,204
IL6, pg/ml	0,59 (0,5-1,14)	0,68 (0,5-1,25)	1,07 (0,48-1,94)	0,57
TNF-α, pg/ml	0,86 (0,78-0,94)	0,86 (0,76-0,94)	1,17 (0,78-2,16)	0,123
MCP-1, ng/ml	0,77 (0,63-1,11)	0,79 (0,64-1,12)	1,22 (0,54-1,52)	0,539
IP-10, ng/ml	1,16 (0,47-39,9)	1,33 (0,49-68,1	2,41 (1,34-26,34)	0,798
Neopterin, ng/ml	1,1 (0,77-1,50)	1,13 (0,83-2,21)	0,8 (0,22-4,15)	0,499
CSF S100Beta Protein, pg/ml median (IQR)	241 (99-380)	203,5 (76,75-376,5)	293 (78,5-343)	0,939

Part B



450 NOX-4 ASSOCIATED NITROSATIVE STRESS AND INEPT REDOX ADAPTATION IN AGED HIV-1 TG RAT

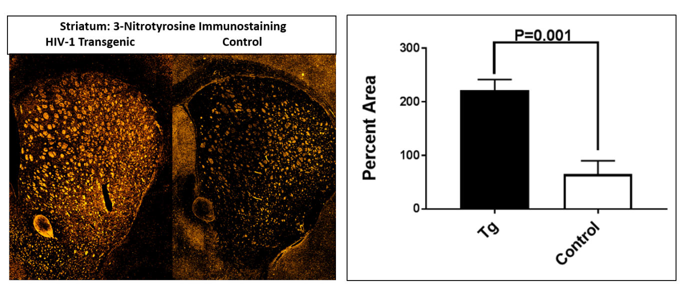
William Reid[1], Swati Shah[1], Frank Denaro[2], Dragan Maric[1], Dima A. Hammoud[1]
[1]NIH, Bethesda, MD, USA, [2]Morgan State University, Baltimore, MD, USA

Background: Due to the success of combined anti-retroviral therapy, HIV-positive (HIV+) patients are living longer with a better quality of life. Nonetheless, human immunodeficiency virus associated neurocognitive disorders (HAND) continue to be a widespread problem with accelerated progression of neurocognitive impairment caused by aging in HIV+ patients. HAND is characterized by increased reactive oxygen and nitrogen species at the cellular level. Motor and behavioral dysfunction are among the common symptoms and it is believed that oxidative and nitrosative stress contributes to mechanistic changes leading to neurocognitive impairment. Our previous imaging, histological, motor and behavioral assessments support a dysregulation in dopaminergic function as the HIV-1 transgenic (Tg) rat ages.

Methods: The goal of this study is to demonstrate the presence of oxidative and nitrosative stress within the neuroanatomic areas associated with dopaminergic dysfunction in the HIV-1 Tg rat brain by using molecular and immunohistological techniques.

Results: We report pathology suggestive of pre-synaptic dopaminergic neuronal loss (decreased striatal tyrosine hydroxylase and dopamine transporter staining in the basal ganglia and decreased NeuN staining in the substantia nigra; p<0.05). In the striatum, we also found 2.6 fold increase in Nox4 expression (p<0.05), 1.6 fold increase in neuronal nitric oxide synthase (nNOS) protein levels (p=0.056) and associated significant increase in 3-nitrotyrosine (3-NT) immunostaining (figure 1) and nitrosylation of axonal neurofilament tyrosine residues (p<0.05) in the aged HIV-1 Tg rats compared to age-matched non-Tg controls. This increase in free radical mediated neuronal pathology occurred without significant induction of the transcription factor nuclear factor-erythroid 2-related factor 2 (Nrf2) and redox adaptation of the Nrf2 responsive thioredoxin and glutathione antioxidant systems.

Conclusion: Our findings suggest increased Nox4 expression and lack of an appropriate redox adaptation in the aging HIV-1 Tg rat, possibly due to chronic exposure to HIV-1 proteins. Increased nitrosative stress and nitrosylation of striatal axonal neurofilament proteins is increased possibly contributing to dopaminergic neuronal structural changes and secondary dopaminergic dysfunction. We therefore propose the HIV-1 Tg rat as an appropriate model of oxidative stress in the setting of HIV infection.



451 CEREBROSPINAL FLUID AND SERUM NEPRILYSIN IN PATIENTS INFECTED WITH HIV CLADES C AND B

Sergio M. de Almeida[1], Clea E. Ribeiro[1], Indianara Rotta[1], Mauro Piovesan[1], Bin Tang[2], Meire S. Batistela[1], Scott L. Letendre[2], Michael Potter[2], Florin Vaida[2], Ronald J. Ellis[2]
[1]Universidade Federal do Paranã, Curitiba, Brazil, [2]University of California San Diego, San Diego, CA, USA

Background: The profile of neural injury biomarkers is not well defined in HIV infection; most previous studies are on HIV subtype B (HIV1-B). How HIV1 Tat induces the development of Aβ deposit in HIV1 patients is not fully understood. Neprilysin (NEP) is the dominant Aβ peptide-degrading enzyme. HIV1-B Tat protein is known to interfere with NEP function, but whether this is true of HIV1-C Tat, which has a defective chemokine dimotif, is not known. This study aimed to analyze the impact of HIV1 subtypes on NEP-mediated cleavage of Aβ by comparing CSF and serum levels of NEP between HIV+ (27 HIV1-B and 26 HIV1-C), healthy HIV- controls (n=13); and patients with Alzheimer's disease (AD, n= 24). This was the first study to analyze NEP in patients with HIV1-C.
Methods: Total NEP (both activated and unactivated forms), as well as Aβ oligomers 38,40 and 42 levels were measured in CSF and serum by immunoassays. Ratios of NEP to Aβ-38,40,42 and total Aβ were calculated for both CSF and serum. To estimate NEP intrathecal synthesis, we calculated CSF/serum indexes of these ratios, and the NEP index=(CSF NEP X Serum Albumin)/(Serum NEP X CSF Albumin). Comparisons between HIV(+) and HIV(-) were adjusted by linear regression for gender and age; HIV subtype comparisons were adjusted for nadir CD4 and plasma viral load suppression. The p-values were corrected for multiple testing with the Benjamini-Hochberg procedure.
Results: Levels of NEP and CSF ratios were comparable for HIV1-C and B. Serum NEP was nonsignificantly lower for HIV1-C than HIV1-B (p= 0.060). The NEP/Aβ-40 ratio in serum was lower for HIV1-C than B (p=0.032). The CSF/serum index of NEP/Aβ-40, NEP/Aβ-42, and NEP/Aβ-total were lower for HIV1-B than C (p= 0.008, 0.005 and 0.017 respectively). The results of CSF/serum indexes corroborated the findings for serum. CSF NEP was comparable for HIV+, HIV-, and AD; although in serum NEP levels were higher for HIV than AD and CTRL.
Conclusion: There was impact of HIV subtype on NEP. The ratio of NEP/Aβ-40 in serum was lower for HIV1-C than HIV1-B. These results are consistent with previous reports of CSF Aß-42 levels decreased in HIV1-C compared with HIV1-B; suggesting higher amyloid ß deposition in HIV1-C than HIV1-B.

452 REGIONAL BRAIN HEME OXYGENASE CORRELATES WITH SIV LOAD IN ACUTE/CHRONIC INFECTION

Rolando Garza[1], Maria Diaz Ortiz[1], Analise Gruenewald[1], Fiorella Rossi[2], Ferzin Sethna[3], Guido Silvestri[4], Michael R. Betts[1], Dennis L. Kolson[1]
[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Nova Southeastern University, Fort Lauderdale, FL, USA, [3]Princeton University, Princeton, NJ, USA, [4]Emory Vaccine Center, Atlanta, GA, USA

Background: Persons with HIV-associated neurocognitive disorders (HAND) have impaired brain antioxidant responses, which is likely pathogenic. The prefrontal cortex shows reduced levels of heme oxygenase-1 (HO-1), an inducible antioxidant enzyme that robustly suppresses oxidative stress and neurotoxin production. Within prefrontal cortex, HO-1 loss correlates with HIV load and macrophage activation. In an SIV macaque model, we determined brain region-specific relationships between HO-1 expression, parenchymal SIV load, and immune activation to validate the model for studies of host antioxidant responses to SIV/HIV infection.
Methods: Rhesus macaques (2-3 yo, male, female) infected IV with SIVmac251 (500 TCID50) were sacrificed 5, 10, 13, 20, 41, and 90 days pi (n=3/day, n=18 total). Nine brain regions (frontal, deep frontal, pre-frontal, parietal, midbrain, basal ganglia, pons, medulla, and cerebellum) were analyzed for antioxidant gene expression (HO-1, HO-2, PRDX1, NQO1, GPX1, SOD1) by western blot and qPCR. Statistical testing was by two-way ANOVA with Tukey and multivariate linear regression.
Results: HO-1 protein levels were lower in deep brain regions (midbrain, basal ganglia, pons, medulla) compared to cortical regions (frontal, pre-frontal cortex; p<.05). In several regions (midbrain, frontal cortex) HO-1 protein inversely correlated with HO-1 RNA (p<.020), suggesting feedback regulation. HO-1 protein correlated negatively with another antioxidant protein (PRDX1; p=0.0007), suggesting a compensatory response to HO-1 protein loss. Regional brain SIV load correlated positively with regional HO-1 RNA level (basal ganglia (p<.0001), pons (p=.026), pre-frontal cortex (p=.030), deep frontal lobe (p=.048). Similarly, regional HO-1 RNA, correlated with plasma SIV load (p<.020 for all regions). These relationships were generally consistent over 90 days of infection.
Conclusion: In the Rhesus macaque brain lower HO-1 protein expression in deep regions (midbrain, basal ganglia, pons, medulla) in comparison to cortical regions might contribute to the selective vulnerability of deep structures to SIV-induced injury. The correlation between regional SIV load and HO-1 RNA level (also seen in HIV-infected human brain prefrontal cortex) suggests that viral replication induces HO-1 transcription, as a host protective response. Similarities between macaque and human brain antioxidant responses to infection support the macaque model for testing HO-1 based neuroprotection strategies for HAND.

453 CSF EXTRACELLULAR VESICLES AS BIOMARKERS OF CNS INJURY IN HIV PATIENTS ON ART

Debjani Guha, Sukrutha Chettimada, Vikas Misra, David Lorenz, Dana H. Gabuzda
Dana–Farber Cancer Institute, Boston, MA, USA

Background: HIV-associated neurocognitive disorders (HAND) remain prevalent despite antiretroviral therapy (ART). The relationship of CSF extracellular vesicles (EVs) to HAND is unclear. We performed a cross-sectional and longitudinal study to investigate the association of CSF EVs with HAND and CNS injury-related biomarkers (NFL, S100B, neopterin) in HIV+ subjects on ART.
Methods: CSF NFL, S100B, and neopterin were measured by ELISA in 112 subjects (67 HIV+ virally suppressed on ART with nadir CD4∠300 cells/µl, age range 36-78 years, 73% male, 57% white and 45 HIV- controls matched for age, gender, race). CSF EVs were isolated from 49 HIV+ (24 cognitively impaired (NCI) and 25 unimpaired) and 16 HIV- controls. EVs were characterized by electron microscopy, nanoparticle tracking analysis, and immunoblotting for exosome markers (CD9, CD63, CD81, FLOT-1). CSF EV protein cargo was analyzed by untargeted LC-MS/MS in 12 subjects. GO analysis used geneXplain TRANSFAC.
Results: CSF NFL, S100B, and neopterin levels were higher in subjects with HIV, detectable plasma VL, low CD4 count, and NCI compared to corresponding controls (p<0.05), and increasing NFL and S100B levels were associated with cognitive decline over 2 years. CSF EVs were more abundant in HIV+ vs. HIV- subjects (p<0.001), and NCI vs. unimpaired subjects (p=0.01). CSF EV concentrations correlated with NFL (r=0.567, p<0.001) and S100B (r=0.389, p=0.0015). Proteomics analysis identified >800 proteins enriched or uniquely detected in CSF EVs compared to EV-depleted CSF, and suggested CSF EVs originate from myeloid cells (CD14, CHI3L1, CSF1R, MARCO, MRC1), astrocytes (S100B, GFAP, PEA15, SLC1A3), and neurons (NFL, NFASC, NPTN, ENO2) and carry proteins related to exosomes (CD9, CD81, FLOT-1, ALIX), inflammatory/immune responses (GAS6, LBP, HLAs), stress responses (HSPs, SOD, PARK7, PRDXs, TXN), and blood-brain-barrier (BBB) (AGRN, AQP4, DAG1, VCAM1). HLA-DR levels were higher in CSF EVs from NCI but not unimpaired subjects vs. HIV- controls (p=0.03), suggesting activated macrophages/microglia are a potential source of CSF EVs in HAND.
Conclusion: CSF EVs are more abundant in HIV+ compared to HIV- individuals, and neurocognitively impaired compared to unimpaired individuals. CSF EVs correlate with known biomarkers of CNS injury and carry protein cargo related to neuronal injury, inflammation, stress responses, and BBB function, suggesting applications as novel biomarkers of CNS injury in HIV patients on ART.

454 DELETERIOUS EFFECTS OF HIV-1 LATENCY-REVERSING AGENTS MEDIATED BY ASTROCYTES

Alizé Proust, Corinne Barat, Mathieu Leboeuf, Jean Drouin, Michel J. Tremblay
Laval University, Quebec City, QC, Canada

Background: Despite the combined antiretroviral therapy potency, HIV-1 persists in long-lived latently infected cells. Thus, therapies capable of eliminating this latent viral reservoir are needed. A shock and kill strategy using latency-reversing agents (LRA) to reactivate HIV-1 has been proposed. However, the impact of these LRA on the central nervous system (CNS) remains elusive.
Methods: In this study, we used primary fetal astrocytes and investigated the effects of LRA on their phagocytic, functional and secretory activities. Astrocytes were infected with VSV-G-pseudotyped HIV-1 before a 24h treatment with various blood-brain barrier (BBB)-permeable LRA at subcytotoxic doses, which allow HIV-1 reactivation based on previous in vitro and clinical studies. Cells and supernatants were then used to evaluate effects of infection and LRA on (i) yeast and amyloid beta (Aβ) phagocytosis by microscopy and flow cytometry, (ii) expression of complement component 3 (C3), a proxy

for astrogliosis, by RT-qPCR, (iii) glutamate uptake capacity by a fluorometric assay, (iv) chemokines and proinflammatory cytokines secretion and gene expression by astrocytes using ELISA and RT-qPCR respectively, (v) modulation of neutrophil transmigration across an in vitro BBB model.

Results: Our results show that JQ1 and bryostatin-1 reduce yeast phagocytosis. Moreover, those two LRA decrease the speed and quantity of Aβ uptake by astrocytes compared to an untreated control. Bryostatin-1 also increases C3 expression and disturbs the astrocytic glutamate uptake/release balance. Moreover, bryostatin-1 increases secretion of chemokines and proinflammatory cytokines CCL2, IL-6, IL-8 and GM-CSF by astrocytes. In contrast, JQ1 represses their production. Lastly, we observed that neutrophil transmigration across our BBB model is increased in response to bryostatin-1, and that this LRA induces neutrophil extracellular traps formation.

Conclusion: Taken together, our results suggest that bryostatin-1 and JQ1 could induce Aβ aggregation and senile plaque formation involved in Alzheimer's disease progression. Moreover, bryostatin-1 could lead to excitotoxicity by disrupting glutamate homeostasis. Chemokines and proinflammatory cytokines secreted by astrocytes in response to bryostatin-1 could induce an inflammatory syndrome and favor neutrophil invasion in the CNS that could lead to neurological disorders. Our study provides evidence that the safety of the shock and kill approach needs to be further investigated in the brain compartment.

455 EFAVIRENZ PHARMACOKINETICS IN HIV/TB COINFECTED PERSONS RECEIVING RIFAPENTINE

Anthony Podany[1], Erin Sizemore[2], Michael Chen[2], Neil A. Martinson[3], Rodney Dawson[4], Sharlaa Badal-Faesen[5], Sachiko Miyahara[6], Ekaterina Kurbatova[2], William C. Whitworth[2], Richard E. Chaisson[7], Susan E. Dorman[7], Payam Nahid[8], Kelly Dooley[7], Susan Swindells[1]

[1]University of Nebraska, Omaha, NE, USA, [2]CDC, Atlanta, GA, USA, [3]Perinatal HIV Research Unit, Soweto, South Africa, [4]University of Cape Town, Cape Town, South Africa, [5]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [6]Harvard University, Cambridge, MA, USA, [7]The Johns Hopkins University, Baltimore, MD, USA, [8]University of California San Francisco, San Francisco, CA, USA

Background: AIDS Clinical Trials Group Study A5349/Tuberculosis Trials Consortium Study 31 (S31) is a phase III trial comparing two short-course TB treatment regimens containing high dose daily rifapentine (RPT) to standard TB treatment. RPT is a known CYP inducer and efavirenz (EFV) is a CYP substrate; thus, there is a potential risk of decreased EFV exposure and consequently increased risk of virologic failure. The pharmacokinetics (PK) of this combination have not been evaluated. An objective of S31 was to evaluate the effect of RPT on EFV PK, initially among a subset of participants on stable EFV-containing antiretroviral therapy (ART) at the time of initiation of RPT-containing TB treatment.

Methods: This substudy included participants already suppressed on at least two months of EFV-containing (600mg) ART, and randomized to one of two regimens containing daily RPT (1200mg), isoniazid (H), pyrazinamide, and either ethambutol or moxifloxacin. Mid interval EFV concentrations were measured in plasma samples collected at weeks 0 (pre-RPT/H), 4, and 8 during concomitant RPT/H. EFV apparent oral clearance (CL/F) was modeled using Bayesian estimation; population PK priors were taken from previous EFV PK studies. Week 4 and 8 EFV concentrations were combined to estimate EFV CL/F during RPT/H therapy. The geometric mean ratio (GMR) and 90% confidence interval (CI) of the pre and during RPT/H EFV CL/F values were calculated. The protocol specified that >80% of participants should have EFV concentrations ≥1 mg/L for enrollment to continue.

Results: Of 23 evaluable participants, 52% were female, 91% Black/African, and median age was 37 years (25-53). All 23 had HIV-1 RNA <200 copies/mL at randomization, 16/16 (100%) had HIV-1 RNA <200 copies/mL at week 8; the median baseline CD4+ count was 401 cells/mm^3 (118-998). The GMR for EFV CL/F was 0.88 (0.75-0.96). The number of participants with EFV concentrations ≥ 1 mg/L at both week 4 and 8, was 21 (91%). Median (IQR) RPT concentrations were 14.7 mg/L (12.2-19.25 mg/L).

Conclusion: The CL/F of EFV decreased slightly with RPT/H. However, the proportion of participants with EFV concentrations ≥1mg/L did not cross below the pre-specified threshold of 80%. Plasma HIV-RNA levels during RPT/H indicated maintenance of viral suppression. These data provide preliminary support for co-administration of high-dose RPT/H with EFV-containing ART. Evaluation of EFV PK in participants starting ART after initiation of study RPT-containing TB treatment is underway.

	Median EFV mg/L (IQR)	**EFV Concentration ≥ 1 mg/L (n, %)**
Week 0 (baseline)	2.54 (1.81-3.96)	23/23 (100%)
Week 4	3.34 (1.95-7.14)	22/23 (96%)
Week 8	2.63 (2.09-7.23)	21/23 (91%)
	Median EFV CL/F (L/hr) (IQR)	
Pre RPT/H	8.02 (5.79-10.57)	
On RPT/H	7.17 (3.38-9.53)	

456 EFAVIRENZ PHARMACOKINETICS WITH RIFAMPIN DOUBLE DOSE IN TB-HIV INFECTED PATIENTS

Daniel W. Atwine[1], Elisabeth Baudin[2], Thibaut Gelé[3], Winnie R. Muyindike[4], Mworozi Kenneth[1], Racheal Kyohairwe[1], Kenneth Kananura[1], Dan Nyehangane[1], Patrick Orikiriza[1], Valérie Furlan[3], Anne-Marie Taburet[5], Aurélie Barrail-Tran[6], Maryline Bonnet[7]

[1]Epicentre, Mbarara, Uganda, [2]Epicentre, Paris, France, [3]Hôpital Bicêtre, Le Kremlin-Bicetre, France, [4]Mbarara University of Science and Technology, Mbarara, Uganda, [5]INSERM, Le Kremlin-Bicetre, France, [6]University of Paris-Sud, Orsay, France, [7]IRD, Montpellier, France

Background: There is increasing interest towards a potential reduction of tuberculosis (TB) treatment duration with use of high-dose rifampicin (R) among HIV-negative patients. Little is known among HIV-positive patients on antiretroviral therapy (ART). The ANRS 12292 Rifavirenz phase 2 trial evaluated efavirenz (EFV) pharmacokinetics (PK) in Ugandan HIV/TB co-infected patients receiving high-dose R (20 mg/kg) as part of their standard TB treatment for the first 2 months.

Methods: Newly diagnosed, confirmed pulmonary TB, ART-naïve, adults were randomized to 3- regimens administered QD. All patients were started on TB treatment and initiated on ART 2-4 weeks after. They received isoniazid(H)/pyrazinamide(Z)/ethambutol(E) and tenofovirDF/lamivudine at standard dosing during the first 8 weeks with R20mg/kg and EFV600mg (group G1); R20mg/kg and EFV 800mg (G2); R10mg/kg and EFV600mg (Control C). At 8 weeks of follow-up, all patients were switched to standard R and EFV doses. Drug intake was observed. Blood samples were drawn 4 weeks after EFV initiation and 4 weeks after R discontinuation. EFV plasma concentrations were assayed by validated High Performance Liquid Chromatography assay. PK parameters were estimated by a model-independent method. The 90% confidence interval (CI) of the geometric mean ratios (GMR) of PK parameters with and without TB treatment was compared to the predefined 0.70-1.43 range for concentrations to remain within the therapeutic window. Plasma HIV-viral load (VL) was monitored 4, 12 and 24-26 weeks after ART initiation and mycobacterial sputum culture (Mycobacteria Growth Indicator Tube) 8 weeks after starting TB treatment.

Results: Of 97 included patients (G1 31; G2 33; C 33), 87 were evaluable for PK. Median age, weight and CD4 count were 33 years, 53.6 kg and 141 cells/µL, respectively and 77% were males. EFV PK parameters are summarized in the table below. TB culture conversion was 85.7% (G1), 86.7% (G2) and 80.0% (C). At 12 weeks post-ART initiation, 92.6%, 86.2% and 92.6% of patients had VL < 400 copies/mL, respectively. No relationship could be evidenced between VL decline and EFV concentrations. During the first 8 weeks, 6 (2 per arm) and 4 (G1=1; G2=2; C=1) patients had alanine aminotransferase increase > grade 3 and neuropsychiatric events > grade 2, respectively.

Conclusion: Despite a trend to lower EFV concentrations when R dosing was doubled, concentration remained in the therapeutic window and there was no sign of decreased tolerance.

Median (range) unless otherwise indicated	EFV PK parameters		
	EFV+R (week 8)	EFV alone (week 28)	GMR [90% CI] EFV+R/EFV
Control group (C): R10mg/kg and EFV 600mg, n=29 patients			
C24-ng/mL	1077 (233; 9407)	1137 (324; 8049)	0.92 [0.79; 1.08]
C24<1000ng/mL, n (%)	14 (48)	11 (38)	
AUC-µg.h/mL	40.2 (13.4; 314.5)	38.9 (14.3; 214.3)	0.96 [0.84; 1.09]
Group 1: R20mg/kg and EFV 600mg, n=27 patients			
C24-ng/mL	1188 (498; 12212)	1496 (457;17967)	0.83 [0.72; 0.96]
C24<1000ng/mL, n (%)	12 (44)	5 (18)	
AUC-µg.h/mL	47.5 (16.2; 308.4)	49.6 (13.4; 486.8)	0.87 [0.75; 1.00]
Group 2: R20mg/kg and EFV 800mg, n=31 patients			
C24-ng/mL	1032 (214; 11555)	1028 (408; 11299)	1.16 [0.97; 1.39]
C24<1000ng/mL, n (%)	13 (42)	15 (48)	
AUC-µg.h/mL	44.5 (12.9; 326.3)	35.2 (14.2; 265.7)	1.12 [0.96; 1.30]

457 PHARMACOKINETICS OF EFAVIRENZ 400MG WITH ISONIAZID/ RIFAMPICIN IN PEOPLE WITH HIV

Maddalena Cerrone[1], Xinzhu Wang[2], Megan Neary[3], Christine Weaver[1], Serge Fedele[1], Isaac Day-Weber[2], Andrew Owen[3], Andrew Hill[3], Myra McClure[2], Marta Boffito[1]

[1]Chelsea and Westminster Hospital, London, UK, [2]Imperial College London, London, UK, [3]University of Liverpool, Liverpool, UK

Background: Antiretroviral (ARV) dose reductions compensate for finite global manufacturing capacity and allow access programmes to reach larger numbers of people living with HIV (PLWH). The ENCORE-1 study showed that efavirenz 400mg (EFV400) is as effective as the standard adult dose of 600mg. WHO recommend EFV400 as an alternative first-line ARV, with a disclaimer that no data on EFV400 with anti-tuberculosis (TB) treatment exist. Many PLWH need TB treatment with isoniazid (INH) and rifampicin (RIF) that affect cytochrome P450 and ARV exposure.

Methods: This open-label study investigated the pharmacokinetics (PK), efficacy, CYP2B6 pharmacogenetics of EFV400 + INH/RIF in PLWH without TB (TB-), receiving tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) and EFV 600mg with a viral load (VL)< 50 copies/mL. They were switched to TDF/FTC/ EFV400. Weekly therapeutic drug monitoring (TDM), steady-state PK profiles of EFV400 without (PK1) and with INH/RIF following 4 (PK2) and 12 (PK3) weeks of co-administration, safety, virologic efficacy, polymorphisms in CYP2B6 (516C>T; 938T>C) were evaluated. Subjects who completed PK2 were included in the full PK analysis.

Results: 34 PLWH were screened and 26 baselined, 22 completed PK2 (3 withdrew for EFV400 TDM results <800ng/mL in >3 consecutive visits, as per protocol stopping rule, and 1 because of non-drug related liver toxicity), and 17 completed PK3 (2 withdrew for liver toxicity, 1 for low EFV levels, 1 was pregnant, 1 is ongoing). Baseline median (range) age and CD4 count (n=22) were 47 (22-60)years and 591 (223-1159)cells/mm^3. 10 were Black Africans, 8 White, 4 other. All had VL<50 at baseline, which was maintained throughout the study. Geometric mean ratios (GMR) PK2/PK1, n=22 (90%CI) of EFV400 C_{max}, AUC, and C24h were 0.91 (0.83-0.99), 0.91 (0.86-1.13), 0.85 (0.72-0.99). GMR (90%CI) of PK3/PK2 and PK3/PK1 (n=17) C_{max}, AUC, and C24h were 0.97 (0.88-1.06), 0.94 (0.88-1.06), 0.91 (0.78-1.05) and 0.85 (0.78-0.94), 0.86 (0.80-1.09), 0.77 (0.64-0.94). 11/22 subjects were carriers of 516T (10) and/or 938C (3) slow metabolisers alleles.

Conclusion: INH/RIF co-administration in TB-PLWH with a VL<50 was associated with limited changes in EFV400 exposure (<23%) and EFV400 concentrations were maintained within ranges of those measured in PLWH in ENCORE-1 (Dickinson et al. 2015). Results from this cohort conclude that EFV400 can be co-administered with anti-TB treatment. This should be confirmed in TB+ PLWH.

458 IN SILICO DRUG INTERACTION OF LONG-ACTING RILPIVIRINE AND CABOTEGRAVIR WITH RIFAMPIN

Rajith Kumar Reddy Rajoli[1], Paul Curley[1], David Back[1], Charles W. Flexner[2], Andrew Owen[1], Marco Siccardi[1]

[1]University of Liverpool, Liverpool, UK, [2]Johns Hopkins Hospital, Baltimore, MD, USA

Background: Cabotegravir (CAB) and rilpivirine (RPV) are two investigational long-acting (LA) agents and their interaction with rifampin (RIF) has not been fully elucidated. The aim of this study was to simulate and predict the influence of RIF on the pharmacokinetics (PK) of CAB and RPV four-weekly intramuscular (IM) administration using a physiologically-based pharmacokinetic (PBPK) model.

Methods: The PBPK model was designed in Simbiology v. 4.3.1 (MATLAB 2013b) and 100 healthy adult individuals were used for simulations. PBPK models were qualified for the three drugs against available oral clinical data. Standard oral doses of 30 mg, 25 mg and 600 mg were used for CAB, RPV and RIF, respectively. Loading doses of 800 mg and 900 mg were used for CAB and RPV, respectively. 400/800 mg and 600/900 mg were used as q4/8-weekly IM maintenance doses for CAB and RPV. Models were also qualified against PK data in the LATTE-2 IM CAB and RPV study. Oral CAB-RIF, midazolam (CYP3A4 probe)-RIF and RPV-RIF drug-drug interaction (DDI) models were also qualified against PK data from clinical studies. The PBPK models were assumed to be qualified if the simulated values were ± 100 % from the mean reported clinical values. We evaluated the effect of 600 mg oral once-daily RIF on the PK of LA IM 4-weekly CAB and RPV loading and maintenance doses. Variation in PK parameters AUC, C_{max} and C_{trough} values are reported.

Results: For the IM loading dose of CAB with 600 mg OD RIF, the PK parameters C_{max}, AUC and C_{trough} decreased by 57.6%, 43.8% and 44.0%, respectively, compared to CAB alone. For the maintenance doses there was an overall reduction between 39% and 46% in the PK parameters. A more marked reduction was observed for rilpivirine PK, with a decrease in C_{max}, AUC and C_{trough} of 90.9%, 83.9% and 83.6% for the loading dose, and a reduction in these parameters between 80.5% and 83% for maintenance doses.

Conclusion: Models were qualified and PK data successfully predicted for CAB and RPV with RIF. This computational approach supports the prediction of potential DDIs for LA regimens, which cannot be readily investigated in vivo due to ethical and logistical barriers. This approach could rationally guide the design of alternative dosing strategies. The co-administration of RIF with CAB and RPV is predicted to substantially decrease ARV concentrations.

	Drug Alone			Drug + 600 mg OD Rifampin			% difference (alone vs. DDI)		
	C_{max}	AUC	C_{trough}	C_{max}	AUC	C_{trough}	C_{max}	AUC	C_{trough}
Cabotegravir 800 mg LD (4-weeks)	2.69 ± 0.68	1129 ± 259	1.41 ± 0.32	1.14 ± 0.31	634 ± 141	0.8 ± 0.18	-57.6%	-43.8%	-44.0%
Cabotegravir 400 mg MD (4-weekly)	2.23 ± 0.49	1340 ± 295	1.40 ± 0.31	1.36 ± 0.32	794 ± 186	0.8 ± 0.2	-39.0%	-40.7%	-40.7%
Cabotegravir 800 mg MD (8-weekly)	3.15 ± 0.74	2291 ± 541	1.42 ± 0.33	1.78 ± 0.46	1247 ± 319	0.77 ± 0.2	-43.5%	-45.6%	-45.8%
Rilpivirine 900 mg LD (4-weeks)	86.1 ± 49.7	29729 ± 15368	34.5 ± 16.3	8.35 ± 3.49	4670 ± 1788	3.7 ± 2.6	-90.3%	-84.3%	-89.3%
Rilpivirine 600 mg MD (4-weekly)	64.9 ± 36.7	39313 ± 22724	37.3 ± 22.3	12.57 ± 5.51	7128 ± 3128	6.7 ± 2.9	-80.6%	-81.9%	-82.1%
Rilpivirine 900 mg MD (8-weekly)	80.3 ± 35.3	59219 ± 28134	37.4 ± 17.9	15.3 ± 6.6	10175 ± 4464	6.6 ± 2.9	-80.9%	-82.8%	-82.4%

LD – loading dose, MD – maintenance dose. Cabotegravir C_{max}, C_{trough} are expressed as µg/ml and AUC in µg.h/ml; Rilpivirine C_{max}, C_{trough} are expressed as ng/ml and AUC in ng.h/ml. Intramuscular loading dose was preceded by 4-weeks of daily oral dose (30 mg- cabotegravir, 25 mg – rilpivirine)

459 DOLUTEGRAVIR INTERACTIONS WITH ARTEMETHER-LUMEFANTRINE AND AMODIAQUINE-ARTESUNATE

Stephen I. Walimbwa[1], Mohammed Lamorde[1], Catriona Waitt[2], Julian P. Kaboggoza[1], Laura Else[2], Pauline Byakika-Kibwika[3], Alieu Amara[2], Joshua Gini[2], Markus Winterberg[4], Joel Tarning[4], Saye Khoo[2]

[1]Infectious Disease Institute, Kampala, Uganda, [2]University of Liverpool, Liverpool, UK, [3]Makerere University College of Health Sciences, Kampala, Uganda, [4]Mahidol University, Bangkok, Thailand

Background: We investigated potential drug-drug interactions between the most commonly used artemisinin-containing therapies artmether-lumefantrine (AL) or artesunate-amodiaquine (AS-AQ) and dolutegravir (DTG).

Methods: We undertook two pharmacokinetic (PK) studies in healthy Ugandan volunteers, using standard clinical treatment doses of AL and AS-AQ and 50mg of DTG once daily given with food. Rich PK sampling was performed after the final dose of AL or AS-AQ. Study A: DTG/AL interaction. Two-way cross-over study design (n=16) with 1:1 randomisation. Subjects received either 3 days of AL dosing or 6 days of DTG (to reach steady state) plus 3 days AL+DTG. Following washout (21 days), the opposite regimen was given. Study B: DTG/ AS-AQ interaction. Parallel study design (n=30) due to the long half-life of the active AQ metabolite, desethylamodiaquine (DEAQ). 1:1 randomisation to either 3 days of AS-AQ alone or 7 days of DTG alone followed by 3 days AS-AQ + DTG. Clinical and laboratory adverse events (AE) were reported using DAIDS criteria. Artemether (ARM), artesunate (ARS), dihydroartemisinin (DHA), lumefantrine (LF), desbutyl-lumefantrine (DLF), amodiaquine (AQ) and DEAQ were measured over 0-264 h (study A) and 0-624 h (study B) using LC-MS. Noncompartmental

analysis was performed (WinNonlin). Geometric mean ratios (GMR; 90% CI) for antimalarials +/- DTG for Cmax, Tmax and AUC to last measurable time point (AUClast) were computed in Study A, and Mann Whitney U tests compared these parameters in Study B.

Results: PK parameters are presented in the Table. Study A: For ARM, GMR of Cmax without (N=7) and with DTG (N=7) was 0.87 (0.67-1.14), of Tmax was 1.06 (0.84-1.34) and of AUClast was 1.05 (0.84-1.32). For DHA, GMR of Cmax was 0.92 (0.79-1.07), for Tmax was 1.17 (0.92-1.49) and for AUClast was 0.92 (0.79-1.07). For LF, GMR of Cmax was 1.12 (0.97-1.29), for Tmax was 1.65 (1.02-2.69) and for AUClast was 1.10 (0.96-1.27). For DLF, GMR of Cmax was 0.96 (0.80-1.15), Tmax was 3.00 (2.06-4.36) and for AUClast was 0.96 (0.80-1.15). Study B: There were no statistically significant differences in AUClast for ARS (p=0.77), DHA (p=0.28), AQ (p=0.17) and DEAQ (p=0.69) between subjects administered AS-AQ alone (N=13) and those receiving DTG (N=12). No AEs ≥ grade 3 were observed in either study, and all drugs were well-tolerated.

Conclusion: Standard doses of the antimalarials AL and AS-AQ can be used in patients receiving DTG 50mg once daily.

	Antimalarial alone			Antimalarial + DTG		
Antimalarial/ Metabolite	C_{max}	AUC_{last}	T_{last}	C_{max}	AUC_{last}	T_{last}
Study A						
ARM	31.9 (20.6-43.2)	129.6 (79.3-179.8)	11.8 (7.1-16.5)	27.9 (10.3-45.5)	136.4 (60.3-212.6)	16.5 (8.5-24.5)
DHA	110.4 (92.9-128.0)	389.3 (344.5-434.0)	11.7 (11.2-12.1)	89.9 (71.1-108.7)	357.3 (274.9-439.6)	13.3 (9.0-17.5)
LF	9976 (8318-11633)	389350 (333608-445092)	264 in all	11203 (9522-12873)	429736 (379911-479561)	264 in all
DLF	51.7 (37.5-66.0)	6699 (4804-7796)	264 in all	50.0 (41.5-58.3)	6049 (5235-6862)	264 in all
Study B						
ARS	61.3 (41.5-81.0)	128.4 (90.8-165.9)	9.15 (7.9-10.3)	52.0 (31.7-72.3)	115.7 (83.2-148.2)	7.4 (6.2-8.7)
DHA	217.7 (157.4-277.9)	788.3 (622.1-954.4)	11.6 (11.1-12.1)	290.4 (197.3-383.6)	946.8 (760.2 – 1133.4)	11.6 (11.1-12.2)
AQ	17.8 (14.9-20.7)	256.1 (222.5-289.8)	17.8 (14.9-20.7)	19.2 (16.0-22.4)	225.0 (198.9-251.1)	60.8 (54.9-66.7)
DEAQ	394.0 (325.9-462.0)	31492 (28720-34265)	624 (624-624)	385.6 (346.8-424.3)	26943 (22913-30973)	510 (430-590)

460 TENOFOVIR HIV-1 PLASMA PROPHYLACTIC CONCENTRATION: iPREX,VOICE,PARTNERS META-ANALYSIS

Katarina Vucicevic[1], Craig W. Hendrix[2], Robert M. Grant[1], Connie L. Celum[3], Jared Baeten[3], Jeanne Marrazzo[4], Peter L. Anderson[5], David Glidden[1], Radojka M. Savic[1]

[1]University of California San Francisco, San Francisco, CA, USA, [2]Johns Hopkins University, Baltimore, MD, USA, [3]University of Washington, Seattle, WA, USA, [4]University of Alabama at Birmingham, Birmingham, AL, USA, [5]University of Colorado Denver, Denver, CO, USA

Background: The results from pre-exposure prophylaxis (PrEP) efficacy trials that evaluated tenofovir disoproxil fumarate (TDF) have hypothesized that individuals who acquired HIV-1 infection had low adherence based on lower rates of quantifiable/protective tenofovir (TFV) levels. However, prophylactic TFV plasma levels are still not fully characterized. Our aim was to perform individual level data meta-analysis from double-blinded randomized trials, establish exposure-response model to define target plasma TFV concentration.

Methods: This analysis included data and participants from iPrEX (men or transgender women who have sex with other men), VOICE (young unmarried women), and Partners PrEP trial (HIV-1 negative partner in heterosexual couples), taking 300mg of TDF daily with/without emtricitibine, with at least one plasma measurement. Longitudinal PK, adherence, HIV-1 status and sexual risk behavior data were available based on the specific protocol. TFV concentrations up to 100 hours post-dose including below lower limit of quantification (BLQ) were used in model building. Adherence-PK-outcome model was developed using NONMEM software and mixture model approach.

Results: A total of 2478 individuals (204 HIV-1 seroconverters) contributed 7868 plasma measurements (43% BLQ), obtained on up to median 3 (1-16) follow-up visits. Significant sigmoidal E-max relationship was identified in all analyses: TFV average daily plasma concentration associated with 50% reduction in probability of HIV-1 infection was estimated to be 23.5ng/mL (95% confidence interval, 16-31ng/mL). This further translates into target trough TFV level of 45.4ng/mL (95% confidence interval, 30.8-59.9ng/mL) associated with 90% decrease in HIV-1 infection. Patient time-dependent adherence patterns were estimated from PK data. Population PK parameters were in agreement with previously reported values, with overall clearance related significantly to creatinine clearance (CrCl). For every 10mL/min decrease in CrCl, TFV clearance will decrease 5.4%. Overall drug intake probability was 63.1% (RSE=3%), with large between-/within- patient variability.

Conclusion: We estimated preventive TFV plasma concentration from the largest database to date. Compliance to TDF daily dosing of 300mg maintains proposed target TFV plasma concentration. In our analyses, 97% of seroconversions were observed in patients whose daily TFV concentrations were less than proposed target at least at one occasion.

461 PERSISTENT LOW-LEVEL VIREMIA IS ASSOCIATED WITH LOW PROTEASE INHIBITOR LEVELS IN HAIR

Alfredo Aguirre[1], Cyra Christina Mehta[1], Sophia A. Hussen[1], Igho Ofotokun[1], Ruth Greenblatt[2], Daniel Merenstein[3], Angela Kashuba[4], Kathryn Anastos[5], Mirjam-Colette Kempf[6], Elizabeth T. Golub[7], Jack DeHovitz[8], Mardge H. Cohen[9], Sheri Weiser[2], Anandi N. Sheth[1]

[1]Emory University, Atlanta, GA, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]Georgetown University, Washington, DC, USA, [4]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [5]Albert Einstein College of Medicine, Bronx, NY, USA, [6]University of Alabama at Birmingham, Birmingham, AL, USA, [7]Johns Hopkins Hospital, Baltimore, MD, USA, [8]SUNY Downstate Medical Center, Brooklyn, NY, USA, [9]Rush University Medical Center, Chicago, IL, USA

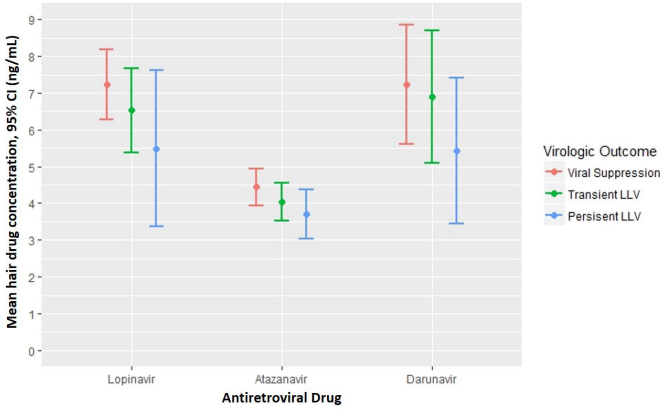
Background: HIV-infected patients on combination antiretroviral therapy (ART) may experience episodes of low-level viremia (LLV). Persistent LLV is associated with antiretroviral (ARV) drug resistance and regimen failure, but its etiology and optimal management are unclear. We evaluated the association between LLV and ARV concentration in hair, a measure of long-term ARV exposure.

Methods: HIV-infected women in the Women's Interagency HIV Study receiving protease-inhibitor (PI)-containing ART for ≥1 year with plasma viral load (VL) <500 copies/mL were evaluated during semiannual visits from 2002-2014 for persistent LLV (≥2 consecutive detectable VL <500 copies/ml), transient LLV (detectable VL <500 copies/mL on non-consecutive visits), or sustained viral suppression (VS, all VL below limit of detection). Participants with virologic failure (any VL ≥500 copies/ml) were excluded. Concentrations of lopinavir, atazanavir, and darunavir were measured from hair samples using liquid chromatography/tandem mass spectrometry and divided into quartiles by drug. Multivariable logistic regression and generalized linear mixed models examined factors associated with persistent or transient LLV (versus VS) including age, race, enrollment site, year of first ART, pre-regimen VL, self-reported adherence, and hair ARV quartile.

Results: Among 730 participants contributing 6266 person-visits of follow-up, 90 (12%) had persistent LLV and 167 (23%) experienced transient LLV. Maximum VL during follow-up was similar for women with persistent and transient LLV (median 132 [IQR 78, 240] and 119 [IQR 119, 210] copies/mL, p=0.12). In models including the above factors except hair ARV quartile, only non-Hispanic African American race was associated with persistent LLV (OR 1.9, 95%CI 1.2–3.0) and transient LLV (OR 1.8, 95%CI 1.0–3.3). Among 440 participants with hair PI levels, mean hair ARV concentration was lowest in the persistent LLV group for all 3 drugs (Figure 1). After adjusting for self-reported adherence, race, and the above factors, hair ARV quartile was significantly associated with persistent LLV (OR 2.5, 95%CI 1.1–5.8) but not transient LLV (OR 1.5, 95%CI 0.8–2.9).

Conclusion: In this cohort of HIV-infected women receiving PI-containing ART, one-third experienced either transient or persistent LLV during >4 years follow-up. Persistent LLV was more likely to occur among women with lower hair PI levels, suggesting that improving ARV exposure could prevent persistent LLV and its adverse consequences.

Figure 1. Antiretroviral drug concentrations in hair (mean, 95% confidence interval) among HIV-infected women receiving protease inhibitor-containing ART by LLV status.



462 EFAVIRENZ LEVEL IN HAIR PREDICTS VIROLOGIC RESPONSE BETTER THAN LEVEL IN BLOOD

Laura Dickinson[1], Marco Siccardi[1], Kathryn Anastos[2], Mardge H. Cohen[3], Deborah Gustafson[4], Gerald Sharp[5], Stephen J. Gange[6], Seble Kassaye[7], Peter Bacchetti[8], **Ruth Greenblatt**[8]

[1]University of Liverpool, Liverpool, UK, [2]Montefiore Medical Center, Bronx, NY, USA, [3]Stroger Hospital of Cook County, Chicago, IL, USA, [4]SUNY Downstate Medical Center, Brooklyn, NY, USA, [5]NIAID, Bethesda, MD, USA, [6]Johns Hopkins University, Baltimore, MD, USA, [7]Georgetown University, Washington, DC, USA, [8]University of California San Francisco, San Francisco, CA, USA

Background: Levels of ARV in blood reflect recent exposure (hours to days), but the outcomes of cART are based on exposure over months. We hypothesized that levels of efavirenz (EFV) in hair, which reflects exposure occurring over several weeks would better predict virologic response than single blood levels.

Methods: Intensive PK (iPK), sparse blood and hair samples (1 cm of scalp) were collected from participants of the Women's Interagency HIV Study who reported current use of EFV. EFV levels were measured in blood and hair by validated liquid chromatography tandem mass spec method. Population PK models were developed including clinical covariates previously shown to influence exposure (area under the curve, AUC). AUC was estimated from sparse blood levels and time of last dose using NONMEM methods and compared directly to level in hair (also an indicator of exposure) using random effects multivariate logistic regression.

Results: AUC by iPK was typically about 50% greater than that estimated from sparse sample, though the values were correlated (median ratio of AUC by iPK to AUC by sparse = 1.47, correlation coef =0.83, p<.0001, n=92). When AUC estimated from sparse blood samples were compared to levels measured in hair as predictors of virologic suppression (in models of 1071 observations made of 315 individuals that adjusted for adherence, decade of age, ethnicity and individual) log level in hair was a statistically significant predictor of suppression, while AUC estimated from sparse samples was not (Table below).

Conclusion: Exposure to EFV estimated from hair samples better predicted virologic response than exposure estimated from single blood specimens and time since dose. These findings support the utility of measures of long term exposure in predicting treatment responses, which may be important for research and in the management of patients who are at high risk for treatment failure.

Predictors of virologic suppression in a random effects logistic regression model

315 women contributed 1071 hair and blood level measures

Predictor	Odds Ratio	Lower 95% CI	Upper 95% CI	p-value
Intercept	9.974	0.406	245	0.16
95-99% adherence	1.023	0.537	1.948	0.95
75-94% adherence	0.789	0.312	1.997	0.62
1-74% adherence	0.224	0.043	1.162	0.075
0 adherence	0.131	0.002	7.5	0.32
Decade of age	1.460	0.895	2.4	0.13
Ethnicity: BLACK	0.270	0.073	1.003	0.051
HISPANIC	0.744	0.171	3.2	0.69
OTHER	2.623	0.138	50	0.52
LOG2 EFV in HAIR	**1.557**	**1.199**	**2.0**	**0.0010**
LOG2AUC EFV in blood	**0.725**	**0.483**	**1.089**	**0.12**

463 PHARMACOLOGIC MEASURES OF PrEP ADHERENCE AMONG HIGH-RISK MSM IN HPTN 067

Jennifer Velloza[1], Monica Gandhi[2], Craig W. Hendrix[3], Peter Bacchetti[2], Pamela Murnane[2], James P. Hughes[1], Maoji Li[4], Marcel Curlin[5], Timothy H. Holtz[6], Sharon Mannheimer[7], Mark A. Marzinke[3], K. Rivet Amico[8], Estelle Piwowar-Manning[3], Susan H. Eshleman[3], Robert M. Grant[9]

[1]University of Washington, Seattle, WA, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]Johns Hopkins Hospital, Baltimore, MD, USA, [4]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [5]Oregon Health and Sciences University, Portland, OR, USA, [6]CDC, Atlanta, GA, USA, [7]Columbia University, New York, NY, USA, [8]University of Michigan, Ann Arbor, MI, USA, [9]Gladstone Institute of Virology and Immunology, San Francisco, CA, USA

Background: The effectiveness of oral emtricitabine (FTC)/tenofovir (TFV) disoproxil-fumarate pre-exposure prophylaxis (PrEP) is highly dependent on adherence. Given limitations of self-reported adherence, pharmacologic measures are useful for understanding patterns of adherence and identifying predictors of consistent PrEP use.

Methods: We analyzed data from HPTN 067, a trial of intermittent and daily PrEP completed in 2014. We included men who have sex with men (MSM) in Bangkok, Thailand, and Harlem, United States. Participants were randomly assigned to daily, time-driven (one dose twice/week plus one dose after sex), or event-driven (one dose before and after sex) oral PrEP regimens. Study visits occurred at weeks 0, 4, 12, and 24 post-randomization to assess FTC and TFV levels. Plasma and hair samples measured short and long-term drug exposure, respectively. Electronic pill bottle data (Wisepill™) were collected weekly. Potential predictors of adherence were measured at baseline (e.g., demographics, alcohol use) and longitudinally (e.g., sexual behavior). We estimated Pearson correlation coefficients among measures and assessed predictors of log-transformed plasma and hair drug levels using linear mixed models. Pharmacologic measures below the detection limit were set equal to that limit prior to log transformation.

Results: Among the 350 randomized MSM at the two sites, half had completed college (N=179; 51.1%) and the median age was 31 years (IQR: 25–38 years). At baseline, 20.6% reported heavy alcohol use (N=72) and the median number of sex partners in the prior three months was 4 (IQR: 2–8). Across all arms and follow-up periods, FTC and TFV hair concentrations were moderately correlated with plasma concentrations and Wisepill™ data (Pearson coefficients >0.28). In multivariate models, being enrolled at the Harlem site, being in the time- or event-driven arms, and having less than college education were associated with lower hair FTC/TFV levels, while heavy alcohol use was associated with higher hair levels (Table). In models evaluating plasma levels, similar results were seen for site and study arm, but older age and greater number of sex partners were significantly associated with higher plasma drug levels.

Conclusion: In HPTN 067, plasma and hair drug concentrations and Wisepill™ data correlated with one another and served as complementary measures of PrEP adherence. Site, study arm, education, age, alcohol use, and sexual behavior influenced patterns of short and long-term PrEP adherence.

Table 1. Estimated multivariate associations of covariates with hair and plasma drug concentrations[1]

	Hair Drug Levels				Plasma Drug Levels			
	TFV (n=381 visits)		FTC (n= 379 visits)		TFV (n= 946 visits)		FTC (n= 946 visits)	
Covariate	Adjusted effect (95% CI)	p-value	Adjusted effect (95% CI)	p-value	Adjusted effect (95% CI)	p-value	Adjusted effect (95% CI)	p-value
Daily dosing arm Time-driven Event-driven Daily	**-0.45 (-0.82, -0.09)** **-0.97 (-1.37, -0.57)** **Reference**	**<0.001**	**-0.69 (-1.13, -0.26)** **-1.57 (-2.03, -1.11)** **Reference**	**<0.001**	**-0.39 (-0.96, 0.18)** **-2.26 (-2.85, -1.68)** **Reference**	**<0.001**	**-0.50 (-1.20, 0.19)** **-2.71 (-3.40, -2.01)** **Reference**	**<0.001**
Site Harlem Bangkok	**-0.70 (-1.16, -0.23)** **Reference**	**0.01**	**-1.13 (-1.55, -0.71)** **Reference**	**<0.001**	**-0.65 (-1.22, -0.09)** **Reference**	**0.02**	-0.53 (-1.22, 0.16) Reference	0.13
Age, years	0.01 (-0.01, 0.02)	0.92	0.01 (-0.01, 0.02)	0.12	**0.03 (0.01, 0.06)**	**0.01**	**0.04 (0.01, 0.07)**	**0.01**
Education Primary or less Secondary school College	**-0.84 (-1.39, -0.28)** **-0.25 (-0.74, 0.23)** **Reference**	**0.01**	**-1.17 (-1.75, -0.60)** **-0.42 (-0.83, -0.01)** **Reference**	**0.01**	-0.83 (-1.65, -0.01) -0.48 (-1.04, 0.09) Reference	0.11	-0.98 (-2.01, 0.05) -0.57 (-1.26, 0.13) Reference	0.13
AUDIT ≥8[2]	**0.40 (0.03, 0.77)**	**0.04**	**0.50 (0.15, 0.86)**	**0.01**	0.20 (-0.24, 0.63)	0.38	0.33 (-0.22, 0.89)	0.24
Number of sex acts since the prior visit (/10 acts)	0.21 (-0.02, 0.45)	0.07	0.14 (-0.11, 0.39)	0.43	**0.28 (0.02, 0.54)**	**<0.001**	**0.38 (0.07, 0.69)**	**<0.001**

CI= Confidence Interval; AUDIT= Alcohol Use Disorders Identification Test
[1]Models included all covariates shown here as well as an interaction term for PrEP dosing arm and number of sex acts since the prior visit (per 10 sex acts) because event-driven adherence was related to sexual activity.
[2]AUDIT score ≥8 is indicative of heavy alcohol use.

464 HIGHER NRTI METABOLITE:ENDOGENOUS NUCLEOTIDE RATIOS IN OLDER HIV+ WOMEN ON TDF/FTC

Julie B. Dumond[1], Camden Bay[1], Julie A. Nelson[1], Craig Sykes[1], Kathryn Anastos[2], Roopali Sharma[3], Seble Kassaye[4], Maria Villacres[5], Ruth Greenblatt[6], Audrey French[7], Stephen J. Gange[8], Igho Ofotokun[9], Margaret Fischl[10], David Vance[11], Adaora Adimora[1]

[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]Albert Einstein College of Medicine, Bronx, NY, USA, [3]Touro College, New York, NY, USA, [4]Georgetown University, Washington, DC, USA, [5]University of Southern California, Los Angeles, CA, USA, [6]University of California San Francisco, San Francisco, CA, USA, [7]Cook County Health & Hospitals System, Chicago, IL, USA, [8]Johns Hopkins University, Baltimore, MD, USA, [9]Emory University, Atlanta, GA, USA, [10]University of Miami, Miami, FL, USA, [11]University of Alabama at Birmingham, Birmingham, AL, USA

Background: The Women's Interagency HIV Study (WIHS) began in 1993, and follow-up of HIV+ women continues as the cohort ages. The altered immune states of aging + HIV may affect intracellular metabolism of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC); increased cellular senescence, as measured by $p16^{INK4a}$ expression, decreases FTC-triphosphate (FTCtp) concentrations. The effect of age and inflammation on the ratio of intracellular metabolites (IM; tenofovir diphosphate [TFVdp], FTCtp) to their endogenous nucleotides (EN; dATP and dCTP), a potential efficacy and toxicity marker, was assessed in the WIHS.

Methods: Frozen paired PBMC and plasma samples from women receiving TDF/FTC 300/200mg with viral load <200 c/mL were obtained and dichotomized by participant age at collection into ≤45yrs and ≥60yrs. PBMC concentrations of TFVdp, FTCtp, dATP, and dCTP were measured by LC-MS/MS. Plasma IL-6 and sCD163 were measured by ELISA. A log-rank test compared ratios between age groups. Spearman's correlation analysis assessed relationships between IM and EN concentrations, cytokines, and clinical variables. Censored normal multiple linear regression, adjusted for race, smoking, EGFR, and background drugs, assessed relationships between IM, EN, and IM:EN ratios, and age.

Results: Demographics are presented in Table 1. Women ≥60yrs had significantly higher TFVdp:dATP (0.54 vs 0.31, p=0.009) and FTC:dCTP (18.9 vs 13.4, p=0.01) ratios compared to women ≤45yrs. In women ≥ 60yrs, TFVdp was correlated with EGFR (rho=-0.38, p=0.002). From the regression analyses, no evidence was found that dATP or dCTP were associated with race, smoking, or EGFR; nor IL-6 or sCD163 with age. In women ≤45yrs, sCD163 and TFVdp were correlated (rho=-0.28; p=0.01); in women ≥60yrs, FTCtp was correlated with sCD163 (rho=0.28, p=0.03) and IL-6 (rho=0.41, p=0.001). In the regression analysis, age influenced dATP and TFVdp, (p=0.02, 0.008, respectively).

Conclusion: In cross-sectional analysis, older women demonstrated higher TFVdp:dATP and FTCtp:dCTP ratios. Decreased renal function may contribute to this, though dATP and TFVdp concentrations remained influenced by age after adjusting for EGFR in a regression analysis. The differing associations between cytokines and IMs by age is interesting and warrants further investigation to determine causal factors. Inclusion of men and additional immune markers are needed to fully elucidate aging effects on TDF/FTC intracellular metabolism and potential clinical consequences.

Table 1. Demographics of participants by age group. Data are presented as median (min-max) or number/percent (n/%) of group total. EGFR: estimated glomerular filtration rate, as calculated by the CKD-EPI equation

	Women ≤45 years (n=84)	Women ≥60 years (n=60)
Age, years (median, min-max)	34.5 (27-41)	62 (60-75)
CD4+ T-cell count, mm³ (median, min-max)	686 (244-2332)	606 (194-1551)
EGFR, mL/min/1.73 m² (median, min-max)	109 (68.5-147)	72.6 (43-110)
Current Smoker, n (%)	59 (70%)	38 (63%)
Race and Ethnicity, n (%)		
African American, Non-Hispanic	70 (83%)	32 (63%)
White, Non-Hispanic	2 (2.5%)	6 (10%)
All Races, Hispanic	10 (12%)	18 (30%)
Other	2 (2.5%)	4 (7%)
Drug Class, 3rd Agent in Regimen		
Nonnucleoside Reverse Transcriptase Inhibitor	32 (38%)	29 (48%)
Protease Inhibitor	21 (25%)	13 (22%)
Integrase Inhibitor	27 (32)	11 (18%)
Other	2 (2.5%)	7 (12%)
Missing	2 (2.5%)	0 (0%)

465 ETRAVIRINE PHARMACOKINETICS IN TREATMENT-EXPERIENCED CHILDREN AGES 1- <6 YEARS

Christine E. MacBrayne[1], Richard Rutstein[2], Ram Yogev[3], Andrew Wiznia[4], Lee Fairlie[5], Bobbie Graham[6], Carmelita Alvero[7], Jack Moye[8], Ellen Townley[9], Herta Crauwels[10], Xavier Woot de Trixhe[10], Lotke Tambuyzer[10], Simon Vanveggel[10], Magda Opsomer[10], Jennifer J. Kiser[1]

[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [2]Children's Hospital of Philadelphia, Philadelphia, PA, USA, [3]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA, [4]Albert Einstein College of Medicine, Bronx, NY, USA, [5]University of the Witwatersrand, Acornhoek, South Africa, [6]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [7]Harvard University, Cambridge, MA, USA, [8]National Institute of Child Health and Human Development, Bethesda, MD, USA, [9]NIAID, Rockville, MD, USA, [10]Janssen, Beerse, Belgium

Background: IMPAACT P1090 is a Phase I/II study of etravirine (ETR) pharmacokinetics (PK), dose- finding, and safety in antiretroviral (ARV) treatment-experienced HIV-infected children 1 to <6 yrs from the U.S., South Africa (SA) and Brazil.

Methods: Treatment-experienced children on a failing ARV regimen for ≥8 wk or on a treatment interruption for ≥4 wk with a history of virologic failure (VF) were enrolled into one of two age cohorts (2-<6 yr; 1-<2 yr). ETR was combined with at least two active ARVs, one of which was a ritonavir-boosted protease inhibitor (PI/r). ETR was dosed by weight-band. Participants 8-<10 kg received 75mg twice daily [bid]; 10-<20 kg, 100mg bid; and 20-<25 kg, 125mg bid. Tablets were swallowed whole or dispersed in liquid. All participants underwent 12-hr PK sampling on day 14 (±4 days). Participants with ETR AUC12h <10th percentile of adults (<2350 ng*hr/mL) had an individual ETR dose increase and repeat PK. For each cohort, PK and safety were confirmed in the first six participants before further enrolling at the same dose. The target geometric mean ETR AUC12h was 2713 to 6783 ng*hr/mL (60-150% of adult AUC12h). Criteria for acceptable safety included no suspected adverse drug reaction resulting in death, life-threatening toxicity, any grade 4 event, or ≥3 participants discontinuing due to grade ≥3 toxicity.

Results: Twenty-one participants (nine each from SA and Brazil, three from U.S.) received ETR weight-band based doses. Demographics, ETR dosing and PK are shown for each cohort in the table. Both cohorts passed pre-determined PK and safety criteria, but seven (33%) children, all taking ETR dispersed, had an AUC12h of <2350 ng*hr/mL and underwent an ETR dose increase. Geometric mean ETR AUC12hr was significantly higher in participants that swallowed the tablet whole vs. dispersed, 7943 ng*hr/mL (n=6) vs. 2697 ng*hr/mL (n=15), respectively (p=0.0002). After a median (range) follow-up of 62 (9-234) weeks, three (14%) participants (2/3 with day 14 AUC12h <2350 ng*hr/mL) have discontinued due to VF. One participant discontinued due to a treatment-related toxicity (grade 4 lipase).

Conclusion: Weight-band based ETR dosing achieved predefined AUC12h targets in HIV-infected children receiving an ARV regimen including a PI/r, but 33%, all taking dispersed tablets, had AUC12h <10th percentile of the adult AUC12h. To date, ETR is well-tolerated and the rate of VF in these 21 treatment-experienced children is low.

	Cohort 1 (2-<6 yr), n=15	Cohort 2 (1-<2 yr), n=6
Demographics and ETR Dosing Parameters, median (range)		
Age at intensive PK, yr	4.8 (2.8, 5.9)	1.8 (1.5, 2.03)
Weight, kg	16.1 (12.5, 24.3)	10.4 (8.3, 13.3)
Body Surface Area (BSA), m^2	0.68 (0.55, 0.85)	0.48 (0.42, 0.55)
Dose, mg	100 (100, 125)	87.5 (75, 100)
PK Parameters, geometric means (%CV)		
AUC12h, ng*hr/mL	3823 (95%)	3328 (94%)
Cmax, ng/mL	466 (84%)	390 (89%)
Last measurable concentration (Clast), ng/mL	232 (124%)	225 (99%)
Individual ETR dose increase	5 (33%)	2 (33%)

466 CYP2B6 VARIANTS ALTER ETONOGESTREL PHARMACOKINETICS WHEN COMBINED WITH EFAVIRENZ

Megan Neary[1], Catherine Chappell[2], Kimberly K. Scarsi[3], Shadia Nakalema[4], Joshua Matovu[4], Sharon L. Achilles[2], Beatrice A. Chen[2], Marco Siccardi[1], Andrew Owen[1], Mohammed Lamorde[4]

[1]University of Liverpool, Liverpool, UK, [2]University of Pittsburgh, Pittsburgh, PA, USA, [3]University of Maryland, Baltimore County, Baltimore, MD, USA, [4]Infectious Disease Institute, Kampala, Uganda

Background: The etonogestrel (ENG) subdermal implant is an effective contraceptive method recommended by the WHO. Our group previously demonstrated ENG concentrations were 82% lower at week 24 in women receiving efavirenz (EFV) based antiretroviral therapy (ART) compared to women not receiving ART. We sought to investigate potential associations between single nucleotide polymorphisms (SNPs) involved in EFV and ENG metabolism with the observed alteration in ENG pharmacokinetics (PK) in the same group of women.

Methods: This study included 39 Ugandan women, 20 not yet receiving ART and 19 receiving EFV (600mg daily) based ART. ENG and mid-dose EFV plasma concentrations were quantified from plasma through week 24 post ENG implant placement, using HPLC/mass spectrometry for ENG and HPLC for EFV. Patient DNA was extracted from whole blood. Samples were genotyped for the following SNPs utilising TaqMan assays: CYP2B6 516G>T, 983T>C and 15582C>T, NR1I2 63396C>T, CYP3A4 293A>G, ABCB1 4036A>G and 3435C>T. Associations between patient genotype and ENG PK parameters were determined through univariate and multivariate linear regression.

Results: Within the EFV group CYP2B6 516G>T was associated with a lower log_{10} ENG Cmin (P=0.003, β=-0.102) and lower log_{10} ENG AUC0-24 weeks (P=0.008, β=-0.106), which equates to a 43% difference in ENG Cmin and a 34% difference in ENG AUC0-24 weeks between homozygous G and homozygous T patients for CYP2B6 516G>T (see table). CYP2B6 983T>C was associated with lower log_{10} ENG Cmax (P=0.003, β=-0.237) and lower log_{10} ENG AUC0-24 weeks (P=0.016, β=-0.158), which equates to a 37% difference in ENG Cmax and a 20% difference in ENG AUC0-24 weeks between homozygous T and heterozygous CT patients for CYP2B6 983T>C (see table). EFV plasma concentration (C12-14hrs) was 76% higher in patients homozygous T for CYP2B6 516G>T compared to patients homozygous G and 69% higher in patients heterozygous CT for CYP2B6 983T>C compared to those homozygous T (see table).

Conclusion: This group has previously described a genetic association between SNPs in CYP2B6 and a reduction in the PK of the levonorgestrel implant within patients receiving EFV. This study shows a similar relationship between CYP2B6 SNPs and ENG PK, which is likely mediated through an indirect effect on EFV. This further demonstrates the influence of patient genetics on the effectiveness of contraceptive implants when prescribed alongside efavirenz.

	CYP2B6 516G>T (rs3745274)			CYP2B6 983T>C (rs28399499)		
	GG (n=6)	GT (n=11)	TT (n=2)	TT (n=16)	CT (n=3)	CC (n=0)
ENG C_{max} (pg/mL)	160 (158-185)	133 (102-207)	97 (85-109)	148 (109-207)	93 (75-102)	-
ENG C_{min} (pg/mL)	81 (63-84)	65 (57-76)	46 (40-52)	67 (53-81)	60 (57-62)	-
ENG $AUC_{0-24weeks}$ (pg*wk/mL)	2052 (1679-2669)	1664 (1537-2146)	1364 (968-1760)	1760 (1587-2405)	1405 (1142-1597)	-
EFV C_{12-14h} (mg/L)	2.1 (2.0-2.7)	3.2 (2.9-6.6)	8.9 (8.1-9.7)	2.9 (2.5-4.3)	9.3 (7.05-11.4)	-

467 NR1I2 RS2472677 AND ABCG2 RS2231142 INFLUENCE DOLUTEGRAVIR CONCENTRATIONS IN PLASMA

Emilie R. Elliot[1], Megan Neary[2], Laura Else[2], Saye Khoo[2], Graeme Moyle[1], Daniel F. Carr[2], Xinzhu Wang[3], Myra McClure[3], Andrew Owen[2], Marta Boffito[1]

[1]Chelsea and Westminster Hospital, London, UK, [2]University of Liverpool, Liverpool, UK, [3]Imperial College London, London, UK

Background: Dolutegravir (DTG) is a preferred agent in most guidelines but real life data are emerging showing higher rates of neuropsychiatric toxicity than seen in licensing trials. Supra-therapeutic DTG concentrations may predispose to side effects in certain individuals, but this remains to be conclusively demonstrated. This study investigated the association between pharmacogenetic variants linked to DTG metabolism and plasma DTG concentrations.

Methods: Pooled data from six Phase I and III clinical studies were analysed in subjects receiving 50 mg DTG once daily alone or as part of combination therapy. Following consent at screening for a pharmacogenetics substudy, whole blood was collected on day 1 of each study. All subjects underwent intensive PK sampling. Steady-state DTG plasma concentrations were determined using validated LC-MS/MS or UPLC. CYP3A4*22 c522-191C>T (rs35599367), CYP3A5*3 6986A>G (rs776746), ABCG2 421C>A (rs2231142), NR1I2 63396C>T (rs2472677) and NR1I2 44477A>G (rs1523130) were genotyped using allelic discrimination assays. UGT1A1 (*1, *28, *36 & *37) were genotyped using an Agena MassArray iPLEX assay. All genotypes were checked for Hardy-Weinberg equilibrium. Variables were tested for normal distribution (Shapiro-Wilk test) and normality was improved using log_{10} transformation where indicated. Associations between subject genotype and DTG Cmax, logCmin and AUC0-24 were determined through univariate and multivariate linear regressions.

Results: 83 subjects were included (58 HIV-infected and 25 healthy adults; 62 men, 21 women). 64 participants were caucasian , 15 black, 2 asian and 2 mixed–race. ABCG2 421C>A (rs2231142) and NR1I2 63396C>T (rs2472677) were associated with higher DTG Cmax (P=0.002, β=1002 & P=0.039, β=318 respectively). There were no other significant genetic associations. Importantly, both genetic associations remained in an analysis restricted to caucasians. Body weight was associated with lower Cmax and AUC (P=0.007, β=-28 and P=0.012, β=-373 respectively) and DTG AUC was significantly higher in the black versus non-black subgroup (P=0.022, β=10204).

Conclusion: This is the first study to demonstrate that NR1I2 63396C>T influences DTG plasma Cmax. Our results also confirm the association between ABCG2 421C>A and Cmax. The association with Cmax but not AUC or Cmin may signal an impact upon DTG absorption but further research is warranted to confirm the associations and their mechanisms and to investigate the putative relationship with pharmacodynamics.

468 PHARMACOKINETICS OF DOLUTEGRAVIR WITH AND WITHOUT DARUNAVIR/COBICISTAT

Emilie R. Elliot[1], Maddalena Cerrone[1], Laura Else[2], Alieu Amara[2], Elisa Bisdomini[1], Saye Khoo[2], Marta Boffito[1]

[1]Chelsea and Westminster Hospital, London, UK, [2]University of Liverpool, Liverpool, UK

Background: Dolutegravir (DTG) combined with boosted darunavir may be a promising NRTI sparing and/or salvage strategy for the treatment of HIV-1 infection. In patients undergoing drug monitoring, DTG trough concentrations doubled when switching from darunavir/ritonavir (DRV/r) to DRV/cobicistat (c), in contrast to a 38% decrease with darunavir/ritonavir (DRV/r) twice daily. However, no formal interaction studies between DTG and DRV/c have been published.

Methods: This phase 1, open label, 57 day, cross over, pharmacokinetic (PK) study, enrolled healthy volunteers aged 18-65years, who were randomized to: i) group 1: DTG 50mg on days 1-14 followed by a 7 day wash out period, DTG+DRV/c 50mg+800/150mg on days 22-35 (co-administration period), which was followed by a 7 day wash out, and finally DRV/c 800/150mg on days 43-56 or ii) group 2: DRV/c 800/150mg on days 1-14 followed by a 7 day wash out period, DTG 50mg+DRV/c 800/150mg on days 22-35 (co-administration period), which was followed by a 7 day wash out and finally DTG 50mg on days 43-56. All doses were administered once daily. Each group underwent intensive PK sampling (0-24 hr post-dose) on days 14, 35 and 56 and DTG/DRV/c concentrations were measured by validated LC-MS methods.

Results: To date, 13 healthy volunteers have been screened, 12 baselined and 9 have completed all PK phases (1 subject withdrew for personal reasons and 2

are ongoing). Median age (range) was 31yrs (24-55), 1 was male, 4 self-reported as white and 5 as black African/Caribbean. DTG geometric mean ratios (GMR, DTG+DRV/c versus DTG alone) and 90% confidence intervals (CI) Cmax, AUC, C24h were 0.89 (0.79-1.02), 0.84 (0.73-0.96), 0.81 (0.66-0.98). DRV GMR (DRV/c+DTG versus DRV/c alone, 90%CI) of DRV Cmax, AUC, C24h were 0.79 (0.71-0.89), 0.87 (0.78-0.96), 0.82 (0.67-1.00), and of c Cmax, AUC, C24h were 0.86 (0.77-0.96), 0.88 (0.78-1.00) 0.98 (0.74-1.28), No grade 3 or 4 adverse events or laboratory abnormalities were observed.

Conclusion: Concentrations of DTG during co-administration with DRV/c decreased by <20% and those of DRV with DTG by <21%, suggesting this combination can be prescribed safely in the treatment of HIV-1, including in patients harbouring resistance that benefit from optimal antiretroviral exposures.

469 PHARMACOKINETICS (PK) OF ETHINYLESTRADIOL/LEVONORGESTREL WITH ATAZANAVIR/COBICISTAT

Emilie R. Elliot[1], Elisa Bisdomini[1], Laura Else[2], Sujan Dilly Penchala[2], Saye Khoo[2], Graeme Moyle[1], Nneka Nwokolo[1], Marta Boffito[1]
[1]Chelsea and Westminster Hospital, London, UK, [2]University of Liverpool, Liverpool, UK

Background: The combined oral contraceptive pill is the preferred method of contraception for many women. However, women living with HIV often need to dose adjust their contraception due to drug drug interactions with antiretrovirals. The concentration of ethinyloestradiol (EE) is increased by unboosted atazanavir (ATV), and decreased by ATV/ritonavir (r) (while progestin exposure is increased and may lead to side effects). Therefore, if an oral contraceptive is administered with ATV/r, it must contain at least 30µg of EE and strict compliance is necessary. However, data on ATV boosted by cobicistat (c) are not yet available.

Methods: This phase 1, open label, 57 day, cross over, PK study, enrolled healthy female volunteers aged 18-35years, who were randomized to: i) group 1 received EE/levonogestrel (LNG, Microgynon) alone on days 1-21, EE/LNG (21 days) + ATV/c (14 days) in the co-administration phase (days 22-43) and ATV/c alone on days 43-56; ii) group 2 received ATV/c alone on days 1-21, EE/LNG (21 days) + ATV/c (14 days) in the co-administration phase (days 22-43) and EE/LNG alone on days 43-56. Each group underwent intensive PK sampling on days 14, 35 and 56, and EE/LNG concentrations were measured by LC/MS.

Results: Of 14 healthy female volunteers screened, 11 were enrolled (1 was not eligible and 2 withdrew consent for personal reasons) and 6 completed all PK phases (5 withdrew consent because of gastrointestinal adverse events, fatigue or rash). Geometric mean ratios (GMR, with vs without ATV/c) and 90% confidence intervals (CI) of EE Cmax, AUC, C24h were 1.05 (0.92-1.19), 1.01 (0.83-1.22), 0.75 (0.60-0.93). GMR and CI (90%) of LNG Cmax, AUC, C24h were 0.83 (0.68-1.02), 0.92 (0.71-1.18), 1.01 (0.73-1.38). No grade 3 or 4 adverse events or laboratory abnormalities were observed in the women who completed the study.

Conclusion: Our findings show that EE C24h decreased by only 25% with ATV/c (versus 37% with ATV/r in previous studies). For the first time LNG PK was investigated during co-administration with cobicistat and no significant changes in its concentrations were measured.

470 THE EFFECT OF ANTACIDS AND MULTIVITAMINS ON RALTEGRAVIR

Helen Reynolds[1], Joseph Lewis[1], Deidre Egan[2], Mas Chaponda[1], Laura Else[2], Justin Chiong[2], Darren M. Moss[2], David Back[2], Andrew Owen[2], Saye Khoo[2]
[1]Royal Liverpool University Hospital, Liverpool, UK, [2]University of Liverpool, Liverpool, UK

Background: Raltegravir (RAL) absorption is influenced by antacids and gastrointestinal pH but it is unclear which of these mechanisms has the predominant effect on pharmacokinetic (PK) variability. We sought to characterise the effect of separate metals on the PK of RAL in healthy volunteers, and to determine the role of intestinal pH in this interaction.

Methods: Open label, randomised, 3 arm, 5 phased controlled healthy volunteer study. Participants received a single dose (sd) of RAL (400 mg tablet), followed by RAL plus Maalox Plus (30 ml), sodium bicarbonate (1 g), Forceval (1tablet) or Maalox Plus (30 ml) 2 h prior to dosing without food, for 4 study days. The Heidelberg pH diagnostic system was used to collect gastrointestinal pH data. Blood samples and pH measurements were collected at 0, 1, 2, 3, 4, 6, 8, 10 and 12 h post dose. Plasma RAL concentrations were determined by validated LC-MS/MS, and PK parameters were estimated (WinNonLin). The primary endpoint was a change in AUC, C12h, CMAX, or TMAX. Secondary endpoints were safety and tolerability of combinations, and correlation of pH with RAL PK.

Results: Of fifteen participants randomised, three withdrew due to adverse events and two withdrew consent. All combinations were well-tolerated with one serious clinical event reported. A significant increase in RAL GMR (90 % CI) AUC0-12 (1.96; 1.04 – 3.72) and CMAX (2.07; 1.00 – 4.30) when RAL was administered with sodium bicarbonate was observed. A significant decrease in TMAX (GMR 0.58; 90 % CI 0.43 – 0.78) was seen when Maalox Plus was administered at the same time as RAL which was not observed when the antacid was taken 2 h prior to RAL. The multivitamin, Forceval, did not significantly affect the PK of RAL. PK data shown below are in keeping with previous studies. Optimal pH (6 to 8) for RAL solubility was achieved on administration of sodium bicarbonate or Maalox Plus (+/- 2 h).

Conclusion: A significant increase in absorption of RAL in the presence of antacid lacking divalent cations (sodium bicarbonate) was observed which is likely to relate to the unopposed 'boosting' effect of a raised pH upon absorption and the known pH-dependent solubility of RAL. In conclusion, not all antacids influence the PK of RAL in the same way. RAL exposure was approximately doubled by sodium bicarbonate, whereas aluminium/magnesium hydroxide did not exhibit this effect.

PK parameter	RAL sd	RAL sd + MP		RAL sd + ViR		RAL sd + SB		RAL sd + MP2	
	GM (% CV)	GM (% CV)	GMR * (90 % CI)	GM (% CV)	GMR * (90 % CI)	GM (% CV)	GMR * (90 % CI)	GM (% CV)	GMR * (90 % CI)
C_{max}	1586 (96)	1628 (91)	0.95 (0.53 – 1.69)	1312 (109)	0.88 (0.32 – 2.38)	3255 (66)	2.07 (1.00 – 4.30)	1276 (105)	0.85 (0.45 – 1.63)
C_{12}	27.92 (71)	19.55 (67)	0.73 (0.52 – 1.03)	23.93 (68)	0.9 (0.60 – 1.35)	39.82 (90)	1.35 (0.95 – 1.91)	16.78 (82)	0.63 (0.49 – 0.81)
AUC_{0-12}	5150 (85)	4518 (83)	0.83 (0.48 – 1.43)	4037 (94)	0.83 (0.33 – 2.08)	9964 (61)	1.96 (1.04 – 3.72)	3768 (101)	0.78 (0.45 -1.35)
T1/2	2.17 (47)	2.32 (53)	1.07 (0.85 – 1.35)	2.55 (103)	1.18 (0.81 – 1.71)	2.20 (131)	1.01 (0.82 – 1.23)	2.09 (27)	0.97 (0.78 – 1.20)
T_{max}	2.46 (33)	1.42 (44)	0.58 (0.43 – 0.78)	2.11 (49)	0.85 (0.68 – 1.05)	2.15 (35)	0.83 (0.66 – 1.04)	2.32 (45)	0.93 (0.68 – 1.28)

* against RAL sd

471 RAVIDASVIR PHARMACOKINETICS AND ARV DRUGS INTERACTIONS IN HCV+/-HIV INFECTED ADULTS

Tim R. Cressey[1], Soek-Siam Tan[2], Hajjah Rosaida Hj Mohd Said[3], Muhammad Radzi Abu Hassan[4], Haniza Omar[2], Tee Hoi Poh[5], Chan Wah Kheong[6], Suresh Kumar[7], Satawat Thongsawat[8], Kanawee Thetket[9], Suparat Khemnark[10], Anchalee Avihingsanon[11], François Simon[12], Isabelle Andrieux-Meyer[12], Marc Lallemant[12]
[1]Program for HIV Prevention and Treatment, Chiang Mai, Thailand, [2]Selayang Hospital, Selayang, Malaysia, [3]Hospital Ampang, Ampang, Malaysia, [4]Hospital Sultanah Bahiyah, Alor Setar, Malaysia, [5]Hospital Tengku Ampuan Afzan, Kuantan, Malaysia, [6]University of Malaya Medical Centre, Kuala Lumpur, Malaysia, [7]Sungai Buloh Hospital, Sungai Buloh, Malaysia, [8]Chiang Mai University, Chiang Mai, Thailand, [9]Nakornping Hosp, Chiang Mai, Thailand, [10]Bamrasnaradura Infectious Diseases Institute, Bangkok, Thailand, [11]HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [12]Drug for Neglected Diseases Initiative, Geneva, Switzerland

Background: Ravidasvir is a NS5A inhibitor that exhibits potent pan-genotypic inhibition of Hepatitis C virus (HCV) replication in vitro. Sofosbuvir plus ravidasvir (SOF/RDV) has shown excellent efficacy and safety in genotype 4 HCV-infected adults in Egypt. SOF/RDV is currently under study in HCV patients (+/- HIV) from South East Asia, where prevalent genotypes are 3, 1 and 6. We assessed the pharmacokinetics (PK) of RDV in this population and the impact of SOF/RDV treatment on the concentrations of commonly prescribed antiretrovirals (ARV) in HIV/HCV co-infected adults.

Methods: Data were analyzed within the ongoing phase II/III trial assessing the efficacy, safety, tolerance, and PK of SOF/RDV in HCV (+/- HIV)-infected adults in Thailand and Malaysia (NCT01671982). To determine the PK of RDV in Asian adults, 25 HCV mono-infected patients had intensive steady-state 24-hour blood sampling. RDV PK parameters were calculated using non-compartmental analysis. To assess possible drug-drug interactions in HIV/HCV co-infected patients, mid-dose or trough ARV drug concentrations were measured before (week 0) and after SOF/RDV treatment initiation (Week 4), and compared with Wilcoxon signed-rank tests.

Results: Of the 25 subjects with intensive PK data: 21 were male (84%) and 21 non-cirrhotic (4 cirrhotic). Median age (range) was 49.2 (21.2-64.0) years, weight was 65.5 (46.2-88.3) kg and body mass index 23.3 (18.3-30.9) kg/m2. Median RDV AUC0-24h, Cmax and C24 were 17.3 (3.2-69.9) µg.hr/mL, 2.3 (0.4-6.4) µg/mL and 0.11 (0.03-1.63) µg/mL, respectively. Sixty-five HIV/HCV co-infected subjects were included: median age (range) was 42.9 (23.4-61.5) years and weight 62.0 (45.0-100) kg. Tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), efavirenz (EFV) and nevirapine (NVP) were the most commonly prescribed ARVs in HIV/HCV co-infected patients. A total of 47 subjects had tenofovir (TFV) ARVs concentrations before and after SOF/RDV treatment, 34 had FTC, 51 had EFV and 7 had NVP. Mid-dose tenofovir (TFV) concentrations were significantly higher with concomitant SOF/RDV treatment, while mid-dose FTC, EFV and trough NVP concentrations were not significantly different (Table).

Conclusion: SOF/RDV had no significant impact on FTC, EFV and NVP concentrations. TFV concentrations were slightly higher with SOF/RDV use but the magnitude is likely not clinically significant. The intensive PK data will aid the development of a population PK model to evaluate the impact of ARVs on RDV exposure.

	Time Post-dose (hours)		ARV Concentration (ng/mL)			
	Without SOF/RDV (Week 0)	With SOF/RDV (Week 4)	Without SOF/RDV (Week 0)	With SOF/RDV (Week 4)	Ratio Conc. Week 4/Week 0	p-value
Tenofovir (n=47)	12.2 (8.5-15.6)	11.5 (8.0-15.3)	94 (22-253)	103 (50-227)	1.08 (0.54-3.7)	0.0003
Emtricitabine (n=34)	12.0 (8.5-13.8)	11.5 (9.5-15.3)	381 (38-963)	390 (75-885)	1.00 (0.35-5.81)	0.98
Efavirenz (n=51)	12.3 (8.5-15.8)	11.6 (9.4-15.2)	2,580 (1,173-22,538)	2,542 (1,266-15,781)	0.96 (0.51-2.1)	0.18
Nevirapine (n=7)	12.5 (11.6-13.3)	11.9 (11.0-12.9)	9,517 (3,535-18,311)	7,678 (2,915-16,280)	0.91 (0.65-1.1)	0.31

Values: Median (range)

472 MAPPING THE DISTRIBUTION OF EFAVIRENZ WITH BRAIN TISSUE CELLS

Nithya Srinivas[1], Elias Rosen[1], Gabriela D. Cruz[1], Craig Sykes[1], Amanda Schauer[1], Lourdes Adamson[2], Paul Luciw[2], Angela Kashuba[1]

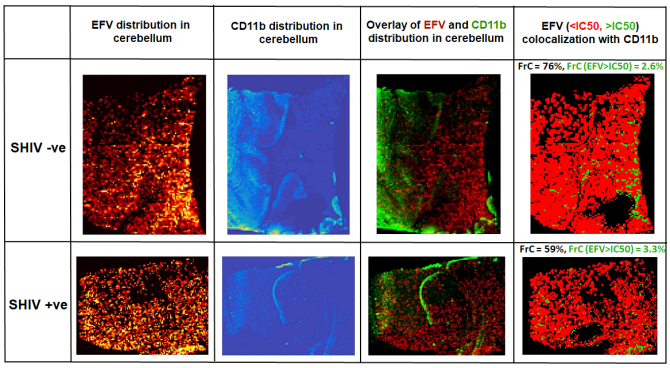
[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]University of California Davis, Davis, CA, USA

Background: Despite ongoing antiretroviral (ARV) therapy, HIV continues to persist in the central nervous system (CNS), as demonstrated by the establishment of latent microglia reservoirs and HIV-associated neurocognitive disorder. HIV persistence in the brain may be due to inadequate drug exposure in HIV-target cells; however, there is little information on brain distribution of ARVs. In this study, we have quantified the concentration of 4 ARVs in brain tissue by LC-MS/MS and infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) while mapping their distribution relative to expression of CD4+ T-cells and CD11b+ microglia.

Methods: In 4 male macaques (2 uninfected; 2 SHIV-infected) dosed to steady-state, concentrations of 4 ARVs – tenofovir (TFV), emtricitabine (FTC), efavirenz (EFV), and raltegravir (RAL) were measured in 10-micron cerebellum tissue slices by LC-MS/MS (LLOQ of homogenate ranged from 0.002-0.01 ng/mL). IR-MALDESI mass spectrometry imaging (MSI) was used to characterize drug distribution. Density of 1.06g/cm^3 was used to convert tissue concentrations to ng/g. Immunohistochemistry (IHC) staining of CD11b+ microglia and CD4+ T-cells was performed on contiguous slices. Image analysis of co-registered MSI and down-sampled IHC images was performed in MATLAB.

Results: TFV, FTC, and RAL were not detected by MALDESI and were <100 ng/g by LC-MS/MS (range of concentration was 9.4-61.2 ng/g). EFV concentrations by IR-MALDESI had a standard deviation of 663 ng/g for all samples and was 2.2-fold greater in SHIV- than SHIV+ brain (median = 1596 and 723 ng/g, respectively). The fractional coverage of target cells co-localized with EFV (FrC) differed based on infection status: for CD11b FrC = 22-59% (SHIV+) and 76-81% (SHIV-) and for CD4 FrC = 14-59% (SHIV+) and 73-77% (SHIV-). However, the FrC of total CD11b and CD4 cells exposed to EFV concentrations above IC50 (0.5 ng/g) was considerably smaller: 0-3.3%, regardless of infection status (Figure 1, panel IV).

Conclusion: EFV accumulation was 12 to 60-fold greater in brain tissue compared to other ARVs in SHIV+ animals but only 14% to 59% of CD11b and CD4 brain cells in these animals were colocalized with detectable EFV. This suggests that ARV coverage may be incomplete for cell populations that harbor, or can become infected, with HIV. We have shown in this preliminary analysis that this approach has the potential to provide ARV concentration-effect relationships in the brain at the cellular level.



473 SWITCHING TO TAF IN EVG-BASED REGIMENS: CSF PHARMACOKINETICS AND ANTIVIRAL ACTIVITY

Qing Ma[1], Andrew Ocque[1], Gene D. Morse[1], Chelsea Sanders[2], Alina Burgi[2], Susan J. Little[3], Scott L. Letendre[3]

[1]University at Buffalo, Buffalo, NY, USA, [2]University of California San Diego, San Diego, CA, USA, [3]University of California San Diego, La Jolla, CA, USA

Background: Tenofovir alafenamide (TAF) co-formulated with elvitegravir (E), cobicistat (C) and emtricitabine (F) has become a recommended regimen, replacing E/C/F/TDF due to improved renal and bone safety. Limited data are available on TAF and EVG pharmacokinetics (PK) in CSF, particularly after switching from TDF. This study aims to measure TAF, EVG, and tenofovir (TFV) concentrations in CSF and compare them to HIV RNA in CSF and neurocognitive (NC) performance.

Methods: This was a single-arm, open-label, single-center study. After an initial assessment, 9 participants switched from E/C/F/TDF to E/C/F/TAF and were followed for 24 weeks. At week 0 and week 24, blood was collected at 2, 4, and 6 hours after an observed dose and CSF was then collected within 1 hour of the 6-hour blood collection. Total plasma and CSF concentrations were determined by LC/MS-MS. The wild-type HIV-1 IC50 for EVG was 3.9 ng/ml. HIV RNA was measured in plasma and CSF by RT-PCR (lower limit of quantitation, LLQ, 20 copies/mL). NC performance was estimated by the Montreal Cognitive Assessment (MoCA) with a score <26 indicating impairment. Adherence was determined by pill count. Changes in drug concentrations between visits were analyzed using paired, two-sided signed rank tests. All concentrations are expressed in ng/ml.

Results: EVG concentrations in CSF remained stable (p=0.203) while EVG concentrations in plasma increased over time (p=0.004, see table). TFV concentrations in both CSF (p=0.004) and plasma (p=0.004) declined over time. The CSF:plasma ratio (CPR) for EVG remained stable over time (p=0.359) while the TFV CPR increased (p=0.004). At 24 weeks, TAF concentrations in plasma peaked 2 hours after the dose [11.05 (2.84-147.11)] but below LLQ at 6 h. TAF was not detected in CSF at 6 h. All HIV RNA levels remained ≤ 40 copies/mL in CSF and plasma. The proportion of EVG concentrations in CSF exceeding the IC50 rose from 56% at week 0 to 88% at week 24, although this difference was not statistically significant (p=0.375). Four participants (29%) had NC impairment at week 0 and 2 (14%) remained impaired at week 24. Across both assessments, higher EVG CPR values (but not TFV CPR) correlated with better NC performance (r=0.426, p=0.078).

Conclusion: Switch to E/C/F/TAF was associated with reductions in TFV concentrations in CSF, and substantially lower TFV concentrations in plasma, but stable EVG concentrations in CSF and plasma. No virological failure or significant NC changes were detected at 24 weeks following switch.

	Concentration [median (range)]		P
	Week 0 (TDF)	Week 24 (TAF)	
EVG-CSF	4.30 (1.65-7.85)	5.58 (3.15-6.76)	0.203
EVG-plasma	1080 (534-2123)	1608 (897-2352)	0.004
EVG CPR	0.380%	0.278%	0.359
TFV-CSF	3.00 (0.528-5.48)	0.481 (0.10-1.80)	0.004
TFV-Plasma	174 (13.8-191)	14.1 (9.67-15.1)	0.004
TFV CPR	1.76%	3.38%	0.004
TAF-CSF 6h	Not taking	≤ 0.1	-
TAF-plasma 2h	Not taking	11.05 (2.84-147.11)	
TAF-plasma 6h	Not taking	≤ 0.5	-

474 DIFFERENTIAL BRAIN TISSUE PENETRATION OF ANTIRETROVIRALS AND FLUCONAZOLE

Melanie Nicol[1], Jonee Taylor[1], Katelyn Pastick[1], James Fisher[1], Carol Karuganda[2], Joshua Rhein[1], Darlisha A. Williams[1], David Meya[2], David R. Boulware[1], Robert Lukande[3]
[1]University of Minnesota, Minneapolis, MN, USA, [2]Infectious Disease Institute, Kampala, Uganda, [3]Makerere University, Kampala, Uganda

Background: The central nervous system (CNS) is believed to be a significant reservoir for pathogens such as HIV and Cryptococcus; however, current understanding of drug penetration into the CNS is limited and largely based on cerebrospinal fluid (CSF) concentrations. However, CSF is not brain tissue. Herein we used tissues collected post-mortem from HIV-infected Ugandan subjects co-infected with Cryptococcus to characterize the relative distribution of antiretrovirals and antifungal agents across plasma and CNS compartments.

Methods: Following obtainment of written, informed consent from next of kin, post-mortems were performed on five subjects co-infected with HIV and cryptococcal meningitis. Tissues from cerebellum, pons, and CSF were snap frozen in liquid nitrogen. Whole blood was collected from femoral vein into EDTA tubes and stored on ice for 1 hour before separating plasma from cell pellets. All samples were transferred to -80 ºC for storage. Following tissue homogenization, drug quantification was performed using high performance (efavirenz) or ultrahigh performance (tenofovir, lamivudine, fluconazole) liquid chromatography coupled with triple quadrupole mass spectrometer. Calibrator standards and quality control (QC) samples were prepared in the matrix to match the sample tested; bovine brain homogenate was used for brain tissue, a solution of salt and proteins for CSF, and lithium heparin for plasma. Data are reported as median (range).

Results: Post-mortems were performed 5.2 (2.2-13.7) hours following death. Three individuals receiving daily tenofovir/lamivudine/efavirenz (300/300/600 mg) had detectable drug in all tissue compartments. Likewise, four individuals receiving fluconazole (400-1200 mg daily) had detectable drug in all compartments. CSF: plasma ratios were similar to values reported in the literature. Drug exposure in brain tissues was consistently lower than CSF for tenofovir, lamivudine, and fluconazole and higher than CSF for efavirenz (see Table).

Conclusion: Tenofovir, lamivudine, and fluconazole exposure in CSF over-predicted brain tissue penetration. In contrast, CSF exposure of efavirenz under-predicted brain exposure. These findings highlight the limitations of CSF as a surrogate for overall CNS drug exposure. Validation in larger cohorts and in additional CNS tissue compartments is warranted. These data support the use of post-mortem tissues to assess drug distribution to and within the CNS, relevant for HIV reservoir eradication.

Table: Relative tissue distribution of antiretrovirals and fluconazole

	N	CSF: Plasma Ratio	Cerebellum: Plasma Ratio	Pons[a]: Plasma Ratio	Cerebellum: CSF Ratio	Pons[a]: CSF Ratio
Tenofovir[b]	3	0.30 (0.29-0.32)	0.05 (0.02-0.42)	0.20 (0.03-0.37)	0.77 (0.7-1.48)	0.69 (0.09-1.30)
Lamivudine[b]	3	0.62 (0.51-0.74)	0.06 (0.05-0.15)	0.15 (0.06-0.25)	0.14 (0.09-0.20)	0.23 (0.12-0.34)
Efavirenz	3	0.03 (0.02-0.03)	0.26 (0.19-0.29)	0.40 (0.32-0.48)	9.20 (8.25-10.16)	14.13 (11.50-16.77)
Fluconazole	4	1.14 (1.08-1.21)	0.16 (0.12-0.17)	0.18 (0.11-0.26)	0.14 (0.11-0.14)	0.15 (0.10-0.23)

[a]Pons tissue was only available from 2 subjects on tenofovir, lamivudine, and efavirenz
[b]One CSF value was removed from analysis due to abnormal internal standard

475 MASS SPEC IMAGING REVEALS ASSOCIATIONS BETWEEN ARVS, VIRUS, AND CELLS IN LYMPH NODES

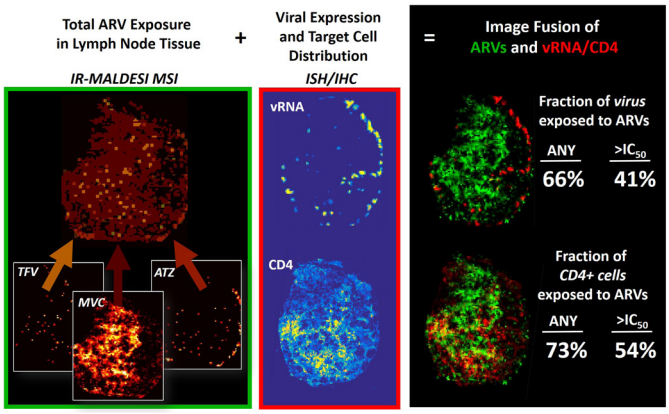
Elias Rosen[1], Claire Deleage[2], Nicole White[1], Craig Sykes[1], Lourdes Adamson[3], Yuri Fedoriw[1], Jacob D. Estes[2], Paul Luciw[3], Angela Kashuba[1]
[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]Frederick National Laboratory for Cancer Research, Frederick, MD, USA, [3]University of California Davis, Davis, CA, USA

Background: Recent data suggest that lymph nodes (LN) may harbor HIV infection despite HAART, possibly due to reduced ARV penetration. Here, we combine mass spectrometry imaging (MSI) and in situ hybridization (ISH) and immunohistochemistry (IHC) to evaluate the biodistribution of ARVs relative to viral and target cell expression in LN of rhesus macaques (RM).

Methods: Axillary LN were collected and snap frozen at necropsy from RT-SHIV infected RM after 10 days of dosing with emtricitabine (FTC) + tenofovir (TFV) (N=6) in combination with either efavirenz (EFV) + raltegravir (RAL) (N=3), cohort 1, or maraviroc (MVC) + atazanavir (ATZ) (N=3), cohort 2. Tissue accumulation of ARVs and metabolites was measured by LC-MS/MS (analyte-specific limits of detection [LOD]: 1-8 ng/ml homogenate) and infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) MSI (LOD: 0.05-0.37 ng/mg tissue) from 10 µm thick cryosections. Tissue and plasma measurements were compared based on an assumed tissue density of 1.06 g/ml. Serial sections of tissue were analyzed for viral RNA (vRNA) by RNAscope ISH and for CD4+ cells by IHC.

Results: Concentrations of ARVs in LN [LC-MS/MS (µg/g): 0.35-2 TFV, EFV, MVC; 0.05 – 0.2 FTC, ATZ; 0.02-0.03 RAL] exceeded concentrations in plasma (6 to 10-fold increase) for all ARVs except RAL (8-fold decrease). MSI revealed that ARVs accumulated in LN heterogeneously, with total ARV LN exposure (total coverage: cohort 1= 33-75%; 2 = 67-100%) and co-localization with target CD4+ cells (CD4+ coverage: cohort 1 = 65-75%; 2 > 90%) varying between dosing regimens. Combination of MSI and ISH showed localization of vRNA in secondary LN follicles where ARV concentration was poor or undetectable. Up to 50% of vRNA was not co-localized with any ARV. Concentrations of ARVs exceeding in vitro IC_{50} values were limited where co-localization was determined, with EFV and MVC providing the greatest exposure ([ARV] > IC_{50}: 3-16% and 41-47%, respectively).

Conclusion: The spatial distributions of drug and viral RNA expression observed provide contextual information underscoring the influence of location and microenvironment within a tissue compartment, otherwise lost by tissue homogenization with LC-MS/MS analysis and single cell analytical methods. Fusing MSI and ISH images can inform drug distribution in the context of viral replication, and provides a unique means of spatially resolving pharmacokinetic-pharmacodynamic relationships.



476 EFFECT OF SEX, SHIV, AND DRUG TRANSPORTERS ON LYMPH NODE ANTIRETROVIRAL PENETRATION

Erin M. Burgunder[1], John K. Fallon[1], Nicole White[1], Amanda Schauer[1], Craig Sykes[1], Lourdes Adamson[2], Jason R. Pirone[1], Paul Luciw[2], Philip C. Smith[1], Angela Kashuba[1]
[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]University of California Davis, Davis, CA, USA

Background: Despite antiretroviral (ARV) therapy, HIV persists in tissue reservoirs throughout the body. Lymph node ARV penetration is crucial for HIV

eradication, and the factors responsible for distribution are largely unknown. This study investigated the influence of drug transporters, sex, and SHIV infection on ARV and active metabolite concentrations within lymph nodes of rhesus macaques.

Methods: Twelve male (6 SHIV-, 6 SHIV+) and three female (2 SHIV-, 1 SHIV+) macaques were dosed to steady-state with six ARVs: emtricitabine (FTC, 16 mg/kg), tenofovir (TFV, 30 mg/kg), efavirenz (EFV, 200 mg/day), raltegravir (RAL, 200 mg/day), maraviroc (MVC, 150 mg/day), and atazanavir (ATZ, 270 mg/kg). At necropsy, 24h post-dose, three lymph nodes per animal were snap frozen and stored at -80°C. ARV and active metabolite (emtricitabine triphosphate, FTCtp; tenofovir diphosphate, TFVdp) concentrations were measured by LC-MS/MS (LLOQ: 0.002-0.01 ng/mL) and converted to ng/g of tissue using a density of 1.06 g/mL. Concentrations of eight (5 efflux, 3 uptake) drug transporters were measured using Quantitative Targeted Absolute Proteomics (QTAP, LLOQ: 0.1 pMol/mg protein). Median lymph node data for each animal was used for analyses. Data are presented as geometric mean (median range) and geometric mean ratio (GMR). Analyses were performed using Pearson Correlation, Kruskall-Wallis, and Mann-Whitney Rank Sum tests ($p<0.05$).

Results: ARV concentrations are summarized in the table, and trended higher for 4/8 ARVs in SHIV- macaques (uninfected vs infected GMRs: 1.7-2.2), and 4/8 ARVs in females (female vs male GMR: 2.0--2.7). 5/8 transporters had low to no expression (>50% values below LLOQ). Concentrations of one efflux (BCRP) and two uptake (ENT1, OCT3) transporters were significantly greater than all others ($p<0.001$). ENT1 concentration was 8-fold higher than both BCRP and OCT3 ($p<0.001$). None of these three differed significantly by infection status ($p=0.05$) or sex ($p>0.06$). Transporter expression was not correlated with ARV or metabolite concentrations across sex or infection status.

Conclusion: Modest differences in lymph node drug concentrations due to sex and infection status were noted. Low drug transporter levels, and lack of correlation between protein and drug concentrations, may indicate that lymph node ARV penetration occurs primarily by passive mechanisms. Future studies are warranted to further investigate sex differences in lymph nodes.

	ARV Concentrations (ng/g)					
	SHIV-	SHIV+	GMR (-/+)	Female	Male	GMR (F/M)
FTC	81 (24, 243) N=8	78 (41, 205) N=7	1.0	52 (24, 93) N=3	88 (41, 243) N=12	0.6
FTCtp	0.5 (0.2, 1.1) N=8	0.5 (0.2, 1.0) N=7	1.1	0.8 (0.6, 1.1) N=3	0.4 (0.2, 1.0) N=12	2.0 (p=0.04)
TFV	1993 (616, 7188) N=8	1146 (360, 2812) N=7	1.7	1587 (616, 2812) N=3	1528 (360, 7188) N=12	1.0
TFVdp	8.3 (0.7, 24) N=8	8.3 (2.5, 20) N=7	1.0	14 (12, 19) N=3	7.2 (0.7, 24) N=12	2.0
EFV	717 (148, 1688) N=4	389 (121, 745) N=3	1.8	148 (148, 148) N=1	687 (121, 1688) N=6	0.2
RAL	107 (56, 181) N=4	49 (28, 67) N=3	2.2	56 (56, 56) N=1	81 (28, 181) N=6	0.7
MVC	2019 (527, 5504) N=4	1036 (599, 1937) N=4	1.9	2439 (1081, 5504) N=2	1215 (527, 4962) N=6	2.0
ATZ	148 (22, 2208) N=4	124 (39, 469) N=4	1.2	282 (170, 469) N=2	106 (22, 2208) N=6	2.7

477 HIV TARGET CELL DISTRIBUTION AND TFV PENETRATION IN FORESKIN AND URETHRA

Alison S. Kohlmeier, Kenji Nishiura, Natalia Makarova, Jessica Radzio-Basu, Gerardo Garcia-Lerma, Charles Dobard
CDC, Atlanta, GA, USA

Background: Female to male HIV transmission represents an important route of HIV infection and yet the immune cell composition of foreskin and urethral tissues and how antiretroviral drugs penetrate into these two anatomical compartments has been largely understudied. We performed a comprehensive immune characterization of HIV target cells in foreskin and urethral tissues from macaques, and investigated the relative penetration of tenofovir following a single oral dose of tenofovir disoproxil fumarate (TDF).

Methods: Foreskin and urethral tissue were harvested from 7 rhesus macaques at necropsy and processed into cell suspensions using enzymatic digestion. CD4 and CD8 T cells, B cells, NK cells, monocytes, conventional dendritic cells (CDC), plasmacytoid dendritic cells (PDC), and HIV susceptibility markers CCR5, α4β7, HLA-DR, and CX3CR1 were measured by flow cytometry. TFV diphosphate (TFV-DP) in foreskin and urethra lymphocytes were measured in 5 macaques 24h after a single oral dose of TDF (22mg/kg).

Results: Both urethral and foreskin had an increased frequency of CD4 T cell populations expressing CCR5 ($p=0.01$ and $p=0.009$) and HLA-DR ($p=0.0005$ and $p=0.001$) compared to PBMC. Consistent with typical immune restricted tissue sites, effector memory T cells were the main CD4 T cell subtype in both urethral and foreskin tissues ($p=0.01$ and $p=0.005$). Urethral tissues contained a greater frequency of both CDC and PDC within leukocyte populations compared to blood or foreskin ($p<0.05$ for all comparisons). The frequency of local CD4 T cells expressing HLA-DR and CX3CR1 was also higher in urethral tissues compared to foreskin ($p=0.007$ and $p=0.05$, respectively). In contrast, foreskin tissues contained a greater frequency of T cells within the leukocyte population ($p=0.03$) and a higher CD4/CD8 T cell ratio ($p=0.006$). Expression of α4β7 on CD4 T cells and frequency of monocytes and NK cells was similar in both tissue compartments. The median TFV-DP concentrations were similar in foreskin (221 fmols/106 cells; range = 1-1,249) and urethral (161 fmols/106 cells; range = 19-756).

Conclusion: We defined differences in immune cell composition in urethral and foreskin tissues based on both CDC and PDC abundance and CD4 T cell expression of HIV susceptibility markers HLA-DR and CX3CR1. High concentrations of TFV-DP in both urethral and foreskin tissues are reassuring, and support findings of protective efficacy seen with oral TDF regimens for PrEP in men.

478 SEMINAL TENOFOVIR CONCENTRATIONS, VIRAL SUPPRESSION AND SEMEN QUALITY WITH TAF VS TDF

Arkaitz Imaz[1], Jordi Niubo[1], Mackenzie L. Cottrell[2], Emilia Perez[3], Angela Kashuba[2], Juan M. Tiraboschi[1], Sandra Morenilla[1], Benito Garcia[1], Daniel Podzamczer[1]
[1]Bellvitge University Hospital, Barcelona, Spain, [2]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [3]L'Hospitalet Clinical Laboratory, Barcelona, Spain

Background: Antiretroviral drugs penetration into the male genital tract (MGT) has been evaluated in the context of suppressing HIV replication and in the prevention of sexual transmission. The efficacy of tenofovir alafenamide (TAF) in the MGT has not yet been described. Additionally, seminal drug concentrations may influence semen quality. There is no information about this for TAF.

Methods: This prospective study enrolled 14 HIV-1 infected men on stable ART with TDF/FTC/EVG/COBI and HIV RNA <40c/mL. ART was switched to TAF/FTC/EVG/COBI. At baseline, and 12 weeks post-switch, RNA in seminal plasma (SP) and blood plasma (BP), tenofovir (TFV) in SP & BP, and TFVdp in peripheral blood mononuclear cells (PBMC) and seminal mononuclear cells (SMC) at the end of the dosing interval (C24h) were measured. Validated LC-MS/MS were used to quantify drug concentrations. HIV-1 RNA was determined by real-time PCR. Semen analyses were also performed at baseline and 12 weeks post-switch and semen quality was assessed according to WHO 2010 guidelines. Data are presented as median (range). Statistical analysis was performed by the nonparametric Wilcoxon signed-rank test.

Results: Patient characteristics at baseline were: age 42 (34-58) years; time on ART 10.5 (1-20) years; time on TDF/FTC/EVG/COBI 18 (7-53) months; time with HIV-1 RNA <40 copies/mL 82 (15-197) months; CD4 count 632 (309-1742) cells/μL. All patients had HIV-1 RNA <40 copies/mL in both BP and SP at baseline and 12 weeks after switching to TAF. Median TFV and TFVdp C24 in BP and SP are shown in the Table. With TAF, TFV C24 in SP was 11.9-fold higher than TFV C24 in BP. This concentration was significantly lower than TFV C24 in SP with TDF dosing but 9.6-fold higher than the IC50 (11.5 ng/mL). In contrast, median TFVdp in SMC achieved with TAF was 6% of TFVdp in PBMC. Although the TFVdp SMC:PBMC ratio was significantly lower with TAF in comparison to TDF, TFVdp C24 achieved in SMC with TAF and TDF were comparable. Median TFVdp C24 in SMC was below the TFVdp EC50 (36.7 fmol/million CD4 cells) for both TAF and TDF. No significant differences were observed in sperm concentration, motility, vitality and morphology between TAF and TDF.

Conclusion: Seminal extracellular and intracellular TFV distribution differs between TAF and TDF. Nevertheless, both formulations plus FTC/EVG/COBI maintained HIV-1 RNA suppression in semen. Differences in MGT distribution between TAF and TDF are not associated with differences in semen quality.

Treatment	TFV BP (ng/mL)	TFV SP (ng/mL)	TFV SP/BP	TFVdp PBMC (fmol/10^6cells)	TFVdp SMC (fmol/10^6cells)	TFVdp SMC/PMBC
TDF	76.8 (43.7-37.8)	540 (236-6980)	5.37 (1.21-91.00)	109.07 (20.4-361.34)	29.83 (3.10-421.14)	0.27 (0.04-5.48)
TAF	9.17 (4.6-14.9)	110 (73-336)	11.96 (7.92-51.16	637.29 (213.65-1154.36)	27.55 (10.41-468.68)	0.06 (0.01-0.41)
P value	0.001	0.001	0.096	0.001	0.433	0.433

479 DESIGN & SYSTEMS PHARMACOLOGY ANALYSIS OF ORAL LONG-ACTING ANTIRETROVIRAL THERAPY

Morgan L. Craig[1], Alison L. Hill[1], Christopher D. Bruno[1], Shirley S. Mo[1], Ameya Kirtane[2], Martin A. Nowak[1], Robert Langer[2], Carlo G. Traverso[2]
[1]*Harvard University, Cambridge, MA, USA,* [2]*MIT, Cambridge, MA, USA*

Background: Universal coverage of antiretroviral therapy (ART) for prevention and treatment is complicated by high pill burdens and suboptimal adherence. Investigational long-acting (LA) ART injections/implants may be impractical in resource-limited settings. Here we develop an oral LA-ART delivery system, together with a systems pharmacology framework for pre-clinical prediction of drug kinetics and treatment outcomes.

Methods: Our device consists of drug-loaded polymer arms with an elastic core. A 1cm capsule expands for gastric retention and slow release. Dolutegravir (DTG), rilpivirine (RPV) and cabotegravir (CAB) were incorporated based on low mass. Drug kinetics were compared to immediate release (IR) forms in pigs. A physiologically-based pharmacokinetic (PBPK) model simulates drug absorption, distribution, metabolism, and excretion to get whole-body kinetics from physiochemical data. ART as treatment was simulated with an existing calibrated multi-strain viral dynamics model. ART as PrEP was simulated with a new calibrated mechanistic model of heterosexual transmission. Dose-response curves were parameterized from ex vivo assays and clinical trials. Fitness effects of known resistance pathways were assembled from the literature.

Results: Prototype oral LA-ART devices in pigs reached Cmax after ~1 d (mean DTG 800, RPV 27, CAB 450 ng/mL) and continued to release drug for 7 d (mean Ctrough DTG 700, RPV 20, CAB 350 ng/mL), while the IR form reached comparable peaks (mean Cmax DTG 500, RPV 22, CAB 1300 ng/mL) but was undetectable by 2 d. The PBPK model recreated human IR kinetics (Cmax 3900, 200, 16200 ng/mL; tmax 2.5, 4.5, 1 hr for DTG, RPV, CAB) and was used to predict LA kinetics for varying doses (20-200% daily IR mass) and adherence. Models 1 yr maintenance monotherapy under simulated kinetics predicted similar rates of treatment failure for IR vs LA-ART in populations with realistically heterogeneous adherence. % of failures due to resistance increased with LA-ART for RPV only. Predicted changes in adherence patterns due to LA-ART could allow for 60% dose reductions. Modeling transmission recreated the observed efficacy of tenofovir-based PrEP, and predicts that LA-DTG reduces 1-year transmission risk by ~98% right after dosing, >50% for 10 days after dose, and may be superior to tenofovir.

Conclusion: Orally-delivered LA-ART devices are feasible to engineer, effective in large animal models, and predicted by pharmacometric modeling to treat/prevent HIV in humans.

480 PRECLINICAL EVALUATION OF A REDUCED DOSE DARUNAVIR/RITONAVIR NANOPARTICLE FORMULATION

Helen J. Box[1], Joanne Sharp[1], Megan Neary[1], Darren M. Moss[2], Lee M. Tatham[1], Hannah Kinvig[1], Alison C. Savage[1], Samantha Ashcroft[1], David Back[1], Steve Rannard[1], Andrew Owen[1]
[1]*University of Liverpool, Liverpool, UK,* [2]*Keele University, Keele, UK*

Background: Enhanced oral pharmacokinetics (PK) has previously been demonstrated for antiretroviral drugs by formation of solid drug nanoparticles (SDNs) using an emulsion-templated freeze-drying approach. Darunavir (DRV) has poor aqueous solubility, low bioavailability, and even with ritonavir-boosting (DRV/r) requires an 800mg daily dose. The current study describes the preclinical development of DRV/r SDNs that provide augmented PK exposure, potentially enabling dose reduction to reduce costs and make better use of available manufacturing capacity. If successful, the approach may also result in smaller oral dosage forms, facilitating future co-formulation strategies.

Methods: A library of DRV/r SDN formulations were manufactured with acceptable excipients (FDA CDER-listed) and characterised to ensure reproducibility in terms of physical properties including size and surface charge. Initial screening was conducted to determine apparent permeability (Papp) across Caco-2, as well as triple culture (Caco-2, HT29-MTX and Raji B cells) monolayers that can more accurately capture particle-specific mechanisms. The single-dose in vivo oral PK and tissue distribution of lead candidates were evaluated in male rats, followed by an assessment of steady-state PK for the best performing SDN. In vivo experiments were conducted at 20 mg / kg doses and compared with an aqueous pre-clinical formulation (20% cremaphor in water). Statistical analysis was conducted using an unpaired t-test.

Results: Three SDNs demonstrated improved Papp providing 115%, 152%, and 200% increases compared to an aqueous DRV/r preparation across Caco-2 monolayers. Augmented single-dose PK was observed in rats for all three formulations. The lead SDN demonstrated a 3-fold increase in AUCτ (28,036 versus 8516 ng.hr/ml; $P = 0.001$) and a 2-fold increase in Cmin (3626 versus 1655 ng/ml; $P = 0.0005$) values at steady-state. Steady-state studies using a loading dose followed by a 50% lower dose maintenance demonstrated the ability for dose reduction while not compromising PK exposure.

Conclusion: These data provide preclinical demonstration of a DRV/r SDN formulation with the potential for dose reduction whilst maintaining PK exposure. The approach utilises accepted excipients, which significantly de-risks future translation. The lead formulation will now be translated to spray-dry manufacturing to achieve scale necessary for first in human clinical evaluation.

481 CHARM-03:SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ORAL AND TOPICAL MARAVIROC

Ian McGowan[1], Rhonda M. Brand[1], Jarret C. Engstrom[2], Aaron Siegel[2], Ashley Myerski[2], Cindy Jacobson[2], Mark A. Marzinke[3], Craig W. Hendrix[3], Alex Rinehart[4], John Steytler[5], Charlene S. Dezzutti[1], Nicola Richardson-Harman[6], Hans M. Spiegel[7], Ross Cranston[1]
[1]*University of Pittsburgh, Pittsburgh, PA, USA,* [2]*Magee–Womens Research Institute, Pittsburgh, PA, USA,* [3]*Johns Hopkins Hospital, Baltimore, MD, USA,* [4]*ViiV Healthcare, Research Triangle Park, NC, USA,* [5]*International Partnership for Microbicides, Paarl, South Africa,* [6]*Alpha StatConsult, LLC, Damascus, MD, USA,* [7]*NIAID, Rockville, MD, USA*

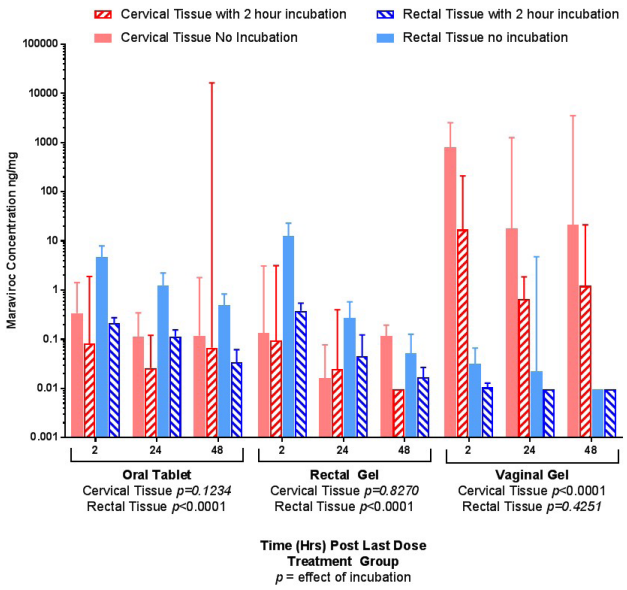
Background: Maraviroc (MVC) is being evaluated as a HIV-1 PrEP agent. In the non-human primate model, oral MVC did not provide protection from SHIV162p3 rectal challenge whereas topical rectal MVC was protective. Phase 1/2 studies have not demonstrated significant viral inhibition in the ex vivo / in vitro colorectal explant challenge model. The purpose of the CHARM-03 study was to characterize the safety, pharmacokinetic (PK), and pharmacodynamic profile of MVC following oral, vaginal, and rectal administration.

Methods: Healthy HIV-1 uninfected men and women with homozygous wildtype CCR5 genotype were enrolled into a randomized open label crossover trial in which they received 300 mg oral MVC daily for 8 consecutive days, 1% MVC rectal gel for 8 consecutive days, and female participants received daily vaginally administered MVC 1% gel for 8 consecutive days. Each product administration was followed by a washout period of 14 to 21 days. Blood and tissue (cervical and rectal) were collected prior to and +2, +24 and +48 hours after the final dose of study product. One biopsy was snap frozen for PK and a second biopsy was incubated in culture medium for 2 hours before being snap frozen for PK. Tissue biopsies were challenged with HIV-1BaL as previously described (McGowan I et al. Lancet HIV 2016).

Results: Twenty participants (11 male) were enrolled in the study. Twenty-five adverse events (24 Grade 1 and one Grade 2) were reported in 11 participants. Rectal PK at Day 8 of dosing (mean ± SD) was: oral tablet (7.9 ± 7.2 ng/mg), rectal gel (29.2 ± 36.5 ng/mg), and vaginal gel (0.1 ± 0.1 ng/mg). HIV-1 p24 inhibition was seen only in rectal tissue after oral dosing and only 1-2 hours post dose ($p<0.05$); inhibition was not detected in cervicovaginal tissue after oral dosing, nor in either tissue site with rectal or vaginal dosing. Pairwise comparison of snap frozen versus cultured tissue showed significant loss of MVC during 2 hours incubation (median Log_{10} ± IQR) in rectal tissue following both oral tablet (1.16 ± 0.7) and rectal gel (0.96 ±1.04) and in cervical tissue following vaginal gel (1.34 ± 0.79) ($p<0.0001$) Figure 1.

Conclusion: Oral and topical MVC were safe and well tolerated and the use of oral MVC was associated with colorectal explant viral inhibition. MVC significantly disassociated from explant tissue during incubation which may account for the absence of viral suppression after rectal and vaginal gel exposure.

Figure 1 Loss of MVC from colorectal and cervical tissue after 2 hours incubation



482 MARAVIROC SOLID DRUG NANOPARTICLES WITH IMPROVED ORAL PHARMACOKINETICS

Lee M. Tatham, Alison C. Savage, Andrew Dwyer, Marco Siccardi, Steve Rannard, Andrew Owen
University of Liverpool, Liverpool, UK

Background: Maraviroc (MVC) is an orally dosed selective CCR5 antagonist used against CCR5-trophic HIV type-1. MVC is a P-glycoprotein (P-gp) and a CYP3A4 substrate, which limit effective absorption. It is estimated that over 60% of the absorbed drug is metabolised at first pass, resulting in a bioavailability of ~33%. Additionally, C_{max}-driven postural hypotension has been described. The aims of this study were to apply an emulsion-templated freeze-drying technique, with and without oil-blending, to develop and optimise MVC-loaded Solid Drug Nanoparticles (SDNs) for improved oral pharmacokinetics (PK).

Methods: An emulsion-templated freeze-drying screen was successfully employed to produce twelve different SDN dispersions of [^{3}H]-MVC, with up to 70 wt.% drug-loading. Additionally, six of the SDNs were blended with soybean oil to identify if oil-blending influences MVC exposure. The apparent permeability (Papp) of each SDN and a conventional MVC preparation (<0.5% DMSO) was determined using Caco-2 monolayers as a model for gut epithelium. Subsequently, male Wistar rats were orally dosed with either an aqueous MVC preparation (<5% DMSO) or the lead SDN which produced the greatest fold increase in MVC Papp.

Results: Dynamic light scattering indicated that MVC SDNs were successfully prepared with z-average sizes ranging from 125 to 956 nm. Significant variations in MVC Papp were observed across the different SDNs investigated, with up to 1.7- and 6.5-fold increases in Papp for the SDNs and the oil-blended SDNs, respectively. Oral dosing of rats with the lead SDNs revealed enhanced MVC exposure compared to rats dosed with a conventional MVC preparation (Table 1). The C_{max}:C_{min} ratio for nanodispersion 1 was over 1.5-fold lower compared to the conventional MVC preparation but over 4.5-fold greater for nanodispersion 2. Additionally, increased MVC concentrations were observed in most dissected tissues obtained from the SDN dosed rats.

Conclusion: These data highlight the development and optimisation of 70 wt.% MVC-loaded SDNs. The potential for improved oral absorption was identified and the lead nanosuspensions were shown to improve MVC exposure following oral dosing. Oil blended SDNs appeared to further modify the PK of MVC, warranting further investigation. This study has highlighted the potential of SDN technology for improving MVC PK, and the scope for dose reduction while reducing the C_{max} to C_{min} ratio.

Table 1. MVC exposure in adult male Wistar rats following oral dosing of [^{3}H]-MVC (10 mg/kg) as a conventional preparation (<5% DMSO) or as a MVC nanodispersion.

Pharmacokinetic parameter	Conventional MVC preparation	MVC nanodispersion 1	MVC nanodispersion 2
C_{max} (ng/ml^{-1})	26.52	50.74	130.31
C_{min} (ng/ml^{-1})	8.16	25.83	8.88
T_{max} (h)	1.5	1.5	1.0
AUC (ng.h/ml^{-1})	58.71	145.33	146.24
C_{max}:C_{min} ratio	3.25	1.96	14.67

483 TOWARDS A LONG-ACTING INJECTABLE (LAI) FORMULATION FOR MARAVIROC

Lee M. Tatham, Andrew Dwyer, Alison C. Savage, Marco Siccardi, Steve Rannard, Andrew Owen
University of Liverpool, Liverpool, UK

Background: Suboptimal adherence to antiretroviral therapy can lead to insufficient drug exposure, leading to viral rebound and increasing the likelihood of resistance. This has driven the development of long-acting injectable (LAI) formulations, which may mitigate the problems with suboptimal patient adherence. Currently, Maraviroc (MVC) is orally dosed with an estimated oral bioavailability of 33%. Given the different resistance profile of MVC compared to more commonly used therapies, a MVC LAI formulation has particular appeal for implementation in Pre-Exposure Prophylaxis (PrEP). The aims of this study were to assess the potential of oil blended MVC Solid Drug Nanoparticles (SDNs) for LAI administration.

Methods: An emulsion-templated freeze-drying screen was successfully employed to produce soybean oil blended SDNs with 50 wt.% [^{3}H]-MVC loading. Rapid Equilibrium Dialysis (RED) was used to determine the rate of MVC release with diffusion across a size selective membrane. Subsequently, male Wistar rats were dosed intramuscularly in the biceps femoris (10 mg/kg MVC) with either an aqueous MVC preparation (<5% DMSO) or the lead SDNs. Plasma samples were taken and analysed via scintillation counting until [^{3}H]-MVC concentrations fell below the limits of quantification.

Results: RED assays revealed three MVC SDNs with slower release rates than a conventional MVC preparation, with the first-order release rate constant, derived from the final sample, over 3-fold lower. Intramuscular injection of the nanosuspensions revealed significant variations in MVC exposure (Table 1). Following the initial burst event (<24 hours), nanosuspensions 1 and 3 were shown to continue releasing MVC at a steady rate for up to 7 and 10 days with over a 3- and 4-fold increase in MVC $AUC_{t-\infty}$ compared to the unformulated MVC preparation, respectively. However, nanosuspension 2 was undetectable in plasma after 3 days with an $AUC_{t-\infty}$ value comparable to the conventional MVC preparation.

Conclusion: The data presented here highlight the development and optimisation of LAI MVC. *In vivo* analysis of the lead formulations demonstrated that the SDN technology is capable of attaining and sustaining MVC exposure for up to 10 days in rats. Using these data, modelling potential MVC exposure in humans is planned with the aim of achieving a bi-monthly or monthly LAI format.

Table 1. MVC exposure in adult male Wistar rats following a single intramuscular injection of [^{3}H]-MVC (10 mg/kg) in the biceps femoris either as a conventional preparation (<5% DMSO) or as a MVC nanodispersion.

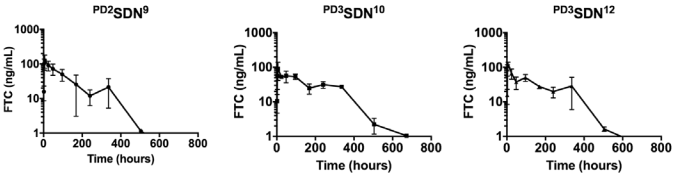
Pharmacokinetic parameter	Conventional MVC	MVC nanodispersion 1	MVC nanodispersion 2	MVC nanodispersion 3
C_{max} (ng/ml^{-1})	71.67	62.88	50.58	69.85
AUC_{t-8} (ng.h/ml^{-1})	567.17	1720.51	628.62	2821.3
AUC_{0-24} (ng.h/ml^{-1})	244.29	472.19	356.76	714.85
Terminal half-life t½ (h)	53.23	121.44	33.19	196.04
C_{24} (ng/ml^{-1})	3.67	9.30	4.11	7.23
C_{48} (ng/ml^{-1})	2.69	7.28	4.08	6.50
C_{72} (ng/ml^{-1})	2.66	4.18	2.84	6.32
C_{168} (ng/ml^{-1})	-	3.81	-	4.67
C_{240} (ng/ml^{-1})	-	-	-	3.30

(-) = below limits of quantification

484 IN VIVO PHARMACOKINETICS OF NOVEL LONG-ACTING INJECTABLE EMTRICITABINE PRODRUGS

Paul Curley[1], James J. Hobson[1], Christopher David[1], Amer Al-Khouja[2], David Meyers[2], Caren Freel Meyers[2], Charles W. Flexner[2], Marco Siccardi[1], Steve Rannard[1], **Andrew Owen**[1]
[1]University of Liverpool, Liverpool, UK, [2]Johns Hopkins Hospital, Baltimore, MD, USA

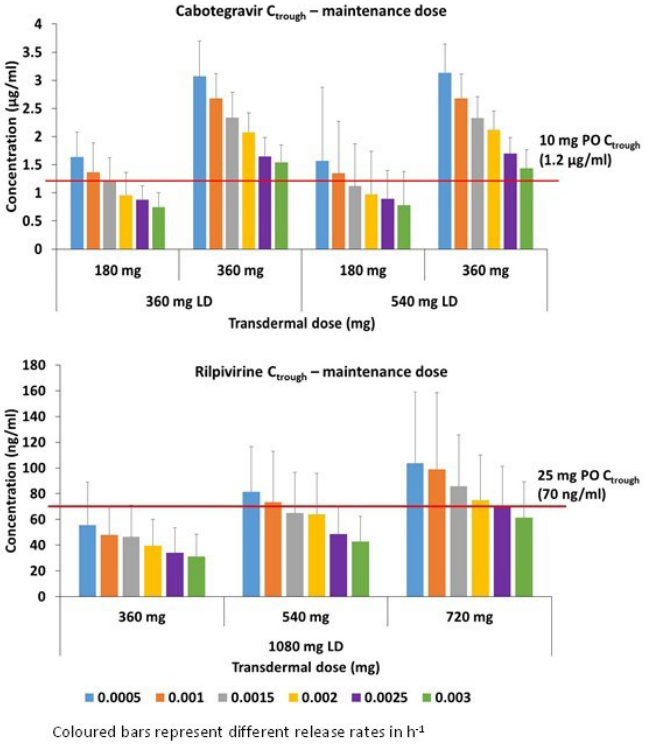
Background: Patient non-adherence to therapy is an ongoing problem, which results in sub-therapeutic drug concentrations that increases the risk for emergence of drug/class resistant strains of HIV. Recently, long-acting injectable (LAI) formulations of antiretroviral drugs have been developed, which may overcome some of the problems with patient non-adherence to oral regimens. We report here a preclinical assessment of LAI solid drug nanoparticle (SDN) formulations of novel emtricitabine (FTC) prodrugs.
Methods: To decrease aqueous solubility for compatibility with SDN formation, 3 varying chain length carbamate/carbonate prodrugs of FTC were produced to mask key hydrophilic groups (PD1, PD2 and PD3). SDN formulations were then generated using a proprietary emulsion-templated freeze-drying technology. An initial screen of 12 candidate formulations was conducted in Wistar rats. Rats were dosed with 10 mg/kg FTC equivalent via a single intramuscular injection in the musculus biceps femoris. Plasma samples were taken over 7 days and analysed via LC-MS/MS. For three promising lead formulations PD2SDN9; PD3SDN10; PD3SDN12), a longer-term in vivo study was conducted. For this, Wistar rats were dosed with two IM injections (20 mg/kg) and plasma drug concentrations were monitored over 28 days.
Results: In the initial screen, FTC concentrations in candidates SDN1-8 and SDN11 fell below the limit of detection (2 ng/mL) within 4 days. PD2SDN9, PD3SDN10 and PD3SDN12 resulted in detectable plasma FTC concentrations for 7 days (FTC > 16 ng/mL). SDN formulations 9, 10 and 12 were therefore progressed to a longer-term study (Figure 1). Cmax was reached at 6 hours for all formulations (SDN9 127 ± 52.9 ng/mL, SDN10 95 ± 39.4 ng/mL and SDN12 119 ±20.9 ng/mL). FTC plasma concentrations were detectable for all three formulations until 14 days (SDN9 21 ± 16.2 ng/mL, SDN10 31 ± 7.1 ng/mL and SDN12 28 ± 22.7 ng/mL). FTC concentrations in all 3 formulations were below the limit of detection (2 ng/mL) by 21 days.
Conclusion: The *in vivo* data presented here demonstrate that the combined prodrug/SDN approach can provide plasma exposure in rats for 14 days. Species differences in renal clearance of FTC mean that exposures longer than 14 days are likely to be achievable in humans. Further studies will aim to optimise formulations to produce exposure beyond 14 days in rats and to elucidate the biological mechanisms involved in LA release of SDN prodrugs.



485 PBPK MODELING OF MICROARRAY PATCHES FOR LONG-ACTING INTRADERMAL DRUG DELIVERY

Rajith Kumar Reddy Rajoli[1], Charles W. Flexner[2], Andrew Owen[1], Ryan Donnelly[3], Marco Siccardi[1]
[1]University of Liverpool, Liverpool, UK, [2]Johns Hopkins Hospital, Baltimore, MD, USA, [3]Queen's University Belfast, Belfast, UK

Background: Intradermal delivery using microarray patches (MAPs) represent a blood-free, minimally invasive and patient friendly route of administration. MAPs can deliver long-acting (LA) nanoformulations (NFs), providing systemic exposure for an extended time period. The aim of this study was to design and evaluate intradermal physiologically-based pharmacokinetic (PBPK) models to simulate the pharmacokinetics (PK) resulting from the administration of rilpivirine or cabotegravir through MAPs.
Methods: Simulations were conducted in 100 healthy individuals using published anthropometric equations. A novel PBPK model for transdermal delivery was constructed using Simbiology v. 4.3.1 (MATLAB 2013b). The model was qualified against observed data in rats for intramuscular (IM) and intradermal rilpivirine, and for clinical data in healthy adults for both oral and IM LA NFs of cabotegravir and rilpivirine. The PBPK models were assumed to be qualified if the simulated values were ± 50% from the mean clinical values. Pharmacokinetics for various four-weekly intradermal loading dose (LD) and maintenance doses (MDs) were predicted following four weeks of oral administration. C_{trough} values obtained from steady-state oral administration were considered as the target C_{trough} values. Optimal drug release rates from the MAPs were identified for both drugs such that the minimal dose and target C_{trough} values at the end of the dosing interval were achieved.
Results: The PBPK models were successfully qualified resulting in a difference of less than ± 50% from the observed pharmacokinetic values. For cabotegravir and rilpivirine, LDs ranging from 180 – 540 mg and 720 – 1080 mg respectively and MDs from 180 – 360 mg and 360 – 720 mg respectively were assessed across six different release rates between 0.0005 – 0.003 h^{-1} (Figure). An LD of 360 mg and MD of 180 mg between 0.001 – 0.0015 h^{-1} for cabotegravir, and LD of 1080 mg and MD of 720 mg between 0.001 – 0.002 h^{-1} for rilpivirine, were identified as the optimal settings for NF and MAP design.
Conclusion: MAPs could be an effective tool for delivery of LA NFs for chronic antiretroviral therapy. PBPK models identified optimal dose and release characteristics for cabotegravir and rilpivirine, supporting rational development of future formulations. This approach can identify potential drug candidates for LA therapy delivered using MAPs.



Coloured bars represent different release rates in h^{-1}

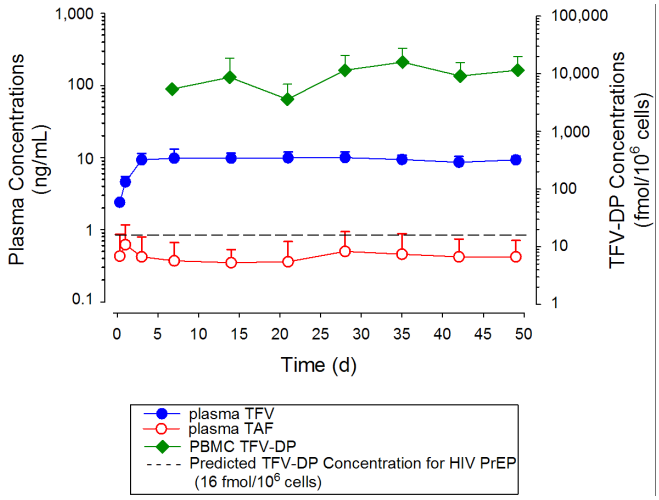
486 PHARMACOKINETICS OF TENOFOVIR ALAFENAMIDE BY SUBCUTANEOUS IMPLANT FOR HIV PrEP

Greg Gatto[1], Natalie Girouard[1], Rhonda M. Brand[2], Leah Johnson[1], Mark A. Marzinke[3], Sudie Rowshan[1], Jarret C. Engstrom[2], Ian McGowan[2], Zach Demkovich[4], Ellen Luecke[4], Ariane van der Straten[4]
[1]RTI International, Research Triangle Park, NC, USA, [2]University of Pittsburgh, Pittsburgh, PA, USA, [3]Johns Hopkins Hospital, Baltimore, MD, USA, [4]RTI International, San Francisco, CA, USA

Background: We evaluated the pharmacokinetics of tenofovir alafenamide (TAF), an antiretroviral prodrug with high potency and potential for HIV Pre-exposure prophylaxis (PrEP), released from polycaprolactone (PCL) implants at the midway point of a 3-month study in rabbits.
Methods: PCL tubes (40 mm x 2.5 mm x 70 µm wall thickness) were fabricated by extrusion and loaded with a slurry of TAF and Castor Oil (2:1 ratio by mass). Devices were sterilized by gamma-irradiation post-fabrication. Ten female New Zealand white rabbits were surgically implanted with active (TAF; n=6) or placebo devices (n=4). Blood samples were taken 6 h post-surgery on day 0 and on days 1, 4, 7 and weekly thereafter, for TAF and tenofovir (TFV) drug quantification (lower limits of quantification: TAF, 0.03 ng/mL; TFV, 0.31 ng/mL). Peripheral blood mononuclear cells (PBMCs) were isolated from blood samples collected on days 7 and weekly thereafter, for TFV-diphosphate (TFV-DP) determination (as fmol/10^6 cells). At day 49, some devices were recovered for residual drug analysis. Similar TAF devices were concurrently evaluated in-vitro in PBS at 37°C. In-vitro sampling occurred every other day and TAF release was measured by UV spectrophotometer.

Results: TAF release in-vitro from the active devices followed a zero-order release kinetics (1.1±0.02 mg/d) during study period. Similarly, plasma concentrations indicated the implanted devices maintained a low systemic exposure of TAF with a median concentration of 0.4±0.1 ng/mL. Low systemic exposure to TFV was also demonstrated attaining a median concentration of 9.4±2.6 ng/mL. PBMC loading with TFV-DP was noted at the first sampling time point and was maintained throughout the study period at a median level of 1825±820 fmol/10^6 cells (or 9125 nM) (Figure 1). Residual drug analysis of the retrieved devices approximated the in-vivo release rate of TAF to be 1.1±0.01 mg/d. Of note, some animals exhibited cutaneous responses (i.e., encapsulation and swelling) to the active devices.

Conclusion: The sustained plasma TAF concentrations and the in-vivo release rate of the active implants correlated well with the in-vitro TAF release from similar devices. TAF implants maintained sustained PBMC TFV-DP concentrations for the duration of the 49d mid-point evaluation well above that predicted for HIV PrEP in humans. Taken together, these data indicate this TAF device is suitable for continued development as a long-acting subcutaneous implant for HIV PrEP.



487 LONG-ACTING 3 HIV-DRUGS-IN-ONE NANOPARTICLE FORMULATION INTENDED FOR ADOLESCENTS

Josefin Koehn, John C. Kraft, Lisa McConnachie, Loren Kinman, Sarah Lane, Wonsok Lee, Ann Collier, Rodney J. Ho
University of Washington, Seattle, WA, USA

Background: It is estimated that about 2.1 million children worldwide are living with HIV. Due to their physio-pharmacological distinction, pediatric drug treatments require age appropriate dosage form. However, the development of therapeutics aimed at suppressing HIV in children and adolescents has been limited. In contrast to a larger selection of oral combination antiretroviral therapies (cART) available for adults, the options for children are somewhat limited. Also, data indicates that only about 30% of adolescents experience durable viral suppression. Even in cases with plasma viral suppression, residual virus can be isolated from tissues, particularly lymph nodes. Therefore, we have developed a drug combination nanoparticle (DcNP) containing three drugs with well-established antiviral potency and safety in pediatrics, targeting three different stages in the viral replication. This DcNP is composed of a protease inhibitor lopinavir (LPV), nonnucleoside reverse transcriptase inhibitor efavirenz (EFZ), and nucleoside inhibitor tenofovir (TFV). The objective of this study was to characterize targeted and long-acting effects of our validated 3-drug single DcNP formulation in HIV host cells and plasma in non-human primates for two weeks.

Methods: Macaques were given a single dose of the DcNP subcutaneously. The drug concentrations in plasma, peripheral blood, and lymph mononuclear cells were analyzed for two weeks. The pharmacokinetic parameters and cell-to-plasma relationship of the three drugs were determined.

Results: The formulation was well-tolerated in primate and no local reactions were noted. We found that protease inhibitor (LPV) and reverse transcriptase inhibitor (EFV, TFV) levels persist in plasma for the two week duration of the study. Intracellular levels for all three drugs also persist for two weeks and exhibit higher levels, especially for EFV and LPV, than those found in plasma. All three drugs also exhibit lymph node drug concentrations higher than plasma (table 1).

Conclusion: Collectively, this 3-in-1 DcNP formulation provided long-acting plasma drug concentration and enhanced HIV host-cell localization in cells in blood and also lymph nodes. This anti-HIV DcNP formulation should be considered for development intended for pediatrics. With long-acting profile and higher penetration/persistence in cells, it may enhance therapeutic efficacy of these well-studied HIV drugs due to co-localization of a combination of three drugs.

Table 1. LPV, EFV, and TFV intracellular concentrations in inguinal lymph nodes excised one and eight days after a single SC dose of DcNPs, and comparisons to drug levels at the same time points in PBMCs and plasma.

	Lopinavir (LPV)		Efavirenz (EFV)		Tenofovir (TFV)	
SC Dose (mg/kg)	25.0		16.7		22.6	
LNMCs						
C_{24h} (µg/mL)	**0.76**	(3.9)	**17.91**	(0.13)	**17.23**	(43.9)
C_{192h} (µg/mL)	**0.65**	(107.1)	**0.18**	(0.12)	**6.83**	(0.6)
LNMCs/PBMCs						
C_{24h}	**1.9**	(77.9)	**6.0**	(63.3)	**1.0**	(77.5)
C_{192h}	**7.3**	(77.9)	**0.7**	(17.2)	**1.5**	(3.4)
LNMCs/Plasma						
C_{24h}	**3.5**	(40.7)	**30.5**	(30.7)	**1.2**	(36.6)
C_{192h}	**65.0**	(39.5)	**221.7**	(21.6)	**0.9**	(5.2)

Arithmetic mean (% coefficient of variation).
LNMC and PBMC cell volume assumed to be 0.2829 pL/cell.
C_{24h} and C_{192h}, drug concentration at 24 hr and 192 hr; LNMCs, lymph node mononuclear cells; PBMCs, peripheral blood mononuclear cells; SC, subcutaneous.

488 LONG-ACTING PHARMACOKINETICS OF 4 HIV DRUGS COFORMULATED IN ONE NANO-FORMULATION

Lisa McConnachie, Loren Kinman, Josefin Koehn, John C. Kraft, Sarah Lane, Wonsok Lee, Ann Collier, Rodney J. Ho
University of Washington, Seattle, WA, USA

Background: Daily oral conventional ART, even in fixed dose combination forms, has inherent limitations such as patient adherence and disparate drug kinetics; both potentially impacting therapeutic outcomes. Oral dosing has also been shown to produce lower and limited tissue exposure where residual virus persists. To address these limitations, we have developed a tissue- and cell-targeted long-acting anti-HIV nanosuspension containing 4 drugs. The aim of this study is to characterize the blood and tissue pharmacokinetics of all four drugs 5 weeks following drug administration.

Methods: Four pigtail macaques received a single subcutaneous injection of a 4-in-1 anti-HIV drug combination nanoparticle (DcNP) formulation composed of lopinavir (LPV), ritonavir (RTV), tenofovir (TFV) lamivudine (3TC) and lipidic excipients. Blood samples and lymph node biopsies were obtained at defined time points up to 5 weeks following drug administration. Drug levels in plasma, lymph node and peripheral blood mononuclear cells (LNMC and PBMC) were analyzed with a validated LC-MS/MS assay.

Results: The injections were well tolerated and no injection site reactions were noted. PBMC and plasma levels of the three active drugs (hydrophobic LPV, hydrophilic TFV and 3TC) were sustained for 5 weeks; these data are depicted in Figure 1. When compared to plasma levels, PBMC drug exposures were 12-, 16-, and 42-fold higher for LPV, RTV, and 3TC, respectively. Notable extended apparent terminal half-lives of LPV, TFV, and 3TC were observed in plasma [219.1 hours (LPV), 63.1 hours (TFV), and 136.3 hours (3TC)]. These were even further extended in PBMCs [1045.7 hours (LPV), 105.9 hours (TFV), and 127.7 hours (3TC)]. Eight days after drug administration, LPV, TFV and 3TC levels in LNMCs were 102-, 2.9-, and 352-fold higher than those in plasma.

Conclusion: A single injection of one DcNP nanosuspension containing four drugs exhibited persistent drug levels in LMNC, PBMC, and plasma for 5 weeks. Though these drugs have disparate physiochemical properties, we were able to successfully co-formulate all into a single nanosuspension. This formulation demonstrated both cell- and tissue-targeted properties in addition to sustained pharmacokinetic profiles. With interspecies scaling and appropriate dose adjustments, this 4-in-1 HIV drug-combination could be considered for long-acting treatment with the potential to overcome lymphatic drug insufficiency and limitations with patient adherence.

Figure 1.

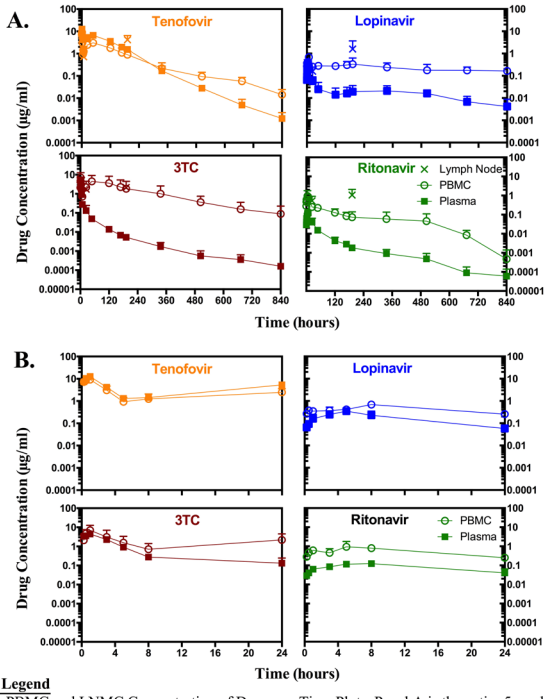


Figure Legend
Plasma, PBMC and LNMC Concentration of Drugs vs. Time Plots. Panel A is the entire 5 week time course and Panel B is time course data from 0-24 hours. The open circles (o) represent the PBMC data, the closed squares (■) are plasma data, and the x is lymph node data. The data plotted are the mean ± (s.d.), n= 4 macaques following a single subcutaneous administration of the 4-in-1 formulation.

489 DRV/R/3TC FDC FOR HIV-1 TREATMENT-NAÏVE PATIENTS: WEEK 48 RESULTS OF THE ANDES STUDY

María I. Figueroa[1], Omar G. Sued[1], Ana M. Gun[1], Waldo Belloso[2], Diego M. Cecchini[3], Gustavo Lopardo[4], Daniel Pryluka[5], Maria J. Rolon[1], Valeria I. Fink[1], Santiago Perez Lloret[6], **Pedro Cahn**[1]
[1]Fundación Huésped, Buenos Aires, Argentina, [2]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Hospital Argerich, Buenos Aires, Argentina, [4]Centro de Estudios Infectológicos, Buenos Aires, Argentina, [5]Consultorio Infectológico, Buenos Aires, Argentina, [6]University of Buenos Aires, Buenos Aires, Argentina

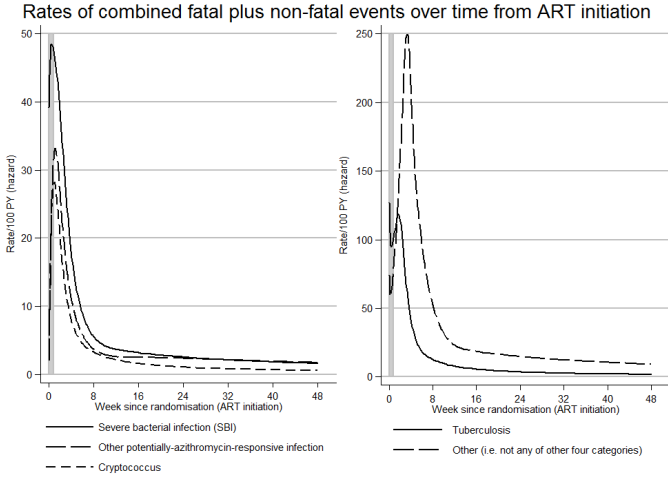
Background: Dual therapy has been explored in different studies. A generic fixed dose combination (FDC) of DRV800/ritonavir100 mg is available in Argentina. We designed a study to compare efficacy and safety of this FDC plus 3TC to standard-of care HAART based on the same drugs plus tenofovir. ClinicalTrials.gov Identifier: NCT02770508
Methods: ANDES is a randomized, open-label, phase IV study, designed to compare dual therapy (DT) with DRV/RTV (800/100 mg) FDC, plus 3TC (300 mg), to triple therapy (TT) with DRV/RTV (800/100 mg) plus 3TC/TDF (300/300mg),FDC in treatment-naïve HIV-1 infected patients. Primary endpoint: proportion of patients with viral load (pVL) <50 copies/mL at week 48 (FDA snapshot -ITTe analysis) Preplanned week 24 analysis was presented at IAS 2017. Week 48 results are reported here.
Results: Out of 182 patients screened, 145 were randomized to receive: DT (n75) or TT (n70). At baseline 92% were on CDC stage A: 24% had pVL> 100,000 copies/mL. At week 48, 93% of patients on DT and 94% on TT achieved pVL <50 copies/mL, difference (95% CI): -1.0% (-7.5; 5.6%). Patients with baseline pVL>100,000 copies/mL showed 92% response in TT arm and 91% in DT. One patient presented virological failure at week 48 (TT arm).Per-protocol analysis: 99% were responders in TT arm and 100% in DT arm. Median CD4+ change between BSL and week 48 was similar in both arms. Thirty six grade 2-4; possible/probable related adverse events (AEs) were reported among 28 patients(TT:17;DT:11),most frequent were gastrointestinal (TT:14%;DT: 7%;p:0.17) and rash (TT:7%;DT: 8%;p:0.95). Laboratory abnormalities were similar in both arms except regarding total cholesterol (TT: 4%; DT: 19%; p: 0.01).LDL-cholesterol and triglycerides showed a non-significant trend in favor of TT(TT: 6%/DT 14% and TT: 14%/DT: 25% respectively). AEs leading to discontinuation were rare and similar between arms. No related SAEs or deaths were reported
Conclusion: A generic FDC of DRV/RTV plus 3TC showed non-inferiority to a standard of care triple drug regimen with ritonavir-bosted Darunavir in FDC plus TDF/3TC at 48 weeks. This study adds further evidence about the efficacy of drug-sparing regimens in treatment-naïve patients

490 MORTALITY/MORBIDITY AFTER INITIATING ART WITH CD4 <100 CELLS/UL IN THE REALITY TRIAL

Frank Post[1], Alexander J. Szubert[2], Andrew Prendergast[3], Victoria Johnston[4], Hermione Lyall[5], Felicity Fitzgerald[6], Peter Mugyenyi[7], James G. Hakim[8], Priscilla Chepkorir[9], Clara Agutu[10], Symon Kaunda[11], Sarah Walker[2], Diana Gibb[2], Sarah Pett[2]
[1]King's College Hospital NHS Foundation Trust, London, UK, [2]MRC Clinical Trials Unit at UCL, London, UK, [3]Queen Mary University of London, London, UK, [4]London School of Hygiene & Tropical Medicine, London, UK, [5]Imperial College Healthcare NHS Trust, London, UK, [6]University College London, London, UK, [7]Joint Clinical Research Centre, Kampala, Uganda, [8]University of Zimbabwe, Harare, Zimbabwe, [9]Moi University, Eldoret, Kenya, [10]KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya, [11]Malawi–Liverpool–Wellcome Trust Clinical Rsr Prog, Blantyre, Malawi

Background: In sub-Saharan Africa, 20-25% of those starting ART have CD4<100 cells/ul; ~10% die within 3 months. We investigated the contribution and timing of different causes of mortality/morbidity in the REALITY trial (ISRCTN43622374).
Methods: Patients starting ART were randomized to enhanced-prophylaxis against infections (cotrimoxazole [CTX] plus 12 weeks isoniazid+fluconazole, single-dose albendazole, 5-days azithromycin (AZ); Px+) vs CTX alone. Events and causes of death were adjudicated by an endpoint review committee blind to randomization, as (non-mutually exclusively) TB, cryptococcus, severe bacterial infection (SBI; septicaemia, meningitis, pneumonia), other infections potentially responsive to AZ (eg diarrhoea, malaria, encephalitis, toxoplasmosis), other events, and unknown (deaths only).
Results: Median pre-ART CD4 was 37 cells/ul. 225(12.7%) of 1805 patients died by week-48. Most fatal/non-fatal events occurred early (median 4.0 (IQR 2.0-11.7) weeks) after ART initiation, then rates declined exponentially. 154 deaths were adjudicated as having single and 71 multiple causes, which included TB in 80(4.5%) patients, cryptococcus 20(1.1%), SBI 33(1.9%), other potentially-AZ-responsive infections 23(1.3%), other causes 63(3.6%) and unknown causes 88(5.0%). Considering the incidence of first fatal/non-fatal events through week-48, TB was diagnosed in 10.9%, cryptococcus 2.5%, SBI 5.1%, other potentially-AZ-responsive infections 3.6% and other events 27.0%. Px+ reduced deaths from cryptococcus (p=0.03) and unknown causes (p=0.03) but not deaths from TB (p=0.34), SBI (p=0.90), other potentially-AZ-responsive infections (p=0.31) or other causes (p=0.66). Px+ reduced the incidence of non-fatal/fatal TB (p=0.007) and cryptococcus (p=0.03) but not SBI (p=0.26), other potentially-AZ-responsive infections (p=0.34) or other events (p=0.81). By 48 weeks, event rates were lowest (<1 per 100 person-years [PY]) for cryptococcus, moderate (1–5 per 100 PY) for TB, SBI, potentially AZ-responsive infections and unknown deaths, and highest (>5 per 100PY) for other events. Median last post-baseline VL before death was 105 c/ml (N=140); CD4 was 59 cells/ul.
Conclusion: Enhanced prophylaxis reduced mortality and the incidence of TB and cryptococcus in those with CD4 <100 cells/ul. The high early incidence of both opportunistic and non-opportunistic infections highlights the need for a broad Px+ bundle at the same time as ART initiation in those with advanced HIV disease.

Rates of combined fatal plus non-fatal events over time from ART initiation



491 SIMILAR EFFICACY & SAFETY BY SUBGROUP IN DRIVE-AHEAD: DOR/3TC/TDF VERSUS EFV/FTC/TDF

Chloe Orkin[1], Kathleen E. Squires[2], Jean-Michel Molina[3], Paul E. Sax[4], Wing-Wai Wong[5], Otto Sussmann[6], Richard Kaplan[7], Anthony Rodgers[8], Xia Xu[8], Gina Lin[8], Sushma Kumar[8], George G. Hanna[8], Carey Hwang[8], Elizabeth Martin[8]
[1]Royal London Hospital, London, UK, [2]Thomas Jefferson University, Philadelphia, PA, USA, [3]University Paris Diderot, Paris, France, [4]Brigham and Women's Hospital, Boston, MA, USA, [5]Taipei Medical University, Taipei, Taiwan, [6]Asistencia Cientifica de Alta Complejidad SAS, Bogota, Columbia, [7]Desmond Tutu HIV Foundation, Cape Town, South Africa, [8]Merck & Co, Inc, Kenilworth, NJ, USA

Background: In the phase 3 DRIVE-AHEAD trial, a once-daily single-tablet regimen of doravirine 100 mg, lamivudine 300 mg, and tenofovir DF 300 mg (DOR/3TC/TDF) demonstrated non-inferior efficacy and a superior safety profile for neuropsychiatric events and fasting lipids compared to efavirenz 600 mg, emtricitabine 200 mg, and tenofovir DF 300 mg (EFV/FTC/TDF) at Week 48. To further characterize the effects of DOR/3TC/TDF, Week 48 results were examined by pre-specified subgroups (efficacy) and selected prognostic subgroups (safety).

Methods: DRIVE-AHEAD is a randomized (1:1), multicenter, double-blind, 96-week non-inferiority trial of DOR/3TC/TDF vs EFV/FTC/TDF in HIV-1 infected treatment-naïve adults. Randomization was stratified by screening HIV-1 RNA (≤/>100,000 copies/mL) and hepatitis B/C co-infection (yes/no). The primary endpoint was the proportion of participants achieving HIV-1 RNA <50 copies/mL at Week 48 (FDA Snapshot approach). For the current analysis, Week 48 efficacy results were summarized within pre-specified subgroups using the Observed Failure approach (participants with data missing for reasons other than lack of efficacy were excluded). Adverse events were also summarized by selected subgroups (gender, race/ethnicity, hepatitis co-infection, and baseline CD4+ T-cell count).

Results: Baseline characteristics were balanced across the treatment groups. In the primary analysis, HIV-1 RNA <50 copies/mL was achieved by 84% of DOR/3TC/TDF recipients and 81% of EFV/FTC/TDF recipients at Week 48 (difference 3.5%, 95% CI [-2.0, 9.0]). Of the 728 participants who received study drug (364 in each treatment group), 677 (93%) were included in the subgroup efficacy analyses. Across the prespecified and selected demographic and baseline prognostic factors, the proportions of participants with HIV-1 RNA <50 copies/mL at Week 48 were comparable between the treatment regimens (table). Similar results were observed using the HIV-1 RNA cutoffs of 40 and 200 copies/mL and in the change from baseline in CD4+ T-cell counts. In the safety analysis, similar adverse event rates between treatment groups were observed across the subgroups.

Conclusion: At Week 48, across all baseline subgroups and prognostic factors, DOR/3TC/TDF demonstrated virologic and immunologic efficacy and safety comparable to that of EFV/FTC/TDF in HIV-1 treatment-naïve adults.

Proportion of participants with HIV-1 RNA <50 copies/mL at Week 48 by Prognostic and Demographic Factors (Observed Failure Approach†)

Prognostic and Demographic Factors	DOR/3TC/TDF QD n/N	DOR/3TC/TDF QD %	EFV/FTC/TDF QD n/N	EFV/FTC/TDF QD %	Treatment Difference % (95% CI)*
All Participants	307/346	88.7	294/331	88.8	-0.2 (-4.9, 4.6)
Gender					
Male	257/290	88.6	250/283	88.3	0.0 (-5.2, 5.2)
Female	50/56	89.3	44/48	91.7	-2.9 (-15.1, 9.3)
Baseline Plasma HIV-1 RNA (copies/mL)					
≤100,000 copies/mL	251/277	90.6	235/258	91.1	-0.5 (-5.5, 4.4)
>100,000 copies/mL	56/69	81.2	59/73	80.8	1.0 (-12.4, 14.3)
≤500,000 copies/mL	301/337	89.3	282/314	89.8	-0.4 (-5.2, 4.3)
>500,000 copies/mL	6/9	66.7	12/17	70.6	0.0 (-41.4, 41.4)
Baseline CD4+ T-Cell Counts (cells/mm^3)					
≤200 cells/mm^3	29/42	69.0	36/43	83.7	-14.6 (-33.2, 3.9)
>200 cells/ mm^3	278/304	91.4	258/288	89.6	1.8 (-3.0, 6.5)
Hepatitis Co-infection Status‡					
Hepatitis B/C positive	8/9	88.9	8/8	100	-12.0 (-42.9, 18.9)
Hepatitis B/C negative	299/337	88.7	286/323	88.5	0.1 (-4.8, 4.9)
Viral Subtype					
Subtype B	195/222	87.8	202/226	89.4	-1.3 (-7.2, 4.6)
Subtype Non-B	110/122	90.2	92/105	87.6	2.1 (-6.3, 10.4)
Geographic Region					
Africa	29/34	85.3	22/27	81.5	3.9 (-16.6, 24.4)
Asia/Pacific	56/58	96.6	51/57	89.5	7.1 (-3.1, 17.3)
Europe	75/83	90.4	79/85	92.9	-4.6 (-13.0, 3.7)
South America	77/89	86.5	75/80	93.8	-7.2 (-16.5, 2.1)
North America	70/82	85.4	67/82	81.7	4.8 (-6.5, 16.1)

† Subjects who prematurely discontinued assigned treatment due to lack of efficacy were classified as failures after treatment discontinuation; subjects with data missing for reasons other than lack of efficacy were excluded from the analysis.
*The 95% CIs were calculated using stratum-adjusted Mantel-Haenszel method.
‡ Hepatitis B surface antigen and/or HCV RNA by polymerase chain reaction (PCR) quantitative test.
n/N = (number of participants with HIV-1 RNA <50 copies/mL) / (number of participants in subgroup).

492 AGE, GENDER, AND RACE ANALYSES OF D/C/F/TAF IN HIV-1 TREATMENT NAÏVE PATIENTS

Bruce Rashbaum[1], Cheryl McDonald[2], Cristina Mussini[3], Christoph D. Spinner[4], John Jezorwski[5], Eric Y. Wong[6], Kimberley Brown[6]
[1]Capital Medical Associates, Washington, DC, USA, [2]Tarrant County Infectious Disease Associates, Fort Worth, TX, USA, [3]University of Modena and Reggio Emilia, Modena, Italy, [4]Technical University of Munich, Munich, Germany, [5]Janssen Research & Development, Pennington, NJ, USA, [6]Janssen Scientific Affairs, LLC, Titusville, NJ, USA

Background: Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) is the only single-tablet regimen in development for HIV-1 infection that contains darunavir and F/TAF. AMBER evaluated the efficacy and safety of D/C/F/TAF 800/150/200/10 mg versus control (D/C+F/tenofovir disoproxil fumarate [TDF]) in antiretroviral treatment (ART)-naïve, HIV-1–infected adults. We present Week 48 results based on age, gender, and race.

Methods: In AMBER, a phase 3, randomized (1:1), non-inferiority trial, the primary endpoint was proportion of patients with virologic response (viral load [VL] <50 copies[c]/mL; FDA snapshot) at Week 48. Patients with baseline resistance-associated mutations to agents other than D, F, or TDF could be included. Safety was assessed by adverse event (AE) rates and changes in bone mineral density and eGFR from baseline to Week 48. Subgroups evaluated were: age ≤50 versus >50 y, men versus women, and non-black/African American (AA) versus black/AA race.

Results: A total of 725 patients were randomized and treated; 68 (9.4%) were >50 y, 85 (11.7%) women, and 80 (11.5%) black/AA. Overall, virologic response rates were 91.4% for D/C/F/TAF and 88.4% for control (difference, 2.7%; 95% confidence interval, –1.6% to 7.1%); response rates with D/C/F/TAF were similar to control across age, gender, and race subgroups (Table). In the total population, patients in the D/C/F/TAF and control arms had similar rates of discontinuation due to an AE (1.9% vs 4.4%, respectively), worst grade 3-4 AEs (5.2% vs 6.1%), and serious AEs (4.7% vs 5.8%). Similarly, there were no clinically relevant differences across subgroups; in general, there were numerically fewer AEs in the D/C/F/TAF arm versus control (Table). There were no deaths. Improvement in bone (bone loss/atrophy AEs, bone mineral density) and renal (eGFR) safety parameters were observed for D/C/F/TAF versus control across subgroups, consistent with results in the total population.

Conclusion: D/C/F/TAF achieved high virologic response rates that were overall non-inferior to control, as well as favorable bone and renal outcomes, and demonstrated consistent results across subgroups by age, gender, and race through 48 weeks in ART-naïve, HIV-1–infected patients.

Table. Summary of Efficacy and Safety in AMBER Week 48 Subgroup Analyses by Age, Gender, and Race (Intention-to-Treat)

	Overall population		Age				Gender				Race			
			≤50 y		>50 y		Men		Women		Non-black/AA		Black/AA	
Parameter	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control
N	362	363	326	331	36	32	318	322	44	41	305	309	40	40
Efficacy, %														
Response*	91.4	88.4	91.7	88.5	88.9	87.5	91.8	89.8	88.6	78.0	92.1	89.0	85.0	85.0
Diff (95% CI)†	2.7 (−1.6, 7.1)		3.2 (−1.4, 8.0)		1.4 (−15.5, 19.8)		2.1 (−2.5, 6.7)		10.6 (−5.8, 28.0)		3.1 (−1.6, 7.9)		0.0 (−16.9, 16.9)	
VF	4.4	3.3	4.0	3.6	8.3	0.0	4.4	3.4	4.5	2.4	4.3	2.9	7.5	7.5
Safety, %														
Discont due to AE	1.9	4.4	2.1	3.9	0.0	9.4	1.6	3.4	4.5	12.2	2.3	4.9	0.0	0.0
Grade 3-4 AE‡	5.2	6.1	4.0	5.7	16.7	9.4	4.7	5.6	9.1	9.8	5.2	6.5	5.0	2.5
Serious AE	4.7	5.8	4.0	5.4	11.1	9.4	4.4	5.3	6.8	9.8	4.9	6.5	5.0	2.5
Bone loss/atrophy (related)§	0.6	2.8	0.6	3.0	0.0	0.0	0.6	3.1	0.0	0.0	0.7	3.2	0.0	0.0
%Δ hip BMD/ spine BMD¶	0.2/ −0.7	−2.7/ −2.4	0.1/ −0.7	−2.7/ −2.4	1.3/ −0.8	−3.1/ −2.1	0.3/ −0.6	−2.8/ −2.3	−1.0/ −1.2	−0.9/ −3.9	0.3/ −0.6	−2.7/ −2.3	−0.2/ −1.4	−4.7/ −3.4
Δ eGFR (cys C)#	5.3	2.9	5.0	2.8	8.0	3.5	5.2	3.1	6.1	1.4	4.7	1.9	9.6	10.3

D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; AA, African American; diff, difference; CI, confidence interval; VF, virologic failure; discont, discontinuation; AE, adverse event; BMD, bone mineral density; cys C, cystatin C; VL, viral load; c, copies. *Virologic response was VL <50 c/mL (FDA snapshot). †Overall population: stratum-adjusted Mantel-Haenszel test where stratification factors are HIV-1 RNA level (≤100,000 or >100,000 c/mL) and CD4+ cell count (<200 or ≥200 cells/μL). Subgroups: exact (unconditional) CIs with confidence coefficient of ≥95%. ‡With ≥1 worst grade 3-4 AE. §Bone AE of interest considered related to study drug (bone loss/atrophy). ¶Mean percent change in BMD from baseline to Week 48 (g/cm^2). Bone investigation substudy population (overall): N=113 (D/C/F/TAF) and N=99 (control). #Mean increase in eGFR (serum cystatin C [CKD-EPI formula]) from baseline to Week 48 (mL/min/1.73m^2).

493 DURABILITY OF INITIAL REGIMENS WHEN STARTING ART WITH -200 CD4 AND +5 LOG HIV-RNA

Nicola Gianotti[1], Patrizia Lorenzini[2], Alessandro Cozzi-Lepri[3], Andrea De Luca[4], Giordano Madeddu[5], Laura Sighinolfi[6], Carmela Pinnetti[2], Carmen Santoro[7], Paola Meraviglia[8], Cristina Mussini[9], Andrea Antinori[2], Antonella D'Arminio Monforte[10]

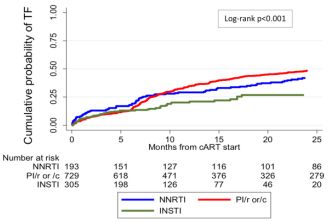
[1]San Raffaele Scientific Institute, Milan, Italy, [2]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, [3]University College London, London, UK, [4]Siena University Hospital, Siena, Italy, [5]University of Sassari, Sassari, Italy, [6]S. Anna Hospital, Ferrara, Italy, [7]University of Bari, Bari, Italy, [8]ASST Fatebenefratelli, Milan, Italy, [9]University of Modena and Reggio Emilia, Modena, Italy, [10]University of Milan, Milan, Italy

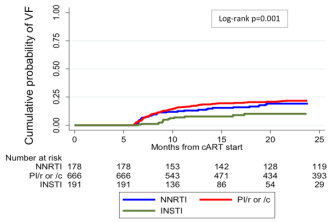
Background: Patients with an active opportunist disease or with -200 CD4+/μL and +5 $\log_{10}$ HIV-RNA copies/mL at antiretroviral therapy (ART) start are largely underrepresented in clinical trials; data from large observational studies may help bridging this knowledge gap. We aimed at studying the durability of different initial ART regimens in these patients.

Methods: All subjects enrolled in the ICONA Study, who started ART with 1 anchor drug (ritonavir or cobicistat-boosted protease inhibitor [bPI], or non-nucleoside reverse transcriptase inhibitor [NNRTI] or integrase strand transfer inhibitor [InSTI]) plus tenofovir(TDF)/emtricitabine(FTC) or abacavir(ABC)/lamivudine(3TC), CD4+ -200 cells/μL and HIV-RNA >5 $\log_{10}$ copies/mL, and at least 1 HIV-RNA assessed both before and after the start of ART, were included in this analysis. Primary endpoint: treatment failure (TF, defined as virological failure [VF, first of 2 consecutive HIV-RNA >50 copies/mL after >6 months of treatment] or discontinuation of class of the anchor drug) as assessed by KaplanMeier method and log-rank test. Independent associations were investigated by Poisson regression analysis, in a model including variables associated with TF at a p-value <.2 at univariate analysis: anchor drug, baseline (BL) HIV-RNA, CDC C stage, HCV co-infection, CD4+, FIB-4, eGRF, ongoing opportunistic disease, nucleos(t)ide backbone.

Results: 1127 patients fulfilled inclusion criteria: 729 started ART with a bPI, 305 with an InSTI and 193 with a NNRTI (95% EFV). Their median (IQR) BL CD4+, CD4+/CD8+, HIV-RNA were 63 (27-125) cells/μL, .11 (.05-.2), 5.55 (5.3-5.87) $\log_{10}$ copies/mL. PYFU were 519, 1533, 264 in the NNRTI, bPI and InSTI group; incidence rates (IRs,95%CI) of TF were 18.1 (14.8-22.2), 29.1 (26.5-31.9), 20.8 (16-27.1) per 100 PYFU and IRs of VF were 5.9 (4.4-8.1), 8.0 (6.9-9.3), 5.2 (3.1-8.7) per 100 PYFU in the NNRTI, bPI and InSTI group. Cumulative probabilities of TF and VF are illustrated in figure. At multivariable analysis, compared to those based on bPIs, regimens based on NNRTIs (IRR .65 [.52-.82]; p less than.001) or InSTIs (.7 [.52-.92];p=.012) were associated with a lower risk of TF; BL HIV-RNA >500K (1.38 [1.17-1.63] compared to less than 500K; p<.001) was associated with a higher risk of TF. The type of regimens was not independently associates with VF.

Conclusion: In patients starting ART with -200 CD4+ and +5 $\log_{10}$ HIV-RNA, the durability of regimens based on EFV or InSTIs was longer than that of boosted PI-based regimens.





494 SAFETY PROFILE OF DOLUTEGRAVIR:REAL-LIFE DATA OF LARGE SCALE IMPLEMENTATION IN BRAZIL

Cynthia Julia B. Batista, Mariana V. Meireles, Fernanda F. Fonseca, Ana R. Pati Pascom, Fernanda Rick, Filipe d. Perini, Robério A. Júnior Carneiro, Karim Sakita, Alexsana S. Tresse, Adele Benzaken

Ministry of Health, Brasilia (DF), Brazil

Background: Since January 2017, Brazil recommends Dolutegravir(DTG) in the first-line regimens for ART-naïve patients. A national online pharmacovigilance system was implemented order to record adverse events (AEs) of the drug. It is well known that only after few years of drug approval AEs, drug interaction and associated risk factors can be thoroughly assessed. In this study we aimed to describe i) the most frequent AEs reported and ii) factors associated with their occurrence in a real-life setting.

Methods: A questionnaire about AEs was filled from the second dispensation of DTG by physicians, ARV dispensers or patients. All information from adults (18+) recorded in the pharmacovigilance system from January to August 2017 were included in the analysis. Data were linked with the laboratory information system, which records data on CD4 and Viral Load (VL) counts. We performed i) a descriptive analysis of the most frequent AE according to groups of systems/major symptoms and ii) univariate and multivariate logistic regression models to assess factors associated with the occurrence of any AE.

Results: We collected information on 26,070 ART-naïve patients, of whom 704 (2.7%) reported 1,016 AEs. The most frequent AEs were gastrointestinal (349, 1.3%), neurological (211, 0.8%), sleep disorders (148, 0.6%), skin disorders (128, 0.5%), mental (40, 0.2%) and systemic symptoms (40, 0.2%) and musculoskeletal (26, 0.1%). Immune reconstitution inflammatory syndrome was reported in only one patient. In the table we present the ORs and aORs of the logistic models. VL was not retained in the multivariate model. Younger (aOR 18-24 1.48 and 1.23 for 25-49, relative to 50+), female patients (aOR 1.30) with CD4 counts below 500 cells/mL (aOR 1.09) were more likely to report adverse events.

Conclusion: Brazil is one of the first countries to implement DTG in a first-line regimen. This study shows data from real life in one of the biggest cohorts using DTG in the world. These data are important for a better understanding of AEs of the drug, and the results of the study demonstrate that DTG is safe and can be used in large scale.

		n	Univariate		Multivariate		
			OR	95% CI	aOR	95% CI	p-value
CD4	**500+**	5763	(ref)		(ref)		0.003
	<500	9400	1.28	(1.05-1.56)	1.09	(0.90-1.33)	
	Unknown	10907	1.35	(1.14-1.61)	0.81	(0.66-0.99)	
Age	**18-24**	5166	1.17	(0.92-1.50)	1.48	(1.12-1.97)	0.019
	25-49	17576	1.37	(1.04-1.80)	1.23	(0.96-1.58)	
	50+	3328	(ref)		(ref)		
Sex	**Men**	20036	(ref)		(ref)		0.003
	Women	6034	1.25	(1.06-1.48)	1.30	(1.09-1.54)	
VL	**<100,000**	9612	(ref)				
	100,000+	4521	1.30	(1.10-1.53)			
	Unknown	11937	1.27	(1.03-1.57)			

495 ARE INTEGRASE INHIBITORS A RISK FACTOR FOR IRIS IN THE ANRS 146 OPTIMAL TRIAL?

Jean-Daniel Lelievre[1], Lambert Assoumou[2], Esther Aznar[3], Federico Pulido[4], Giuseppe Tambussi[5], Manuel Crespo[6], Agnes Meybeck[7], Jean-Michel Molina[8], Fanny Cardon[9], Constance Delaugerre[8], Rémi Lancar[2], Lydie Béniguel[2], Yves Levy[2], **Dominique Costagliola**[2]

[1]University of Paris-Est, Paris, France, [2]INSERM, Paris, France, [3]Fundación SEIMC-GeSIDA, Madrid, Spain, [4]Hospital Universitario 12 de Octubre, Madrid, Spain, [5]Ospedale San Raffaele, Milano, Italy, [6]Vall d'Hebron Research Institute, Barcelona, Spain, [7]Centre Hospitalier de Tourcoing, Tourcoing, France, [8]Hôpital Saint-Louis, Paris, France, [9]France Recherche Nord & Sud Sida-HIV Hépatites, Paris, France

Background: At CROI 2017, two observational studies based on retrospective assessment of IRIS occurring within 6 to 12 months after first antiretroviral treatment (ART) initiation have reported an increased risk of IRIS with integrase inhibitor (II) based regimen. We evaluated this association in the context of the ANRS 146 trial, an European, multicentre, randomized, double-blind, phase III trial, in France, Spain and Italy, in ART-naïve HIV1-infected adults with CD4+ count<200/µL or an ADE, in which IRIS was a component of the composite primary endpoint prospectively validated by an event review committee.

Methods: Participants were randomized (1:1) to receive cART plus placebo or maraviroc for 72 weeks and no significant effect of maraviroc was evidenced on the composite primary endpoint (any new ADE, serious non-AIDS-defining event, IRIS, or death from any cause). IRIS was defined as 2 major criteria (A=atypical presentation of opportunistic infection or tumour in patients responding to ART, B=decrease in plasma HIV RNA >1log/mL) or major criterion A plus 2 minor criteria (increase in CD4 count after starting ART, increase in immune response to the relevant pathogen, spontaneous resolution of the disease without antimicrobial or tumour therapy with ART continuation). We compared the risk of IRIS using Kaplan-Meier estimates and multivariable Cox proportional-hazards models.

Results: Between October 2011 and November 2014, 409 patients were included. At baseline, median HIV viral load (VL) was 5.39 $\log_{10}$ copies/mL, median CD4+ count 80 cells/µL and 42% of participants had an ADE. Sixty-two individuals initiated with II (55 with raltegravir) and 347 did not (PI/r=283, NNRTI=64). No difference was seen in baseline characteristics of individuals (treatment arm, baseline CD4, VL, geographical origin) depending on whether initiating with II or not. Overall, 28 documented IRIS occurred, 26 within the first six months including 6 KS, 5 PCP, 4 folliculitis, 2 CMV, 2 cryptococcal infections. The 72 week rate of IRIS was 9.7% in individuals initiating with II (6) versus 6.5% in those not initiating with II (22), with a crude hazards ratio of 1.52(95%CI:0.61-3.74) and an adjusted one (on treatment arm, origin, baseline CD4 count and VL) of 1.49(95%CI:0.60-3.71).

Conclusion: No strong association was detected between the risk of IRIS and initiating ART with an integrase inhibitor in individuals presenting at an advanced stage in the ANRS Optimal trial, where IRIS was a prospectively validated endpoint.

496 RALTEGRAVIR-BASED ART IS EFFECTIVE AND SAFE IN HIV+ LIVER TRANSPLANT RECIPIENTS

Christian Manzardo[1], Lucia Serrano[2], Jesús Fortún[3], Marino Blanes[4], Montserrat Tuset[1], Miguel Montejo[5], Miguel Jiménez[6], Elisa Cordero[7], Raquel Lastras[8], Esteban Ribera[9], Maria Luisa Gonzalez-Dieguez[10], Asunción Moreno[1], Antoni Rimola[1], Jose M. Miro[1]

[1]Hospital Clinic of Barcelona, Barcelona, Spain, [2]Fundación SEIMC-GeSIDA, Madrid, Spain, [3]Hospital Ramon y Cajal, Madrid, Spain, [4]Hospital Universitario La Fe, Valencia, Spain, [5]Hospital Universitario de Cruces, Barkaldo, Spain, [6]Hospital Regional Carlos Haya, Malaga, Spain, [7]Hospital Universitario Virgen del Rocio, Sevilla, Spain, [8]Hospital Universitario de Bellvitge, Barcelona, Spain, [9]Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, [10]Hospital Universitario Central de Asturias, Oviedo, Spain

Background: Liver transplantation (LT) is safe in selected HIV-infected individuals. However, management of interactions between immunosuppressants (IS) and some antiretroviral families (especially protease inhibitors [PI] and non-nucleoside reverse transcriptase inhibitors [NNRTI]) remains a challenge. Raltegravir (RAL) is a non-boosted integrase inhibitor that did not interact with IS in a small trial in HIV-infected transplant recipients (Tricot, Am J Transplant 2009). Nevertheless, clinical experience in this setting is limited. The aim of this study was to analyze the efficacy and safety of RAL plus 2 nucleos(t)ide analogs (NUCs) vs. other antiretroviral therapy (ART) regimens in LT HIV-infected recipients.

Methods: We performed a nationwide, multicenter cohort study, including 272 consecutive patients who underwent LT from 2002 to 2012 and were followed until December 2016. For the efficacy analysis, the study population comprised 211 patients who had started any of 4 post-LT ART regimens (table) and had completed at least 1 year of follow-up. For the safety analysis, we included 246 patients who died or underwent retransplantation (reLT) during the first year.

Results: Patients receiving the 4 ART regimens (table) had comparable baseline donor and recipient characteristics (data not shown). In terms of virological suppression, no differences were found between the 4 ART regimens at 1 year after LT. However, a trend towards better CD4+ T-cell count recovery at 48 weeks was observed in the RAL group (table). As for safety, the survival analysis did not reveal any differences in mortality and/or reLT rates after 1 year between the 4 ART groups (p=.204 at 1 year for the combined endpoint by the log-rank test). Nevertheless, patients receiving RAL+2 NUCs had a significantly lower cumulative probability of experiencing acute graft rejection during the first 6 months after LT (12% [95%CI 3-21%] for RAL-based ART vs. 28% [95%CI 22-35%] for the other combined ART regimens; p=.021 [log-rank]).

Conclusion: A post-LT ART regimen based on RAL+2 NUCs was as virologically effective as other ART regimens (PI, NNRTI) at 48 weeks. In addition, the regimen showed a trend towards better immune reconstitution and was associated with significantly lower rates of acute rejection. One-year mortality and reLT were similar between the 4 ART regimens. Whenever possible, RAL+2 NUCs should be the preferred ART regimen for HIV-infected individuals undergoing LT.

Table. Efficacy at 48 weeks by antiretroviral treatment (ART) combination (N=211)

		2 NUCs+RAL (n=40)	PI-based ART (n=59)	2 NUCs+EFV (n=85)	Other ART (n=27)	P-value
Plasma HIV-RNA level <200 copies/mL after LT, %	12 weeks	100.0	93.8	91.8	92.0	0.415
	24 weeks	100.0	98.0	97.3	92.3	0.329
	48 weeks	97.3	96.2	98.7	92.0	0.406
CD4 T-cell count (cells/µL) at 48 weeks	Median (IQR)	355 (221;522)	212 (165;303)	292 (200;445)	265 (165;334)	**0.014**
	Median (IQR) increase from baseline	102 (–42 ;192)	7.0 (–43;133)	5.0 (–98;141)	86.0 (–43;116)	0.174
	> 200 (%)	76.3	54.9	74.0	61.9	0.076
	> 350 (%)	52.6	19.6	35.1	23.8	**0.009**

NUCs = nucleos(t)ide analogs; RAL = raltegravir; PI = protease inhibitor; EFV = efavirenz; LT = liver transplant; IQR = interquartile range.

497 INSTI-BASED INITIAL ART IN A US COHORT OF HIV-INFECTED ADULTS

Stockton Mayer[1], Nabil Rayeed[2], Rachel Hart[2], Richard Novak[1], Bienvenido Yangco[3], Frank J. Palella[4], Benjamin Young[5], Kate Buchacz[6]

[1]University of Illinois at Chicago, Chicago, IL, USA, [2]Cerner Corp, Kansas City, MO, USA, [3]Infectious Disease Research Institute, Tampa, FL, USA, [4]Northwestern University, Chicago, IL, USA, [5]APEX Family Medicine, Denver, CO, USA, [6]CDC, Atlanta, GA, USA

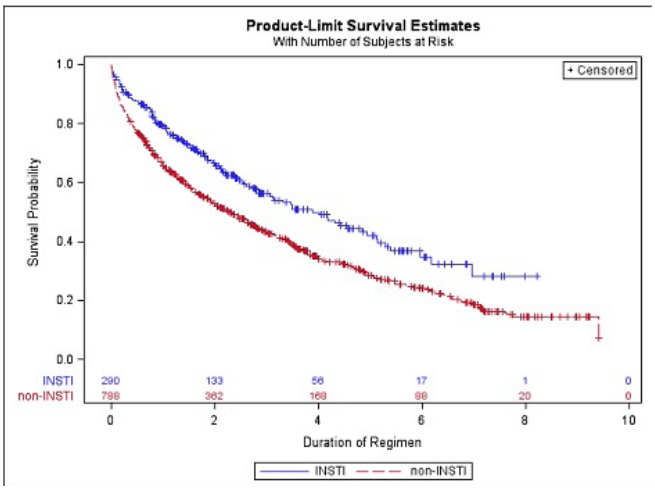
Background: The duration of antiretroviral (ART) regimens is important to HIV management. We compared duration of integrase strand transfer inhibitor (INSTI)-based ART regimens versus other contemporary regimens among adults in routine HIV care.

Methods: We analyzed data records of HIV Outpatient Study (HOPS) cohort participants seen at ten United States (U.S.) HIV clinics during January 1, 2007 to June 30, 2016. We studied patients who initiated ART (baseline date) and had ≥2 HOPS clinic visits thereafter. We assessed the probability of remaining on a regimen (i.e., no drug additions or substitutions other than nucleoside reverse transcriptase inhibitors) and rates of achieving virologic suppression (HIV RNA < 200 copies/ml) on initial INSTI versus non-INSTI regimens by performing Kaplan Meier survival and Cox proportional hazards regression analyses.

Results: Among 1,140 eligible patients, 290 were prescribed an INSTI regimen (163 raltegravir, 84 elvitegravir, 43 dolutegravir) and 850 were prescribed non-INSTI regimen. In both groups, most patients were male (76% INSTI, 79% non-INSTI), non-white (59% INSTI, 64% non-INSTI), and under 50 years old (85% INSTI vs. 86% non-INSTI). For the INSTI and non-INSTI groups, respectively, median baseline viral load (VL, copies/ml) was 36,120 (interquartile range [IQR], 11065, 139196) vs. 33,635 (IQR 7448, 127229) and median CD4 + cell count (CD4, cells/mm^3) was 335 vs. 305. In Kaplan-Meier analysis, the estimated probabilities of remaining on initial regimens at 2 and 4 years were 60% and 55% for INSTI and 50% and 40% for non-INSTI regimens, respectively (overall Log rank test p = 100,000: HR 0.6; CI 0.4,0.9). INSTI regimens were also associated with higher rates of achieving viral suppression (HR 1.5; CI 1.3, 1.8), irrespective of baseline VL (100,000: HR 2.0; CI 1.5, 2.6).

Conclusion: In our cohort of patients in HIV care, initial INSTI-based ART regimens had longer durations than non-INSTI regimens. They were also associated with improved rates of virologic suppression. Results support the use of INSTI regimens as the initial therapy in U.S. treatment guidelines.

First Line INSTI vs non-INSTI: KM depicting duration of first-line ART regimen initiated between January 1, 2007 and June 30, 2016 by ART type (N=1078)



498 IMPACT OF PREVIOUS M184V ON VIROLOGICAL OUTCOME OF SWITCH TO 3TC-BASED DUAL THERAPIES

Roberta Gagliardini[1], Arturo Ciccullo[1], Alberto Borghetti[1], Franco Maggiolo[2], Dario Bartolozzi[3], Vanni Borghi[4], Monica Pecorari[4], Antonio Di Biagio[5], Anna Paola Callegaro[2], Bianca Bruzzone[5], Francesco Saladini[6], Stefania Paolucci[7], Lara Bellazzi[7], Simona Di Giambenedetto[1], Andrea De Luca[8]

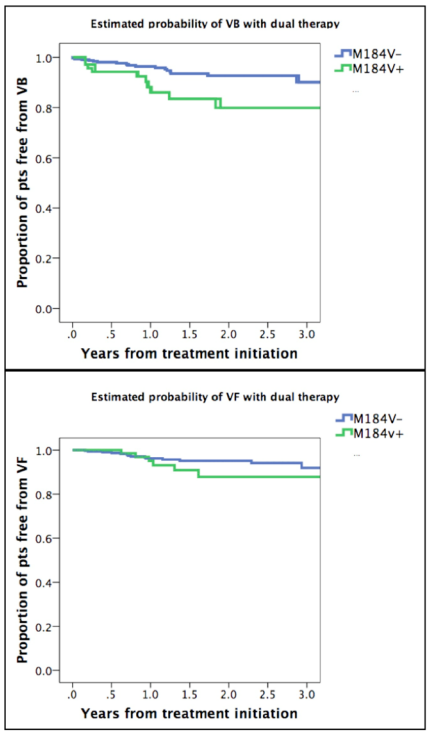
[1]Catholic University of the Sacred Heart, Rome, Italy, [2]Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy, [3]Azienda Ospedaliero– Universitaria Careggi, Firenze, Italy, [4]University of Modena and Reggio Emilia, Modena, Italy, [5]IRCCS AOU San Martino-IST, Genoa, Italy, [6]University of Siena, Siena, Italy, [7]IRCCS Policlinico San Matteo Foundation, Pavia, Italy, [8]Siena University Hospital, Siena, Italy

Background: A randomized study showed higher efficacy of maintenance dual therapy (DT) with protease inhibitors(PI)/ritonavir(r) + 3TC despite the presence of M184V. Aim of this study was to compare virological efficacy of DT in pts with a history of M184V detection (M184V+) and without (M184V-).

Methods: We retrospectively analyzed HIV+ pts with HIV-RNA50 copies/ml switching to DT and with at least one previous genotype in the Italian ARCA database. Pts were followed from baseline (BL, starting of DT) until discontinuation or virological failure (VF). The primary endpoints were: VF [viral load (VL)>50 cps/mL in 2 consecutive determinations or one 200 cps/mL] and virological blips (VB) (VL 51-199 cp/mL not confirmed). M184V was assessed in the historical genotypic resistance tests (hGRT).

Results: 436 pts were included, 45(10%) switched to 3TC with lopinavir/r, 106(24%) with atazanavir/r, 155 (36%) with darunavir/r, 126(29%) with dolutegravir,4(1%) with raltegravir. 87/436 pts were M184V+ according to hGRT, 85/436 according to last GRT. The M184V+ group more frequently included females, IDU, had older age, lower CD4+ at nadir, longer duration of ART and of viral suppression. Median follow-up was 1.2 years (ys) (IQR 0.6;2.4). VF occurred in 17/369 M184V- pts and in 7/87 M184V+ pts. The 3-year probability of remaining free from VF was 91.9% (95% CI 86.6;97.2) in M184V- and 87.8% (78.4;97.2) in M184V+ (log rank p=0.323). In a multivariate model adjusting for M184V, class of 2nd drug and duration of viral suppression only zenith VL (aHR 2.07 per 1-log higher, p=0.034) was independently associated with VF. In pts without VF, VB occurred in 18/332 (5%) M184V- and 10/80 (13%) M184V+ pts. The 3-y probability of not having VB was 90.1% (84;96.2) in M184V- and 79.8% (67.8;91.8) in M184V+ (p=0.016). At multivariate analysis, only M184V resulted to be predictor of VB (aHR 2.84, p=0.040). Similar results were found with different definitions of VF and VB. Selecting pts with viral suppression 6.6ys (median of M184V+ group) (n=308), the 3-y probability of remaining free from VF was 92.5% in M184V- and 82.9% in M184V+ (p=0.080): zenith VL was the only predictor of VF; VB were 13/239 and 8/37, respectively, and the probability of remaining free of VB was 91.1% - and 69.4% (p<0.001).

Conclusion: M184V did not seem to be associated to higher risk of VF with 3TC+PI/r or DTG, but with a higher probability of VB. The shorter time of viral suppression appears to increase the risk of VF and of VB in those with M184V.



499 HIV TREATMENT EXPERIENCED PATIENTS SWITCHED TO D/C/F/TAF: AGE, GENDER, RACE ANALYSES

Gregory D. Huhn[1], Edwin DeJesus[2], Pierre-Marie Girard[3], Romana Petrovic[4], Eric Y. Wong[5], Kimberley Brown[5]

[1]Ruth M. Rothstein CORE Center, Chicago, IL, USA, [2]Orlando Immunology Center, Orlando, FL, USA, [3]University Pierre & Marie Curie, Paris, France, [4]Janssen, Beerse, Belgium, [5]Janssen Scientific Affairs, LLC, Titusville, NJ, USA

Background: Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) is the only darunavir and F/TAF-containing single-tablet regimen in development for the treatment of patients with HIV-1 infection. EMERALD evaluated the efficacy and safety of switching to D/C/F/TAF 800/150/200/10 mg versus continuing use of a boosted protease inhibitor+emtricitabine/tenofovir disoproxil fumarate (control). We report Week 48 results in subgroups based on age, gender, and race.

Methods: EMERALD is a phase 3, randomized (2:1), non-inferiority trial of treatment experienced, virologically suppressed HIV-1–infected adults (viral load [VL] <50 copies [c]/mL for ≥2 months; 1 VL ≥50 and <200 c/mL allowed in 12 months before screening; previous non-darunavir virologic failure [VF] allowed). The primary endpoint was proportion of patients with virologic rebound (confirmed VL ≥50 c/mL or premature discontinuation with last VL ≥50 c/mL) cumulative through Week 48. Virologic response was defined as VL <50 c/mL (FDA snapshot). Safety was assessed by adverse events (AEs) and changes in bone mineral density and eGFR from baseline to Week 48. Results were evaluated in subgroups by age (≤50 vs >50 y), gender, and race (non-black/African American [AA] vs black/AA).

Results: Of the 1141 patients randomized and treated, 382 (33.5%) were >50 y, 205 (18.0%) women, and 237 (20.8%) black/AA. Overall, virologic rebound rates were similar in the D/C/F/TAF and control arms (2.5% vs 2.1%); results were consistent across age, gender, and race subgroups (Table). Virologic response rates were similar for D/C/F/TAF (94.9%) and control (93.7%) in the total population and consistent across subgroups. No resistance to study drugs was observed. Overall rates of adverse events (AEs) and discontinuations due to an AE were generally similar for D/C/F/TAF and control, with no significant differences across subgroups. Consistent with the total population, improved bone safety (bone loss/atrophy AEs related to study drug; bone mineral density) and renal function (eGFR [serum cystatin C]) were seen with D/C/F/TAF versus control across subgroups.

Conclusion: In HIV-1–infected adults, switching to D/C/F/TAF led to low rates of cumulative virologic rebound over 48 weeks that was overall non-inferior to continuation of prior antiretroviral therapy. Low rebound rates, as well as improved bone safety and renal function, were observed with D/C/F/TAF versus control regardless of age, gender, or race.

Table. Summary of Efficacy and Safety in EMERALD Week 48 Subgroup Analyses by Age, Gender, and Race (Intention-to-Treat)

	Overall population		Age				Gender				Race			
			≤50 y		>50 y		Men		Women		Non-black/AA		Black/AA	
Parameter	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control
N	763	378	507	252	256	126	623	313	140	65	597	293	155	82
Efficacy, %														
Rebound*	2.5	2.1	2.6	2.8	2.3	0.8	2.2	2.2	3.6	1.5	2.2	2.4	3.9	1.2
Diff (95% CI)†	0.4 (–1.5, 2.2)		–0.2 (–3.3, 2.1)		1.6 (–2.3, 4.4)		0.0 (–2.5, 2.0)		2.0 (–5.1, 7.0)		–0.2 (–2.9, 1.8)		2.7 (–3.2, 7.3)	
Response‡	94.9	93.7	95.5	93.7	93.8	93.7	95.2	93.6	93.6	93.8	95.6	92.8	92.3	96.3
VF	0.8	0.5	1.0	0.8	0.4	0.0	0.6	0.6	1.4	0.0	0.7	0.7	1.3	0.0
Safety, %														
Discont due to AE	1.4	1.3	1.2	0.4	2.0	3.2	1.6	1.6	0.7	0.0	1.3	1.7	1.9	0.0
Grade 3-4 AE§	6.8	8.2	6.3	7.9	7.8	8.7	6.7	8.3	7.1	7.7	7.5	8.9	3.9	6.1
Serious AE	4.6	4.8	3.9	3.6	5.9	7.1	5.0	4.5	2.9	6.2	5.2	4.4	2.6	6.1
Bone loss/atrophy (related)¶	0.7	2.6	0.6	2.4	0.8	3.2	0.6	2.9	0.7	1.5	0.8	3.1	0.0	1.2
%Δ hip BMD/ spine BMD#	1.4/ 1.5	–0.3/ –0.6	1.4/ 1.3	–0.2/ 0.0	1.5/ 2.0	–0.5/ –1.8	1.5/ 1.5	–0.3/ –0.6	1.0/ 1.4	–0.2/ –0.9	1.5/ 1.5	–0.2/ –0.7	1.1/ 1.6	–0.4/ –0.9
Δ eGFR (cys C)**	–0.4	–1.9	–0.6	–1.7	0.1	–2.3	–0.4	–2.0	–0.2	–1.2	–0.4	–2.0	–0.5	–1.5

D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; AA, African American; diff, difference; CI, confidence interval; VF, virologic failure; discont, discontinuation; AE, adverse event; AEOI, adverse event of interest; BMD, bone mineral density; cys C, cystatin C; VL, viral load; c, copies; ATV, atazanavir; rtv, ritonavir; LPV, lopinavir. *Virologic rebound was confirmed VL ≥50 c/mL or premature discontinuation with last VL ≥50 c/mL (cumulative through Week 48). †Overall population: Mantel-Haenszel test adjusted for boosted protease inhibitor at screening (ATV with rtv or COBI, DRV with rtv or COBI, LPV with rtv). Subgroups: exact (unconditional) CIs with confidence coefficient of ≥95%. ‡Virologic response was VL <50 c/mL (FDA snapshot). §With ≥1 worst grade 3-4 AE. ¶Bone AE of interest considered related to study drug (bone loss/atrophy). #Mean percent change in BMD from baseline to Week 48 (g/cm^2). Bone investigation substudy population (overall): N=209 (D/C/F/TAF) and N=108 (control). **Mean change in eGFR (serum cystatin C [CKD-EPI formula]) from baseline to Week 48 (mL/min/1.73m^2).

500 SWITCHING TO BICTEGRAVIR/EMTRACITABINE/TENOFOVIR ALAFENIMIDE (B/F/TAF) IN WOMEN

Cissy Kityo[1], Debbie Hagins[2], Ellen Koenig[3], Anchalee Avihingsanon[4], Ploenchan Chetchotisakd[5], Khuanchai Supparatpinyo[6], Natalya Gankina[7], Vadim Pokrovsky[8], Evgenly Voronin[9], Jeffrey L. Stephens[10], Edwin DeJesus[11], Hui Wang[12], Erin Quirk[12], Hal Martin[12], Tariro Makadzange[12]

[1]Joint Clinical Research Centre, Kampala, Uganda, [2]Chatham CARE Center, Savannah, GA, USA, [3]Instituto Dominicano de Estudios Virológicos, Santo Domingo, Dominican Republic, [4]Thai Red Cross AIDS Research Center, Bangkok, Thailand, [5]Srinagarind Hospital, Khon Kaen, Thailand, [6]Chiang Mai University, Chiang Mai, Thailand, [7]Krasnoyarsk Territorial Center for Prevention and Control of AIDS and Infectious Diseases, Krasnoyarsk, Russian Federation, [8]Center for Prevention and Control of AIDS, Moscow, Russian Federation, [9]Ministry of Health, Saint-Petersburg, Russian Federation, [10]Mercer University, Macon, GA, USA, [11]Orlando Immunology Center, Orlando, FL, USA, [12]Gilead Sciences, Inc, Foster City, CA, USA

Background: The unboosted integrase inhibitor containing single-tablet regimen (bictegravir/emtricitabine/tenofovir alafenamide, B/F/TAF) has shown efficacy and safety in HIV-1 infected patients. Bictegravir is a novel, unboosted INSTI that has been coformulated with F/TAF in an STR that has shown high rates of suppression with no resistance in phase 3 studies of treatment naïve patients. We now report Week 24 (W24) safety and efficacy of switching to B/F/TAF versus staying on baseline regimen (SBR) [elvitegravir (E)/cobicistat (C)/F/TAF, E/C/F/tenofovir disoproxil fumarate (TDF) or atazanavir (ATV)+ritonavir (RTV)+F/TDF] in an all-women, international multi-centre, randomized, open-label, phase 3 trial.

Methods: HIV-1 infected, virologically suppressed women on a protease inhibitor or boosted elvitegravir-containing regimen were randomized (1:1) to switch to B/F/TAF or stay on baseline regimen (SBR). The primary efficacy endpoint was the proportion of women with HIV1 RNA >50 copies (c)/mL at W48 with 4% noninferiority margin (FDA snapshot). A secondary efficacy endpoint of HIV-1 RNA <50 c/mL at W24 is reported here. Other secondary endpoints include safety (adverse events (AEs), laboratory abnormalities). This interim W24 efficacy and safety analysis was pre-specified.

Results: We randomized and treated 470 women (234 B/F/TAF, 236 SBR (E/C/F/TAF n=125; E/C/F/TDF n=98; ATV+RTV+FTC/TDF n=13). Demographic and baseline characteristics were balanced; overall 37% black, 28.3% white, 21.7% Asian, median age was 39 years and CD4 count was 686 cells/µl. At W24 98.7% in the B/F/TAF group vs. 99.2% in the SBR group achieved HIV-1 RNA <50 c/mL (difference -0.4% (95%CI: 3.0% to 1.9%, p=0.68). Two participants, one in each group, had resistance testing; neither developed resistance to any study drug. No participant discontinued treatment due to an AE; there were no differences between groups in grade 3 or 4 treatment-emergent AEs (3.8% B/F/TAF, 5.5% SBR group). Grade 3 or 4 laboratory abnormalities occurred in 17% of participants on B/F/TAF and 18% on SBR.

Conclusion: At W24 women who switched to B/F/TAF maintained high levels of virologic suppression with comparable efficacy to those who remained on a baseline regimen. B/F/TAF was safe and well tolerated. This analysis supports the efficacy and safety of B/F/TAF in women observed in other B/F/TAF phase 2 and 3 studies.

501 EFFECT OF SWITCHING TO INTEGRASE INHIBITOR ON THE HIV RESERVOIR IN ILEUM BIOPSIES

Sara Moron-Lopez[1], Victor Urrea[1], Jordi Navarro[2], Maria C. Puertas[1], Ariadna Torrella[2], Maria Salgado[1], Cristina Gálvez[1], Bibiana Planas[2], Linos Vandekerckhove[3], Julià Blanco[1], Manuel Crespo[2], Javier Martinez-Picado[1]

[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [2]Vall d'Hebron Research Institute, Barcelona, Spain, [3]HIV Cure Research Center, Ghent University, Ghent, Belgium

Background: Antiretroviral therapy optimization, including switching towards newer drugs, is a potential strategy to impact the HIV reservoir. A previous study suggested that switching to raltegravir might be associated with a decrease in total HIV-1 reservoir in blood after 48 weeks. However, the effect of integrase inhibitors on the HIV reservoir in tissues remains unknown. Thus, we evaluated the effect of switching from PI to dolutegravir (DTG) in cART on the HIV reservoir size in blood and ileum biopsies.

Methods: INDOOR study (EUDRACT 2014-004331-39), a phase IV and opened clinical trial, randomly included 44 HIV-1 infected individuals on effective cART: 22 switched from PI to DTG based-cART (switch group), and 22 remained in PI-based regimens (control group). We collected four to eight endoscopic ileum biopsies and blood samples at weeks 0 and 24 from 33 subjects: 13 from the switch group and 20 from the control group. We performed a DTT/EDTA-based treatment for epithelial layer removal followed by disruption of the tissue in absence of an enzymatic method to obtain an LPL cell suspension. CD45+ cells were subsequently purified by flow sorting. Total HIV DNA was determined by ddPCR in total peripheral blood mononuclear cells (PBMC) and in sorted leukocytes (CD45+ cells) from ileum biopsies. Statistical analyses were performed using R software and GraphPad.

Results: This switching strategy was safe and well tolerated for all the patients, with no changes in viremia suppression (<50 cp/ml). Two patients, one from each arm, did not finish the study protocol. One patient with prior psychiatric history suffered a psychotic attack and the second one was lost to follow-up at the last visit; however, his last viral load was undetectable. We positively detected total HIV DNA in all samples, and a significant correlation of the HIV reservoir size was observed between tissue and blood samples (p=0.01, Rho=0.43 at week 0). Moreover, the reservoir size was consistently higher in tissue CD45+ cells than in PBMC in both groups (p<0.01). However, we did not observe significant longitudinal changes in the total HIV reservoir size, either in CD45+ cells of ileum biopsies or in PBMC, in any study group.

Conclusion: The INDOOR study evaluated for the first time changes in the HIV reservoir size in ileum biopsies in individuals switched from PI- to DTG-based cART. This treatment switch was safe and well tolerated, but had no impact on the HIV reservoir size, measured as total HIV DNA, in CD45+ cells of ileum.

502 ANALYSIS OF HIV PATIENTS SWITCHING TO D/C/F/TAF BY PRIOR ARV TREATMENT EXPERIENCE

Joseph J. Eron[1], Chloe Orkin[2], Jean-Michel Molina[3], Erika Van Landuyt[4], Erkki Lathouwers[4], Romana Petrovic[4], Richard E. Nettles[5], Kimberley Brown[5]

[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]Royal London Hospital, London, UK, [3]St. Louis Hospital, Paris, France, [4]Janssen, Beerse, Belgium, [5]Janssen Scientific Affairs, LLC, Titusville, NJ, USA

Background: HIV-1–infected patients enrolled in switch studies may not be representative of switch patients in clinical practice due to strict inclusion/exclusion criteria. EMERALD allowed entry of patients with previous virologic failure (VF) or experience with multiple antiretrovirals (ARVs); we report Week 48 results by ARV treatment experience.

Methods: EMERALD was a phase 3, randomized (2:1), non-inferiority trial that evaluated the efficacy and safety of switching to the single-tablet regimen darunavir/cobicistat/emtricitabine/ tenofovir alafenamide (D/C/F/TAF; 800/150/200/10mg), or continuing use of a boosted protease inhibitor+F/tenofovir disoproxil fumarate (control), in virologically suppressed, HIV-1–infected adults. Patients had viral load (VL) <50 copies(c)/mL for ≥2 months (1 VL ≥50 and <200 c/mL allowed in 12 months before screening) and, if available, absence of historical darunavir resistance mutations. Those with previous non-darunavir VF and prior experience with multiple ARVs were allowed. The primary endpoint was proportion of patients with virologic rebound (confirmed

VL ≥50 c/mL or premature discontinuation with last VL ≥50 c/mL) cumulative through Week 48. Secondary endpoints included virologic response and VF by FDA snapshot (50 c/mL threshold). Results were evaluated by prior VF and number of ARVs previously used.

Results: In total, 1141 patients were randomized and treated; 14.8% (N=169) had prior VF, including 7.0% (N=80) of all patients with PI VF, 11.4% (N=130) with NRTI VF, and 6.5% (N=74) with NNRTI VF, and 27.3% (N=312) had used >7 ARVs. Overall rebound rates were 2.5% for D/C/F/TAF and 2.1% for control. Response rates were 94.9% and 93.7%, respectively. No resistance associated with any study drug was observed post-baseline. In patients with ≥1 prior VF, rebound rates were 2.6% for D/C/F/TAF and 0% for control (Table); response rates were 95.7% (D/C/F/TAF) and 92.5% (control), and VF rates were 1.7% and 0%, respectively. Overall, patients in the D/C/F/TAF and control arms had low and similar rates of discontinuation due to an adverse event (AE; 1.4% vs 1.3%), grade 3-4 AEs (6.8% vs 8.2%), and serious AEs (4.6% vs 4.8%). Virologic response rates were high and safety results were consistent across subgroups by ARV treatment experience.

Conclusion: Virologically suppressed, HIV-1–infected adults, including those with prior VF and experience with numerous ARVs, who switched to D/C/F/TAF had low cumulative virologic rebound and high virologic response rates over 48 weeks.

Table. Summary of Efficacy in EMERALD Week 48 Subgroup Analyses by Prior Treatment Experience (Intention-to-Treat)*

		N	Time since dx, y†	Rebound, n (%) [95% CI]‡	Diff, % (95% CI)§	Response, % [95% CI]¶	VF, n (%)¶
Total population							
D/C/F/TAF		763	9.3	19 (2.5) [1.5; 3.9]	0.4 (–1.5; 2.2)	94.9 [93.1; 96.3]	6 (0.8)
Cntrl		378	8.9	8 (2.1) [0.9; 4.1]		93.7 [90.7; 95.9]	2 (0.5)
Prior VF							
0	D/C/F/TAF	647	7.8	16 (2.5) [1.4; 4.0]	0.0 (–2.6; 2.0)	94.7 [92.7; 96.3]	4 (0.6)
	Cntrl	325	7.5	8 (2.5) [1.1; 4.8]		93.8 [90.7; 96.2]	2 (0.6)
≥1	D/C/F/TAF	116	18.0	3 (2.6) [0.5; 7.4]	2.6 (–4.8; 7.5)	95.7 [90.2; 98.6]	2 (1.7)
	Cntrl	53	18.1	0		92.5 [81.8; 97.9]	0
Number of ARVs previously used#							
4	D/C/F/TAF	316	4.5	7 (2.2) [0.9; 4.5]	0.3 (–3.4; 3.1)	95.9 [93.1; 97.8]	2 (0.6)
	Cntrl	160	4.4	3 (1.9) [0.4; 5.4]		96.3 [92.0; 98.6]	1 (0.6)
5	D/C/F/TAF	98	7.6	2 (2.0) [0.2; 7.2]	0.3 (–7.8; 5.9)	94.9 [88.5; 98.3]	0
	Cntrl	56	7.2	1 (1.8) [0.0; 9.6]		89.3 [78.1; 96.0]	1 (1.8)
6	D/C/F/TAF	69	9.0	5 (7.2) [2.4; 16.1]	3.9 (–11.0; 13.7)	92.8 [83.9; 97.6]	2 (2.9)
	Cntrl	30	9.0	1 (3.3) [0.1; 17.2]		96.7 [82.8; 99.9]	0
7	D/C/F/TAF	69	16.2	0	–3.3 (–17.5; 2.7)	95.7 [87.8; 99.1]	0
	Cntrl	30	15.4	1 (3.3) [0.1; 17.2]		90.0 [73.5; 97.9]	0
>7	D/C/F/TAF	211	19.8	5 (2.4) [0.8; 5.4]	0.4 (–5.0; 3.9)	93.8 [89.7; 96.7]	2 (0.9)
	Cntrl	101	19.0	2 (2.0) [0.2; 7.0]		92.1 [85.0; 96.5]	0

Dx, diagnosis; CI, confidence interval; diff, difference; VF, virologic failure; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; cntrl, control; ARVs, antiretrovirals; c, copies; VL, viral load; ATV, atazanavir; rtv, ritonavir; LPV, lopinavir. *Efficacy data for patients with no VL data in Week 48 window not reported. †Median time since HIV-1 diagnosis. ‡Virologic rebound was confirmed VL ≥50 c/mL or premature discontinuation with last VL ≥50 c/mL (cumulative through Week 48). §Difference in virologic rebound rate. Overall population: Mantel-Haenszel test adjusted for boosted PI at screening (ATV with rtv or COBI, DRV with rtv or COBI, LPV with rtv). Subgroups: exact (unconditional) CIs with confidence coefficient of ≥95%. ¶Virologic response and VF by FDA snapshot (50 c/mL threshold). #Includes ARVs used at screening. Data not reported for 1 patient who had 3 ARVs previously used.

503 WHO WANTS TO SWITCH? GAUGING INTEREST IN POTENTIAL NEW ANTIRETROVIRAL THERAPIES

Jan Ostermann[1], Caroline Derrick[1], Amy Hobbie[2], Andrew Weinhold[2], Noor Al-Shareef[1], Valerie Yelverton[3], Sharon Weissman[1], Helmut Albrecht[1], **Nathan Thielman**[2]

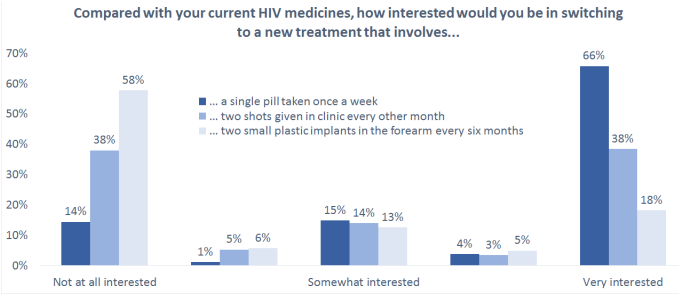
[1]University of South Carolina at Columbia, Columbia, SC, USA, [2]Duke University, Durham, NC, USA, [3]Hochschule Neubrandenburg University of Applied Sciences, Neubrandenburg, Germany

Background: Despite increased numbers of easily tolerated and highly effective antiretroviral regimens, adherence rates for many populations remain suboptimal. Novel drug delivery systems and drugs with extended half-lives may allow for dramatically reduced dosing frequency of specific antiretroviral regimens. To explore initial interest in such regimens, we gathered detailed treatment history and antiretroviral preference information from 263 treatment experienced patients.

Methods: Between February and August 2017, a convenience sample of 263 HIV-infected patients from Infectious Diseases clinics at Duke University and the University of South Carolina were surveyed about HIV treatment experiences and attitudes. Participants were asked about characteristics of their current regimen as well as their interest, on 5-point scales (1=not at all interested; 5=very interested), in switching to either a single pill once a week, two shots in clinic every other month, or implanting and removing two small plastic rods about the size of matchsticks in each forearm every six months. Multivariate linear regression methods identified correlates of patients' interest in switching to these alternatives from their current regimen.

Results: Survey participants were highly experienced (mean 14.3 years on therapy), predominantly minority (80.5%), with a mean age of 46.7 years, and 41.4% had received more than high-school education. In multivariate analysis, clinic, gender, race/ethnicity, time on treatment, taking more than 1 pill a day, and administration restrictions, were not associated with interest in switching to novel regimens. Those who had previously switched regimens expressed greater interest in switching to a single pill once a week (p=.03); higher education was associated with greater interest in switching to injection and implants (p<.01), and younger age was associated with greater interest in switching to injection (p=.02).

Conclusion: Across a highly treatment-experienced cohort of HIV-infected patients, we describe greatest interest in switching to an oral regimen taken once weekly, followed by injections taken every other month. Those with higher education expressed greater interest in novel drug delivery systems and younger patients were more interested in injections. Having taken more prior regimens was associated with greater interest in a weekly oral pill. Understanding drivers of preference heterogeneity for new treatment modalities may help to inform their development and predict uptake.



504 SWITCHING TO RPV/FTC/TAF FROM RPV/FTC/TDF OR EFV/FTC/TDF: WEEK 96 RESULTS

Anthony Mills[1], Cynthia Brinson[2], Claudia Martorell[3], Gordon Crofoot[4], Eric Daar[5], Olayemi Osiyemi[6], Bruce Rashbaum[7], David Shamblaw[8], Hans-Jurgen Stellbrink[9], Daniel Podzamczer[10], Hui Liu[11], Ya-Pei Liu[11], Danielle Porter[11], Sean Collins[11], Devi SenGupta[11]

[1]Southern California Men's Medical Group, Los Angeles, CA, USA, [2]Central Texas Clinical Research, Austin, TX, USA, [3]Infectious Disease and The Research Institute, Springfield, MA, USA, [4]Crofoot Research Center, Houston, TX, USA, [5]Harbor–UCLA Medical Center, Torrance, CA, USA, [6]Triple O Research Institute, West Palm Beach, FL, USA, [7]Capital Medical Associates, Washington, DC, USA, [8]La Playa Medical Group, San Diego, CA, USA, [9]ICH Study Center, Hamburg, Germany, [10]Bellvitge University Hospital, Barcelona, Spain, [11]Gilead Sciences, Inc, Foster City, CA, USA

Background: Tenofovir alafenamide (TAF) is a novel tenofovir prodrug with reduced risk of bone and renal toxicities compared to tenofovir disoproxil fumarate (TDF). TAF (25 mg) is coformulated with emtricitabine (FTC, 200 mg) and rilpivirine (RPV, 25 mg). The impact of switching to RPV/FTC/TAF single tablet regimen (STR) from other NNRTI-containing STRs RPV/FTC/TDF or efavirenz (EFV)/FTC/TDF was evaluated in two Phase 3 clinical trials. Final efficacy and safety results from Week 96 are presented.

Methods: We conducted two randomized, double-blind, active controlled, 96 week, Phase 3 clinical studies in virologically suppressed (HIV-1 RNA <50 c/mL), HIV-1-infected adults with estimated glomerular filtration rate > 50 mL/min, taking either RPV/FTC/TDF (Study 1216) or EFV/FTC/TDF (Study 1160) for at least 6 months. The secondary virologic efficacy (HIV-1 RNA <50 c/mL) endpoint

was at Week 96 using the FDA snapshot algorithm with a pre-specified non-inferiority margin of 8%. Bone mineral density (BMD) was measured by DXA and percentage change from baseline compared between treatment groups using ANOVA. Percentage changes from baseline in renal markers were compared between treatment groups using Wilcoxan rank sum test. Adverse events and tolerability were evaluated.

Results: A total of 630 participants were randomized and treated in Study 1216 and 875 in Study 1160. In Studies 1216 and 1160 the median ages were 45 and 49 years, 10% and 13% women, 19% and 27% black respectively. In both studies, switching to RPV/FTC/TAF was non-inferior to continuing baseline therapy through week 96. Study 1216: 89% vs 88% (difference: 0.7%; 95% CI -4.3 to +5.8); Study 1160: 85% vs. 85% (difference 0%; 95% CI -4.8 to +4.8). No participant on RPV/FTC/TAF had treatment emergent resistance versus two on EFV/FTC/TDF and one on RPV/FTC/TDF who was found to have pre-existing NRTI and NNRTI resistance at baseline. Significant increases from baseline in hip and spine BMD and improvements in renal tubular markers were observed in the RPV/FTC/TAF groups compared to continued therapy ($p < 0.001$, Table 1). Fanconi syndrome occurred in one subject on EFV/FTC/TDF, no renal tubulopathy cases occurred on RPV/FTC/TAF.

Conclusion: Switching to RPV/FTC/TAF was safe and maintained high rates of viral suppression through 96 weeks with no cases of treatment emergent resistance. Switching patients to RPV/FTC/TAF is an effective option with improved safety in long-term follow-up.

Table 1: Virologic efficacy, bone and renal safety at week 96.

	Study 1216			Study 1160		
	RPV/FTC/TAF (n=316)	RPV/FTC/TDF (n=314)		RPV/FTC/TAF (n=438)	EFV/FTC/TDF (n=437)	
Virologic Outcomes						
HIV RNA <50 c/mL	89.2%	88.5%		85.2%	85.1%	
Difference in % <50 c/mL (95% CI)	0.7% (-4.3% to 5.8%)*			0.0% (-4.8% to 4.8%)*		
HIV RNA ≥ 50 c/mL	0.6%	1.0%		0.7%	0.9%	
Difference in % ≥50 c/mL (95% CI)	-0.3% (-2.2% to 1.5%)**			-0.2% (-1.7% to 1.2%)**		
No data	10.1%	10.5%		14.2%	14.0%	
Safety Outcomes			**p value**			**p value**
BMD†						
Hip (% change) ǂ	+1.6	-0.6	<0.001	+1.8	-0.6	<0.001
Spine (% change) ǂ	+2.0	-0.3	<0.001	+1.7	+0.1	<0.001
Renal biomarkers						
eGFR[a] ml/min§	+5.9	-0.2	<0.001	-4.6¥	-1.1	0.004
UACR[b] (% change)§	+9.3	+32.9	<0.001	-1.0	+39.6	<0.001
RBP:Cr[c] (% change)§	+6.5	+55.8	<0.001	-7.3	+87.1	<0.001
β2M:Cr[d] (% change)§	-15.5	+43.7	<0.001	-31.7	+68.4	<0.001

*The lower bound of the 2-sided 95% CI of the difference is greater than -8%.
** The upper bound of the 2-sided 95% CI of the difference is less than 4%.
†BMD bone mineral density Study 1216 BMD substudy: RPV/FTC/TAF hip n= 160, spine n= 162; RPV/FTC/TDF hip n= 156, spine n= 158. Study 1160: RPV/FTC/TAF hip n= 322, spine n= 327; EFV/FTC/TDF hip n= 345, spine n= 344.
ǂ Mean
§ Median
¥ RPV inhibits tubular secretion of creatinine, raising serum creatinine and estimated GFR without changing glomerular filtration
Abbreviations: [a]eGFR, estimated glomerular filtration rate calculated by Cockroft-Gault; [b] UACR, urine albumin to creatinine ratio; [c]RBP:Cr, urine retinol binding protein to creatinine ratio; [d] β2M:Cr, urine beta-2 microglobulin to creatinine ratio

505 FACTORS PREDICTING VIROLOGICAL FAILURE DURING DOLUTEGRAVIR MAINTENANCE MONOTHERAPY

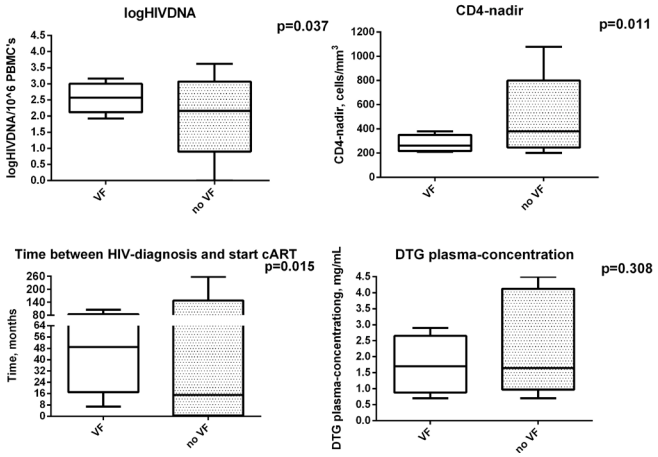
Ingeborg Wijting[1], Sofie L. Rutsaert[2], Casper Rokx[1], David M. Burger[3], Elrozy Andrinopoulou[1], Linos Vandekerckhove[2], Bart Rijnders[1]
[1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]HIV Cure Research Center, Ghent University, Ghent, Belgium, [3]Radboud University, Nijmegen, Netherlands

Background: In the DOMONO-study (CROI 2017 451LB), dolutegravir (DTG) monotherapy was non-inferior to combination antiretroviral therapy (cART) in maintaining viral suppression during 24 weeks. However, the study had to be discontinued prematurely as 3 patients on DTG monotherapy developed integrase inhibitor resistance. Data about clinical and virological factors associated with virological failure (VF) are scarce. We aim to determine factors associated with VF during DTG maintenance monotherapy.

Methods: DOMONO (NCT02401828) was a randomized clinical non-inferiority trial, randomizing HIV-1 patients suppressed on cART to DTG monotherapy either immediately or after 24 weeks of continued cART. Eligible patients were suppressed on cART for at least 6 months, with an HIV-RNA zenith < 100.000 c/ml and a CD4-nadir ≥ 200 cells/mm^3. We analyzed which baseline patient characteristics were associated with VF. Because the number of events was small, only univariable analysis was possible (unpaired T-test and Mann Whitney U Test as appropriate).

Results: The OT-population consisted of 95 patients, of whom 8 had VF. The analyses showed that mean (SD) log total HIV DNA/10^6 PBMCs (2.16 (0.53) versus 2.57 (0.40), p=0.037), median (Q1-Q3) CD4-nadir (380 (290-520) versus 260 (223-320) cells/mm^3, p=0.011), and median (Q1-Q3) time between HIV-diagnosis and start cART (15 (1-38) versus 49 (27-64) months, p=0.015) all differed significantly at baseline between patients without and with VF respectively (Figure 1). Median (Q1-Q3) DTG plasma concentrations in the 8 patients with VF and 20 random patients without VF did not differ (1.65 (1.23-3.75) versus 1.70 (1.05-2.40) mg/mL, p=0.3). Other factors that were not associated with VF were the time that the patient had been virologically suppressed on cART before switching to DTG monotherapy, gender, the HIV-RNA zenith before cART initiation, nor did age, CD4-count, CD4:8-ratio and C-reactive protein and type of cART that was used (all at the start DTG monotherapy).

Conclusion: In patients using DTG maintenance monotherapy, a larger HIV reservoir, lower CD4-nadir and longer time to cART initiation were associated with VF. This study supports that starting treatment early limits the viral reservoir and may facilitate therapy simplification strategies.



506 RESISTANCE ANALYSES OF BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE SWITCH STUDIES

Kristen Andreatta[1], Madeleine Willkom[1], Ross Martin[1], Silvia Chang[1], Hal Martin[1], Hiba Graham[1], Erin Quirk[1], Kirsten L. White[1]
[1]Gilead Sciences, Inc, Foster City, CA, USA

Background: The novel, unboosted integrase strand transfer inhibitor (INSTI) bictegravir (B) has been coformulated with the nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone emtricitabine (F)/tenofovir alafenamide (TAF). In 2 phase 3 clinical studies, stably suppressed HIV-1 infected adults who switched to B/F/TAF from regimens consisting of either a boosted protease inhibitor (PI) + 2 NRTIs (N=290; Study 1878) or the INSTI dolutegravir (DTG) + NRTIs abacavir (ABC)/lamivudine (3TC) (N=282; Study 1844) had low rates of virologic failure (VF; HIV-1 RNA ≥50 copies/mL by snapshot analysis) through week (W) 48, and switching was noninferior to comparator arms. Here, integrated resistance analyses are described.

Methods: Available historical plasma HIV-1 RNA genotypes and retrospective proviral DNA genotyping of baseline viral isolates were analyzed. Viral isolates from patients with HIV-1 RNA ≥200 copies/mL at confirmed VF, discontinuation, or W48 were analyzed for protease (PR), reverse transcriptase (RT), and integrase (IN) genotype and phenotype.

Results: Of the 572 patients who switched to B/F/TAF, pretreatment historical genotypes and/or retrospective proviral DNA genotypes of baseline viral isolates were obtained from 394 patients for PR/RT and from 158 patients for IN. Preexisting primary INSTI resistance (-R), NRTI-R, nonnucleoside RT inhibitor (NNRTI)-R, and PI-R substitutions were observed in 0.6% (1/158), 14.0% (55/394), 18.3% (72/394), and 6.3% (25/394), respectively. Pre-switch resistance to F and/or TAF was retrospectively detected at baseline in 8.9% (35/394) of patients and consisted of K65N/R (n=5), M184V/I (n=30), and/or ≥3

thymidine analog mutations (TAMs) that include M41L or L210W (n=4) in RT. Overall, 1.4% (8/572) of B/F/TAF treated patients experienced VF through W48. Of the 35 patients with preexisting F/TAF resistance, 1 (2.9%) experienced VF due to nonadherence. Postbaseline resistance analyses were conducted on viral isolates from 5 patients in the B/F/TAF group and 7 patients in the comparator groups. No patients on B/F/TAF developed de novo resistance to study drugs. One patient on boosted darunavir + ABC/3TC developed a treatment-emergent L74V substitution in RT.

Conclusion: Low rates of virologic failure occurred among the 572 patients who switched to B/F/TAF, including the 35 with preexisting F/TAF resistance. Through W48 there was zero treatment-emergent resistance in B/F/TAF treated patients demonstrating the utility of B/F/TAF in HIV-1-suppressed patients.

507 IN SILICO CLINICAL TRIALS FOR EVALUATION OF HIV SHORT-CYCLE STRATEGIES

Melanie Prague[1], Chloé Pasin[1], Linda Wittkop[1], Pierre Duffau[2], Estibaliz Lazaro[2], Charles Cazanave[2], Marc Vareil[3], Fabrice Bonnet[2], **Rodolphe Thiébaut**[1]
[1]INSERM, Bordeaux, France, [2]CHU de Bordeaux, Bordeaux, France, [3]Centre Hospitalier de la Côte Basque, Bayonne, France

Background: The challenge associated with lifelong combination antiretroviral treatments (cART) taken by HIV infected patients have motivated the development of strategies for therapeutic relief. The cART simplification reduces toxicity and drug costs, and improves patients' quality of life. Short-cycles treatment interruptions (SCT) have been shown as promising and are still under investigation (ANRS 170 QUATUOR, PENTA Trial group). We propose a pipeline for computer-based simulations of trials which aim at quantifying and predicting in silico the effect of SCT in order to accelerate and personalize their development.

Methods: HIV and CD4+ T cells trajectories under treatment conditions were modelled using dynamical mechanistic models based on Ordinary Differential Equations (Perelson et al., Science, 2011; Prague et al., Biometrics, 2016). Data from 2550 patients of the ANRS CO3 Aquitaine HIV cohort were used and supplemented with information from in vitro assays (Siliciano et al., Lancet, 2011). Estimates of the in vivo cART effect were obtained from a populational statistical approach. Here, we focused on efavirenz (EFV)-based cART associated with two nucleosides analogues. Generating pseudo subjects with statistically controlled heterogeneity and using predictions based on parametric empirical Bayes, we simulate in silico data of realistic SCT trials. Computer-based success of the SCT is evaluated regarding the probability of detectable viral load and the mean basic reproduction number (R0, if R0 is below 1 the infection will die out in the long run) at 48 weeks.

Results: We estimate that most of the investigated EFV-based cART will be potent enough to guarantee the success of 5/7 designs (5 days on, 2 days off cART). However, 4/7 designs will lead to more virological failure depending on patients' characteristics. From Table 1, we can derive in silico results of the BREATHER PENTA 16 trial (Butler et al., Lancet HIV, 2016), which is a 5/7 design for EFV-based cART. Simulations predict 1% [0%; 11.9%] of 50 copies/mL virological failure and show a mean R0 of 0.82 [0.63; 0.99]. Because the 95% confidence interval includes the true outcome (8.1% of 50 copies/mL virological failure at 48 weeks), in silico and in vivo results are consistent.

Conclusion: The computer-based approach correctly predicts the outcome of existing SCT trials. Thus, our pipeline for in silico trials is a promising tool for accelerating the development of novel strategies based on existing cART.

	4/7 designs			5/7 designs		
CART	Probability virological failure (>1cp/mL)	Probability virological failure (>50cp/mL)	Mean R0 95% CI	Probability virological failure (>1cp/mL)	Probability virological failure (>50cp/mL)	Mean R0 95% CI
EFV+ Tenofovir + Lamivudine	5.3% [2.2%; 9.0%]	2.0% [0.0%; 4.0%]	0.91 [0.71; 1.11]	**0.9% [0%; 5%]**	**0.5% [0%; 4%]**	**0.77 [0.59; 0.92]**
EFV+ Abacavir+ Lamivudine	17.1% [11%; 23%]	11.9% [6%; 17%]	0.96 [0.74; 1.16]	**1.1% [0%; 14%]**	**0.6% [0%; 11%]**	**0.82 [0.64; 0.99]**
EFV+ Zidovudine+ Lamivudine	21.4% [16%; 28%]	16.4% [10%; 23%]	0.97 [0.75; 1.18]	2.4% [0%; 19%]	1.0% [0%; 16%]	0.84 [0.65; 1.02]

Table 1 – Probability of 1 and 50 copies/mL virological failure at 48 weeks and mean basic reproductive number for Short-Cycle Therapies (SCT) with 4/7 and 5/7 designs (respectively 4 and 5 days on cART during a week) evaluated in silico with computer-based simulations. Number in brackets are 95% confidence intervals (CI). The most promising strategies, such as 1 is not included in mean basic reproduction number (R0) 95%CI, are in bold. In BREATHER PENTA 16, cART repartition is the following 25% EFV+Tenofovir+Lamivudine, 22% EFV+Abacavir+Lamivudine and 53% EFV+Zidovudine+Lamivudine.

508 DTG VERSUS LPV/R IN SECOND LINE (DAWNING): OUTCOMES BY WHO-RECOMMENDED NRTI BACKBONE

Michael Aboud[1], Carlos Brites[2], Hongzhou Lu[3], Khuanchai Supparatpinyo[4], Luis Hercilla[5], Jörg Sievers[6], Maria Claudia Nascimento[7], Judy Hopking[8], Mark Underwood[7], Dannae Brown[6], Martin Gartland[7], Kim Smith[7]
[1]ViiV Healthcare, Branford, CT, USA, [2]Federal University of Bahia, Salvador, Brazil, [3]Fudan University, Shanghai, China, [4]Chiang Mai University, Chiang Mai, Thailand, [5]Hospital Nacional Alberto Sabogal Sologuren, Callao, Peru, [6]ViiV Healthcare, Brentford, UK, [7]ViiV Healthcare, Research Triangle Park, NC, USA, [8]GlaxoSmithKline, Uxbridge, UK

Background: DAWNING is a non-inferiority study comparing dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) with a WHO-recommended regimen of lopinavir/ritonavir (LPV/r) + 2 NRTIs in HIV-1 infected adults failing first-line therapy (HIV-1 RNA ≥400 copies [c]/mL) of a non-nucleoside reverse transcriptase inhibitor (NNRTI) + 2 NRTIs (ClinicalTrials.gov: NCT02227238).

Methods: Subjects were randomised (1:1, stratified by plasma HIV-1 RNA and number of fully active NRTIs) to 52 weeks of open-label treatment with DTG or LPV/r combined with 2 investigator-selected NRTIs, including at least one fully active NRTI based on Screening resistance testing. The primary endpoint was the proportion of subjects achieving HIV1 RNA <50 c/mL at Week 48 (Snapshot algorithm) with an interim analysis at Week 24. Post-hoc efficacy analyses were performed based on whether WHO-recommended second-line NRTIs were chosen per subjects' first-line NRTIs; 59 subjects not taking WHO-recommended first-line NRTIs were excluded.

Results: Of 968 subjects screened, only 78 (8%) were screen failures due to not having one fully active NRTI available; 624 were randomised and treated. At Week 24, DTG+2NRTIs was superior to LPV/r+2NRTIs, with 82% (257/312) and 69% (215/312) of subjects, respectively, achieving HIV-1 RNA <50 c/mL (adjusted difference 13.8%, 95% CI: 7.3% to 20.3%, p<0.001). The difference was mainly driven by lower rates of Snapshot virologic non-response in the DTG group. 56% (347/624) of subjects received WHO-recommended second-line NRTIs, and their response rates within each arm were higher than those for subjects who did not. Regardless of WHO-recommended NRTI use, response rates were higher with DTG versus LPV/r-based regimens (Table). The overall safety profile of DTG+2NRTIs was favourable compared to LPV/r+2NRTIs with more drug-related adverse events reported in the LPV/r group. In this analysis, there were no treatment-emergent primary integrase-strand transfer inhibitor or NRTI resistance mutations in the DTG group through the randomisation phase.

Conclusion: In DAWNING, response rates were highest in subjects receiving DTG + WHO-recommended second-line NRTIs. Further, within each arm, subjects had higher response rates when receiving WHO-recommended versus other second-line NRTIs suggesting resistance testing to guide NRTI selection may not be necessary in this population. DAWNING provides important information to help guide second-line treatment decisions in resource-limited settings.

Table **Week 24 Snapshot virologic success by subgroup**

WHO-recommended second-line NRTIs	Treatment	Responders	Difference (95% CI)
Yes	DTG	87% (157/181)	15.1 (6.6, 23.5)[1]
	LPV/r	72% (119/166)	
No	DTG	75% (77/103)	8.7 (-3.4, 20.7)[1]
	LPV/r	66% (76/115)	
Yes	DTG	87% (157/181)	12.0 (2.2, 21.7)[2]
No		75% (77/103)	
Yes	LPV/r	72% (119/166)	5.6 (-5.4, 16.6)[2]
No		66% (76/115)	

[1] Proportion on DTG – proportion on LPV/r
[2] Proportion with WHO-recommended NRTIs – proportion without WHO-recommended NRTIs

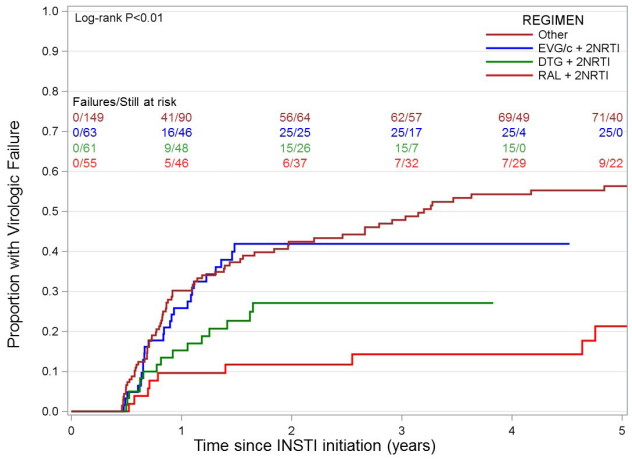
509 INTEGRASE STRAND TRANSFER INHIBITOR (INSTI) EFFECTIVENESS IN ART-EXPERIENCED PATIENTS

Thibaut Davy-Mendez, Sonia Napravnik, Oksana Zakharova, David Wohl, Claire E. Farel, Joseph J. Eron
University of North Carolina Chapel Hill, Chapel Hill, NC, USA

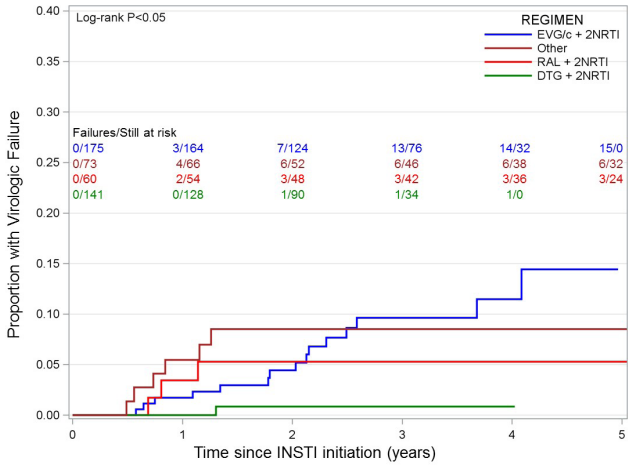
Background: Given increasing INSTI use among ART-experienced patients, we examined virologic and immunologic outcomes of INSTI therapy in the UNC CFAR HIV Clinical Cohort.

Methods: ART-experienced patients on first INSTI 2007-2016 were followed from INSTI initiation (baseline) until: death, loss to follow-up (LTFU-1 year without clinical visit), or August 2017. Time to CD4>500 was estimated among patients with baseline CD4<500 censoring patients at virologic failure, stratified by nadir CD4 and baseline VL. Virologic failure (VF) was defined as first of 2 consecutive viral loads (VL) >200 copies/mL >2 weeks apart, or 1 VL>200 before LTFU, 24 weeks post-baseline. Kaplan-Meier curves were fit and Cox proportional hazard models estimated hazard ratios (HR), adjusting for baseline age, race, sexual risk group, CD4, and VL. Patients were stratified by VL
Results: The 777 patients were 32% female, 43% MSM, and 59% African American, with baseline median age of 47 years (IQR 38, 54), CD4 509 (274, 738), and prior exposure to 6 (4, 8) antiretrovirals. At baseline, 328 (42%) had VL>50, with median VL 4.2 log_{10} copies/mL (3.0, 4.9). Among 247 patients with CD4<500 and VL>50 at baseline, patients with nadir CD4>200 had a shorter median time to CD4>500 (1.3 vs. 4.3 years, P<0.01). Among patients with VL<50 at INSTI start, 2 and 4% experienced VF after 1 and 2 years, compared to 23% and 34%, among patients with VL>50 (respectively, P<0.01). Time to VF differed by INSTI agent among patients with and without VL suppression at baseline (Figure 1 A/B, both P<0.05). In patients with baseline VL>50, time to VF was longer for raltegravir vs elvitegravir (EVG) (aHR 0.30, 95% CI, 0.14, 0.64). In patients with baseline VL<50, time to VF was longer for dolutegravir (DTG) vs EVG (aHR 0.13, 95% CI, 0.02, 0.97). Prior exposure to ≥8 drugs increased risk of VF among patients with baseline VL>50 (aHR 1.63, 1.12, 2.38).
Conclusion: In suppressed patients who switch to INSTI-based therapy, INSTI regimens are highly effective, with a possible lower risk of VF with DTG-based therapy. Patients with viremia at INSTI start have high VF rates, associated with prior exposure to many drugs. Low nadir CD4 is associated with worse CD4 recovery while on INSTI therapy.

A. Time to virologic failure in patients with VL>50 at INSTI start, by INSTI agent



B. Time to virologic failure in patients with VL<50 at INSTI start, by INSTI agent

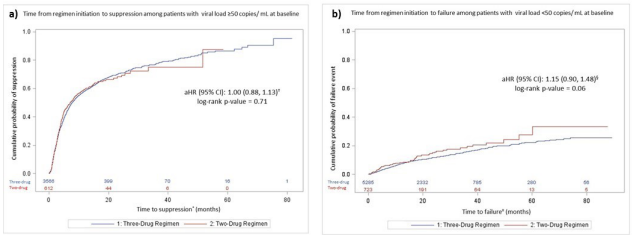


510 VIROLOGIC RESPONSE TO 2-DRUG ART REGIMENS AMONG TREATMENT-EXPERIENCED HIV+ PATIENTS

Gerald Pierone[1], Cassidy Henegar[2], Jennifer Fusco[2], Vani Vannappagari[3], Michael Aboud[4], Leigh Ragone[3], Gregory Fusco[2]
[1]Whole Family Health Center, Vero Beach, FL, USA, [2]Epividian, Durham, NC, USA, [3]ViiV Healthcare, Research Triangle Park, NC, USA, [4]ViiV Healthcare, London, UK

Background: Drug-sparing regimens have the potential to reduce complexity, toxicity, and cost of antiretroviral therapy (ART). Our objectives were to describe two-drug regimen (2-DR) use among ART-experienced HIV+ patients in a large clinical cohort, and to compare virologic outcomes of 2-DRs and three-drug regimens (3-DRs) following switch during the study period.
Methods: Between 1/1/2010 and 6/30/2016, ART-experienced patients starting a new 2-DR or 3-DR, were selected from the OPERA cohort. Patients were observed from regimen start date (baseline) until regimen discontinuation (d/c), loss to follow-up, death, or study end (6/30/2017). Outcomes were stratified by viral load (VL) at baseline (switched while viremic: ≥50 copies/mL; stable switch: <50 copies/mL). Suppression during follow-up was defined as a VL <50 copies/mL; failure following suppression was defined as 2 consecutive VLs >200 copies/mL or a VL>200 copies/mL + d/c. Cox models for each outcome were fit to estimate adjusted hazard ratios (aHRs).
Results: We identified 10,190 ART-experienced patients who switched during the study period; 1,337 (13%) switched to a 2-DR, and 8,853 (87%) to a 3-DR. At baseline, 2-DR patients were older, more likely to have AIDS, had been on ART longer and experienced more treatment lines, had more comorbidities, and were less likely to be a stable switch compared to 3-DRs (p<0.0001). The most common 2-DRs (55%) comprised a protease inhibitor and an integrase strand transfer inhibitor combination, regardless of baseline VL. Among those switching while viremic (2-DR: 612 (15%), 3-DR: 3566 (85%)), suppression during follow-up was comparable among patients on 2-DRs (61%) and 3-DRs (67%; aHR 1.00, 95% CI 0.88, 1.13) [Figure]. After achieving suppression during follow-up, 13% of 2-DR and 15% of 3-DR patients went on to experience a failure event. Among stable switch patients (2-DR: 723 (12%), 3-DR: 5285 (88%)), the difference in risk of virologic failure during follow-up was not statistically significant between 2-DR and 3-DR patients (10% vs. 11%; aHR 1.15, 95% CI 0.90, 1.48) [Figure].
Conclusion: Virologic outcomes were comparable between ART-experienced patients switching to two- and three-drug regimens, regardless of whether patients were virologically controlled at switch. These findings support the continued evaluation of 2-DRs in clinical trials and real-world settings. Long-term outcomes require further assessment.

Kaplan-Meier estimations of (a) time to suppression among treatment-experienced patients not suppressed at regimen initiation and (b) time to virologic failure among treatment-experienced patients suppressed at regimen initiation, stratified by regimen type



* Suppression: viral load <50 copies/mL
† aHR (95% CI) – adjusted hazard ratio (95% confidence interval); adjusted for age, race, sex, baseline viral load, ADAP/Ryan White assistance, history of substance abuse, time on ART, prior lines of ART, and comorbidity diagnoses
‡ Failure: two consecutive viral loads >200 copies/mL or one viral load >200 copies/mL followed by discontinuation
§: adjusted for age, race, sex, history of substance abuse, baseline CD4, comorbidity, prior lines of ART, time on ART, and comorbidity diagnoses

511 TREATING MULTICLASS-RESISTANT HIV+PATIENTS IN RWANDA USING A PUBLIC HEALTH APPROACH

Sabin Nsanzimana[1], Muhayimpundu Ribakare[2], Remera Eric[1], Amitabh B. Suthar[3], Riedel J. David[4], Edward J. Mills[5], Heiner C. Bucher[6]
[1]Rwanda Biomedical Centre, Kigali, Rwanda, [2]Swiss Tropical and Public Health Institute, Basel, Switzerland, [3]Stellenbosch University, Stellenbosch, South Africa, [4]University of Maryland, Baltimore, MD, USA, [5]McMaster University, Hamilton, ON, Canada, [6]University Hospital Basel, Basel, Switzerland

Background: While the vast majority (≥90%) of the 19 million individuals currently receiving ART are on first- and second-line regimens, the number of people requiring third-line regimens is rising. Most developing countries do not currently provide third-line ART because of limited resistance testing, alternative treatment options and high cost. We report outcomes from

Rwanda's national HIV program, one of the first cohorts receiving third-line ART in sub-Saharan Africa.

Methods: We assessed outcomes on third-line therapy for a period of 5 years. Virological failure was defined as 2 VL >1,000 copies/mL separated by at least three months and appropriate adherence counseling. We calculated the proportion of patients achieving VL suppression after 3rd-line initiation.VL suppression were defined as < 1000 copies/mL. Patients were censored at date of death, date of stopping ART, or June 2016. We reported treatment-limiting adverse and drug resistance mutations on third line ART.

Results: Of 7,625 patients on 2nd line ART in Rwanda, 38 with treatment failure on PIs based regimen, started 3rd line ART. one patient died (2,6%) and 37 were retained over a median follow-up time of 30 months (IQR 12-38), median age was 42 years (IQR 26-50) and 40.5% were male.Median CD4 cell count at start of 3rd-line was 165 cells/µL (IQR 70-329) and median VL was 57,000 copies / mL (IQR 16,200-151,000). Genotyping was performed in 83.8% of participants prior to 3rd-line initiation; across all drugs, 96.5%, 63.4% and 75.8% had two or more mutations on NRTI, NNRTI and protease inhibitors, respectively.Overall, the majority of patients were susceptible to raltegravir and darunavir/ritonavir (Table1). Twenty-five of 28 self-reported good adherence to medication; 71.4 % achieved viral suppression < 1000 copies/mL; 8.8% of participants experiencing adverse events on ART.

Conclusion: Our report is one of the few evaluations of 3rd-line ART program in SSA. Almost 3 in 4 patients achieved viral suppression.Our findings demonstrate the feasibility of providing third-line ART in a routine programme setting and indicate a need for strong surveillance to achieve better clinical outcomes.

512 ADHERENCE IN EARLY VERSUS LATE ART INITIATION IN SUB-SAHARAN AFRICA

Jessica E. Haberer[1], Bosco M. Bwana[2], Catherine Orrell[3], Stephen Asiimwe[4], Gideon Amanyire[5], Nicholas Musinguzi[2], Mark J. Siedner[1], Kathleen Bell[1], Annet Kembabazi[2], Stephen Mugisha[4], Victoria Kibirige[2], Anna Cross[3], Nicola Kelly[3], David R. Bangsberg[1]

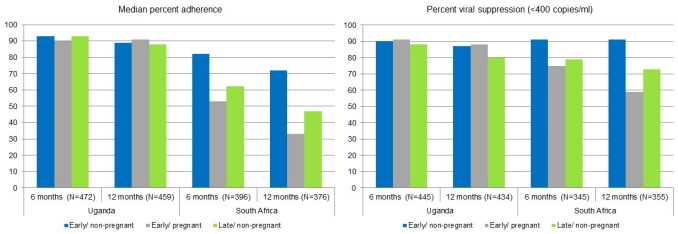
[1]Massachusetts General Hospital, Boston, MA, USA, [2]Mbarara University of Science and Technology, Mbarara, Uganda, [3]Desmond Tutu HIV Foundation, Cape Town, South Africa, [4]Kabwohe Clinical Research Center, Kabwohe, Uganda, [5]Makerere University Joint AIDS Program, Kampala, Uganda

Background: Universal ART access policies and aspirations for an AIDS-free generation depend on high ART adherence with early stage HIV infection; however, adherence may be difficult in the absence of illness and associated support.

Methods: We prospectively observed 3 cohorts initiating ART in routine care in southwestern Uganda (UG) and Cape Town, South Africa (SA): early (CD4≥350 cells/µl) initiation for men and non-pregnant women; early initiation for pregnant women; and late (CD4‹200 cells/µl) initiation for men and non-pregnant women. Socio-behavioral questionnaires and viral load were performed at 0, 6 and 12 months. Adherence was monitored in real-time (Wisepill). Loss to follow-up was treated as non-adherence/viremia and death as viremia; data were censored at disenrollment. Predictors of adherence were assessed by multivariable linear regression; sites were analyzed separately given socio-economic/cultural differences. Changes over time were assessed by fixed effects regression.

Results: Of 904 individuals enrolled, data were available for 868 (96%): 322 (37%) early/non-pregnant, 198 (23%) early/pregnant, and 348 (40%) late/non-pregnant. Deaths were similar (19 in UG, 15 in SA; p=0.21). In UG, median adherence was 89% (IQR 74-97) and viral suppression was 85%, and did not differ among cohorts (p>0.10; Figure). In SA, median adherence was higher in early/non-pregnant vs early/pregnant or late/non-pregnant (72%, 33%, 47%, respectively, p<0.001), with similar trends in viral suppression (91%, 59%, 73%; p<0.001). Adherence was higher with increasing year of age (0.5 percentage points [pp] in UG and SA), employment (10.9pp in UG, 9.2pp in SA), and marriage (12.3pp in SA). Adherence was lower with heavy alcohol (-20.5pp in UG), depression (-20.5pp in SA), and food insecurity (-6.5pp in SA). Non-significant predictors were sex, education, physical well-being, prior knowledge of HIV, stigma/disclosure, and other medications. Adherence was lower in months 0-6 vs months 6-12 (median difference -5.6pp in UG, -13pp in SA; p<0.001).

Conclusion: ART adherence with early initiation is as high or higher than with late initiation, suggesting current universal access policies may indeed lead toward an AIDS-free generation. However, challenges remain for some, including pregnant women and those with late ART initiation in South Africa. Significant contextual differences highlight need for differentiated care with attention to alcohol use, depression, food security, youth, marital status, and employment.



513 ADHERENCE TO COMBINATION ANTIRETROVIRAL THERAPY (ART) IN SUB-SAHARAN AFRICA

Judith J. Lok[1], Elisavet Syriopoulou[2], Dustin J. Rabideau[1], Beverly Musick[3], Jeffrey N. Martin[4], Kara K. Wools-Kaloustian[3], Ronald Bosch[1], Ann Mwangi[5], Constantin T. Yiannoutsos[3]

[1]Harvard University, Cambridge, MA, USA, [2]University of Leicester, Leicester, UK, [3]Indiana University, Indianapolis, IN, USA, [4]University of California San Francisco, San Francisco, CA, USA, [5]Moi University, Eldoret, Kenya

Background: Accurate estimation of adherence to ART is crucial for assessing the effectiveness of HIV treatment programs. Routine estimates of adherence to ART are based on crude percentages among patients in HIV care in the treatment program. These crude percentages significantly overestimate program effectiveness, because they do not consider data from patients who are deceased or no longer in care. Dead patients obviously can't have perfect adherence, but they could perhaps have been alive with perfect adherence in a different treatment program. Or, patients who died because of poor adherence in another treatment program could perhaps have been alive with perfect adherence in this treatment program. We should analyze death and adherence jointly, and optimize the number of patients with the most favorable prognosis: alive with perfect adherence.

Methods: We examined data from 25,260 HIV-positive patients from the East Africa IeDEA Consortium. Adherence was self-reported. We considered additional information obtained from a subset of patients who were lost to program but were traced later (the "outreach sample"). We used Inverse Probability of Censoring Weighting (IPCW) adapted to Missing Not At Random data to adjust for patient characteristics predicting loss to program. In the absence of treatment information in the outreach sample, we assumed (rather conservatively in this setting) that the probability of being on ART among those alive and lost to program was half the probability of being on ART among similar patients still in the treatment program.

Results: 9190 of 25,260 patients (36%) were male; median age 37 years (IQR 31-44); median CD4 count at ART initiation 112 cells/µl (IQR 49-180). 7974 (32%) were lost to program through 36 months after starting ART. Of these, 1053 (13%) were traced. The crude one-year estimate of on-ART and perfect adherence was 94%, which is substantially higher than the adjusted estimate of 74%, which considers the patients who left the program or died. The adjustment was larger for later times.

Conclusion: Ignoring mortality and disengagement from overestimates adherence to ART among all patients initiating ART and significantly exaggerates the effectiveness of treatment programs. IPCW methods aimed at outreach data are broadly applicable, particularly also to viral suppression, which is associated with death and disengagement from care and which may also be substantially overestimated by excluding individuals not in care.

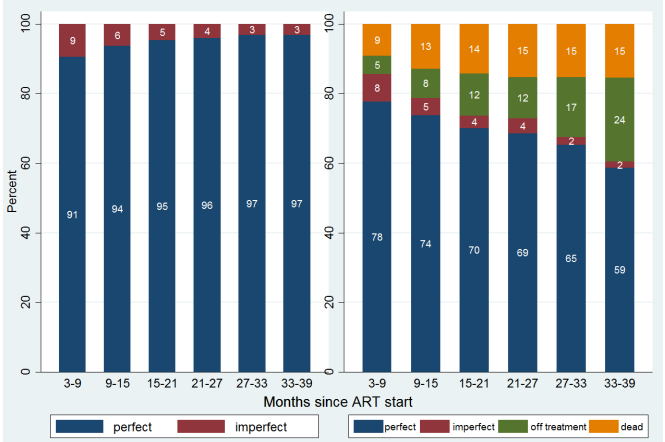


Figure 1: Routine estimates of adherence (left), among patients still in care and in the program. Adjusted estimates of outcomes (right): adherence and death among all patients initiating ART in the program.

514 USING INPATIENT DOT TO IDENTIFY TRUE ART FAILURE AND IMPROVE TREATMENT OUTCOMES

Nicole E. Winchester[1], Safia S. Kuriakose[2], Frank Maldarelli[3], Michael Proschan[1], Yolanda Mejia[2], Holly Ann Baus[1], Megan Anderson[1], Robin L. Dewar[2], H. Clifford Lane[1], Alice K. Pau[1]

[1]NIAID, Bethesda, MD, USA, [2]Leidos Biomedical Research, Inc, Frederick, MD, USA, [3]NCI, Rockville, MD, USA

Background: Treatment failure (TF) remains a complex problem for some HIV+ patients (pts) despite potent ART. Most cases result from non-adherence, inadequate drug levels, or drug resistance. Regimen changes in response to TF may improve outcomes, however, they can also jeopardize future ART options and increase failure risk. In this observational study, we used an 8-day inpatient directly observed therapy (DOT) to assess the viral potency of the failing regimen before ART switches.

Methods: Pts with multiple ART failures were eligible for enrollment if they failed at least 2 regimens with 2 last VL >1000 copies/mL. Efficacy of the current ART regimen was assessed using an 8-day inpatient DOT (DOT1) and VL was performed on days 1, 3, 5, and 8. A DOT Responder [DOT1-R] was defined as one who has a VL decline of ≥0.5 $\log_{10}$c/mL from screening to Day 8. Non-responders [DOT1-NR] were prescribed new regimens, if available, and returned for a 2nd DOT (DOT2) to assess viral efficacy. Follow up occurred at wks 2, 4, 8, and 12, and then every 3 mos. HIV/ART education and adherence counseling were provided during DOT and at all follow-up visits by team members including medical, nursing, pharmacy, and social work staff per patient needs; patients were also contacted by phone between clinic visits.

Results: 18 pts were enrolled; 16 completed DOT1. 1 pt had AKI at screening, had to stop TDF and did not have DOT1, 1 was lost to f/u before DOT. The remaining 16 pts comprise the analysis cohort and were 62.5% male; 87.5% black; mean age 43 yrs; mean CD4 80.3 cells/mm^3; median VL 4.39 $\log_{10}$c/mL. 8/16 (50%) had >0.5 $\log_{10}$c/mL decline with DOT1. The median VL changes for DOT1-R and DOT1-NR were -1.56 and -0.08 $\log_{10}$c/mL, respectively. DOT1-R, relative to DOT1-NR, had fewer yrs on ART (13.8 vs 19.9), fewer prior ARVs (9.1 vs 13.5), fewer DRM (9.5 vs 24.4), higher GSS scores (2.6 vs 0.2), and less education. 7 DOT1-NR underwent DOT2 on optimized ART. 5/7 (71%) of these pts responded to the new regimen with median VL change from day 1 to day 8 of -1.78 (-1.91 to -1.74) $\log_{10}$c/mL. 3 DOT1-NR had no active drugs as ART options.

Conclusion: Using an 8-day inpatient DOT with intensive counseling, 50% of our pts with longstanding TF had substantial viral responses without ART changes. 5/7 (71.4%) DOT1-NR were virally suppressed after DOT2 with an optimized regimen. DOT is a valuable tool in identifying sub-optimal adherence as the cause of TF, reducing the frequency of unnecessary ART switches.

	Overall (N=16)	DOT1-R (N=8)	DOT1-NR (N=8)	*p*-value
Demographics				
Age (yr), mean ± s.e.	43.0 ± 12.9	39.5 ± 15.2	46.4 ± 9.8	0.300
n (%) Male	10 (62.5%)	4 (50.0%)	6 (75.0%)	0.527
n (%) Black	14 (87.5%)	7 (87.5%)	7 (87.5%)	1.000
n (%) Self-reported drug use	9 (50.0%)	5 (62.5%)	2 (25.0%)	0.096
n (%) Some college	10 (55.6%)	2 (25.0%)	8 (100.0%)	0.058
Screening VL and CD4 Counts				
Screening VL ($\log_{10}$copies/mL), median (IQR)	4.39 (4.32 to 4.65)	4.33 (4.16 to 4.43)	4.60 (4.37 to 4.66)	0.959
Screening CD4 count (cells/ mm^3)	80.3 ± 91.9	67.3 ± 57.5	93.4 ± 120.1	0.588
ART Experience and Resistance				
Time on ART (yr), mean ± s.e.	16.8 ± 6.7	13.8 ± 6.4	19.9 ± 5.9	0.067
No. of ARV Drugs, mean ± s.e.	11.3 ± 3.9	9.1 ± 3.8	13.5 ± 2.7	0.019
Total No. of DRM	16.9 ± 9.2	9.5 ± 6.7	24.4 ± 3.5	<0.001
No. of NRTI DRM	4.2 ± 3.0	2.4 ± 3.2	6.0 ± 1.4	0.011
No. of NNRTI DRM	2.9 ± 1.6	2.0 ± 1.2	3.8 ± 1.6	0.021
No. of PI DRM	8.8 ± 5.1	5.0 ± 3.5	12.5 ± 3.3	<0.001
No. of INSTI DRM	1.1 ± 1.4	0.1 ± 0.4	2.1 ± 1.2	<0.001
GSS of failing regimen	1.4 ± 1.3	2.6 ± 0.7	0.2 ± 0.3	<0.001
DOT1 Viral Results				
Log Δ HIV RNA DOT1, median (IQR)*	-0.12 (-1.00 to +0.38)	-1.56 (-2.02 to -1.46)	-0.08 (-0.17 to +0.17)	<0.001

All data are Mean ± Standard Error of Means, unless otherwise specified
*From screening to DOT1 day 8

515 PATTERNS OF WISEPILL DEVICE USE IN AFRICAN ADULTS TAKING ANTIRETROVIRAL THERAPY (ART)

Catherine Orrell[1], Nicholas Musinguzi[2], Norma C. Ware[3], Anna Cross[1], Bosco M. Bwana[2], Stephen Asiimwe[4], Gideon Amanyire[2], David R. Bangsberg[5], Jessica E. Haberer[6]

[1]Desmond Tutu HIV Foundation, Cape Town, South Africa, [2]Mbarara University of Science and Technology, Mbarara, Uganda, [3]Harvard University, Cambridge, MA, USA, [4]Kabwohe Clinical Research Center, Kabwohe, Uganda, [5]Oregon Health and Sciences University, Portland, OR, USA, [6]Massachusetts General Hospital, Boston, MA, USA

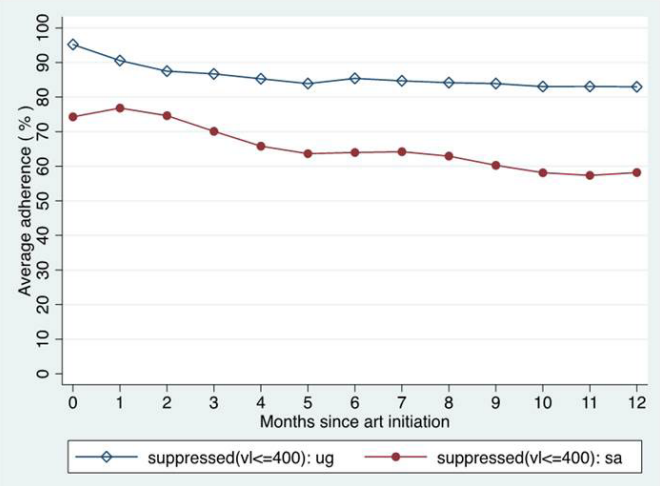
Background: ART adherence measured with electronic devices closely predicts virological outcomes. Use of such devices may not be consistent across settings or populations. Device non-use may explain some discrepancy between adherence data and virological outcomes, as has been suggested elsewhere. Other factors may play a role.

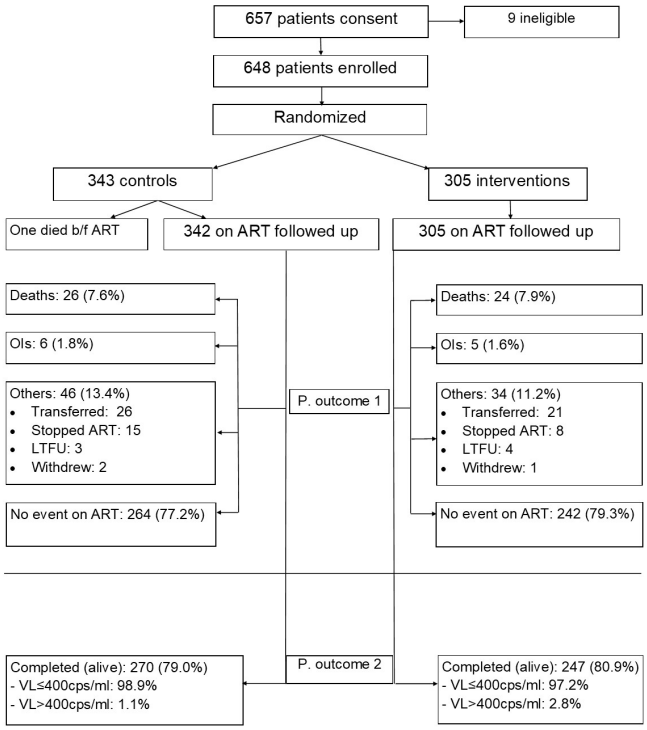
Methods: This research was part of the Measuring Early Treatment Adherence (META) study examining ART adherence in early vs. late stage HIV disease, with sites in Cape Town, South Africa (SA) and south-western Uganda (UG) (NCT02419066). Real-time electronic monitoring, using the Wisepill®, was used to measure adherence. All participants were on TFV/3TC/EFV. For those with viral suppression (<400 copies/ml) at month 12, we plotted monthly adherence over a year after ART initiation by site and used linear regression modelling to explore predictors of average adherence. Independent variables were baseline age and CD4 count, site and number of >7day treatment interruptions. Those lost to follow up were considered to be virological failures.

Results: Of 904 enrolled individuals, Wisepill data was available for 397 (94%) in SA and 472 (98%) in UG. Individuals in SA were older [mean age 34 years (sd 10) vs. 31 years (sd 9), p<0.001] with lower CD4 cell counts [median 370 (IQR 124-444) vs. 401 (IQR 155-490), p<0.001] at baseline. Women were in the majority at both sites (70% vs 68%, p=0.613). Viral suppression for those who had reached month 12 to date was achieved in 283/355 (80%) individuals from SA and 384/434 (88%) from UG. Adherence in suppressed individuals in SA was measured as 13-26% poorer than in UG across the observed year (Figure). Site (p<0.001) and longer gaps in adherence (non-linear, p<0.001) influenced the difference in adherence among individuals with viral suppression. The model accounted for 70% of the variance in adherence [F(7,659)=218.28, p<0.01, R2=0.70].

Conclusion: Many factors contribute to differences in adherence among those achieving viral suppression. Patterns of device use may differ by site and population. The site level effect may indicate device non-use due to stigma/ disclosure, suggested by qualitative findings (presented separately). Further support in the use of adherence monitoring devices in some populations and/ or device modifications to optimise use may be needed. Additionally, given the remaining ambiguity in the model, other potentially influential factors, such as inflammation, warrant investigation.

Figure: Adherence over time in those with viral suppression (≤400 copies/ml) at month 12, for both Ugandan and South African sites.





516 ROUTINE VS TARGETED VIRAL LOAD STRATEGY AMONG PATIENTS STARTING ART IN HANOI, VIETNAM

Todd Pollack[1], Duong T. Hao[1], Thuy T. Pham[2], Thang D. Nguyen[2], Howard Libman[1], Long Ngo[1], Julian Elliot[3], Cuong D. Do Duy[2], Donn Colby[4]
[1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]Bach Mai Hospital, Hanoi, Vietnam, [3]Alfred Hospital, Melbourne, VIC, Australia, [4]SEARCH, Bangkok, Thailand

Background: HIV viral load (VL) testing is recommended by the WHO as the most accurate method for monitoring patients on antiretroviral therapy (ART). VL monitoring has higher sensitivity and positive predictive value for diagnosing treatment failure compared to immunologic or clinical monitoring and allows earlier detection of virological failure and switch to 2nd-line ART before the accumulation of drug resistance mutations. However, evidence that routine VL (RVL) monitoring improves clinical outcomes is lacking.

Methods: We conducted a prospective, randomized controlled trial of RVL monitoring every 6 months versus standard targeted VL (TVL, VL testing to confirm suspected treatment failure) in patients starting ART at Bach Mai Hospital in Hanoi. 648 HIV+ adults (median CD4 count=130 cells/mm^3, IQR=33-287) were randomized and followed for 3 years. Primary endpoints were death or WHO clinical stage IV events after 6 months of ART and rate of virological suppression at 3 years. Proportions were calculated and compared using Chi-squared test. Survival analysis was used to compare time to occurrence of death or stage IV event between two groups. Person-time at risk was calculated from date of ART initiation up to date of death, new or recurrent stage IV event, or last study visit.

Results: Of 648 patients, 343 were assigned to TVL and 305 to RVL. Approximately 44% of study events (death, lost to follow up, withdrawal, or new or recurrent stage IV event) and 68% of deaths occurred within the first 6 months of ART. Among patients on ART at 6 months, death or stage IV event occurred in 3.6% of RVL and 4.0% of TVL (p=0.805). Survival analysis showed no difference between the two groups (p=0.826). Viral suppression at 36 months of ART was 97.2% in RVL and 98.9% in TVL (p=.157) at a VL threshold of 400 cps/mL and was 98.0% in RVL and 98.9% in TVL (p=.404) at a threshold of 1000 cps/mL. There was no difference in switching to 2nd-line ART (3.61% in RVL; 2.05% in TVL, p=.228).

Conclusion: We found no difference in death, stage IV events, virological suppression, or switching to 2nd line ART in patients with RVL monitoring compared to those followed with a TVL strategy after 3 years of follow-up. Overall, patient outcomes were remarkably good in both groups. Most adverse events occurred within the first 6 months of ART, suggesting that earlier HIV diagnosis and ART treatment may be needed to improve treatment outcomes. VL monitoring every 6 months did not improve clinical outcomes in this population.

517 CLINICAL AND VIROLOGICAL IMPACT OF LOW-LEVEL VIREMIA IN TREATED HIV INFECTED PATIENTS

Enrique Bernal[1], Inma Jarrin[2], Alfredo Cano[3], Antonia Alcaraz[3], Angeles Muñoz[3], Pascual Balsalobre[4], Jorge Romero[5], Jose-Ramón Blanco[6], Federico García[7], Miguel Górgolas[8], Félix Gutiérrez[9]
[1]Catholic University of Murcia, Murcia, Spain, [2]Institute of Health Carlos III, Madrid, Spain, [3]Hospital Universitario Reina Sofia, Murcia, Spain, [4]University Hospital Gregorio Marañon, Madrid, Spain, [5]Centro Sandoval, Madrid, Spain, [6]Hospital San Pedro, La Rioja, Spain, [7]Hospital Universitario San Cecilio, Granada, Spain, [8]Fundacion Jimenez Diaz, Madrid, Spain, [9]Hospital General Universitario de Elche, Elche, Spain

Background: There are patients where complete control of viral load is not achieved. The clinical impact of persistent low-level viremia (LLV) is unknown. The objetive was to assess the impact of different levels of LLV on AIDS/death, virological failure and any serious non-AIDS events (NAE)

Methods: We analyzed adults, naïve to antiretroviral therapy (ART) from the cohort of the Spanish AIDS Research Network (CoRIS) who initiated ART from 2004 to 2015 and achieved viral load (VL) ≤50 copies/ml within 3–9 months after ART initiation. LLV50-199 was defined as two consecutive VL between 50 and 199 copies/ml, and LLV200-499 as two consecutive VL between 50 and 499 copies/ml with at least one between 200 and 499 copies/ml. Multivariable Cox models, modeling LLV as a time-varying covariate, were used to estimate the association of LLV with AIDS events/death, any serious NAE (non-AIDS-defining malignancies, cardiovascular-, renal, and liver-related) and virological failure (at least two consecutive viral loads ≥500 copies/ml) after virological suppression.

Results: Of 5986 patients included, 237 (4.0%) experienced at least one episode of LLV50–199 with no LLV200-499 and 168 (2.8%) at least one episode of LLV200–499. Median follow-up time after viral suppression was 3.5 (IQR: 1.5 – 5.5) years in patients not experiencing neither LLV50-199 nor LLV200-499, 4.9 (IQR: 3.5 – 7.2) in patients experiencing at least one episode of LLV50-199 without LLV200-499 and 6.3 (IQR: 4.8 – 8.3) in those experiencing at least one episode of LLV200-499. One hundred seventy-one patients died or developed an AIDS event, 245 had any serious NAE and 280 had virological failure. In multivariable analyses, LLV200-499 was strongly associated with a higher risk of both AIDS event/death [adjusted hazard ratio (aHR): 2.89; 95% confidence interval (CI): 1.41 – 5.92] and virological failure (aHR: 3.25; 95% CI: 1.77 – 5.99), while no differences were observed between LLV50-199 and no LLV neither for AIDS event/death (aHR: 1.84; 95% CI: 0.89 – 3.82) nor virological failure (aHR:

1.42; 95% CI: 0.78 – 2.58). Neither LLV50-199 nor LLV200-499 was associated with occurrence of any serious NAE (aHR: 0.81; 95% CI: 0.37 – 1.75 and aHR: 0.83; 95% CI: 0.34 – 2.07, respectively)

Conclusion: In this Spanish cohort, LLV200–499 was strongly associated with AIDS event/death and virological failure, but not with any serious NAE. Therefore, vigorous treatment should be implemented in patients with more than 200 copies

518 VL SUPPRESSION AT ULTRASENSITIVE LEVELS IS ASSOCIATED WITH INSTI-INITIATION ART

Sidonie Lambert[1], Anders Boyd[2], Djeneba Bocar Fofana[3], Nadia Valin[3], Jean-Luc Meynard[3], Rachid Agher[4], Vincent Calvez[1], Christine Katlama[1], Pierre-Marie Girard[1], Anne-Geneviève Marcelin[1], Laurence Morand-Joubert[1]
[1]Pierre and Marie Curie University, Paris, France, [2]INSERM, Paris, France, [3]Saint-Antoine Hospital, Paris, France, [4]Pitié-Salpêtrière Hospital, Paris, France

Background: Some HIV-infected patients on antiretroviral therapy (ART) present ultrasensitive HIV RNA viral loads (US-VL) below detection levels of current VL assays. Little is known regarding the determinants of ultrasensitive detection and its relation to virological failure (VF) in patients undergoing current ART regimens, such as integrase strand transfer inhibitors (INSTI).

Methods: HIV-infected, ART-naïve patients from two French university hospitals were included if they had HIV RNA >200 copies/ml at ART-initiation, achieved <50 copies/mL during ART, and had ≥2 follow-up time points. Patients were followed while on continuous ART. Plasma HIV-1 RNA quantification was performed using COBAS TaqMan Roche. US-VL was considered below 1 copy/mL when no signal was detected. Determinants for incidence of US-VL<1 copy/mL were evaluated using mixed-effect Poisson regression and VF (HIV RNA >200 copies/mL once or >50 copies/mL twice) using conditional risk-set Cox proportional hazards models.

Results: Between 2009 and 2013, 716 patients initiated ART containing 2 nucleos(-t)ide reverse transcriptase inhibitors (NRTI) plus either a non-NRTI (NNRTI, 29.5%), protease inhibitor (PI, 58.4%) or INSTI (12.2%). Patients were followed for a median 3.4 years (IQR=2.3-4.5), while first-line therapy lasted a median 2.7 (IQR=1.3-5.1) years. US-VL <1 copy/mL was achieved in 674 (94.3%) patients, while suppression at this level was either transient or lasted a median 1.2 years (IQR=0.7-2.0) at most. In multivariable analysis, US-VL<1 copy/mL over time was associated with decreased age (p<0.001), female gender (p=0.03), lower baseline VL (p<0.001), baseline CD4+ >500 versus <350/mm^3 (p<0.001), and ART containing an INSTI versus NNRTI (p=0.03) or versus PI (p=0.02). VF was observed in 132 (18%) patients during follow-up and was associated with higher baseline VL (p=0.02), and HIV RNA tests/year (p=0.001) after adjustment. In post-hoc analysis, cumulative duration under <1 copy/mL was significantly and inversely associated with VF in the multivariable model (aHR/year of suppression=0.40, 95%CI=0.26-0.62, p<0.001).

Conclusion: VL suppression at ultrasensitive levels is associated with the use of INSTI-class ART along with common determinants of undetectable HIV RNA at conventional thresholds. Longer periods at ultrasensitive detection appear to protect against VF.

519 STIMULANT USERS RECEIVING ART DISPLAY INCREASING RATES OF HIV SUPPRESSION

Adam W. Carrico[1], Elise D. Riley[2], Torsten B. Neilands[2], Samantha E. Dilworth[2], Jeffrey N. Martin[2], Steven G. Deeks[2], Peter W. Hunt[2]
[1]University of Miami, Miami, FL, USA, [2]University of California San Francisco, San Francisco, CA, USA

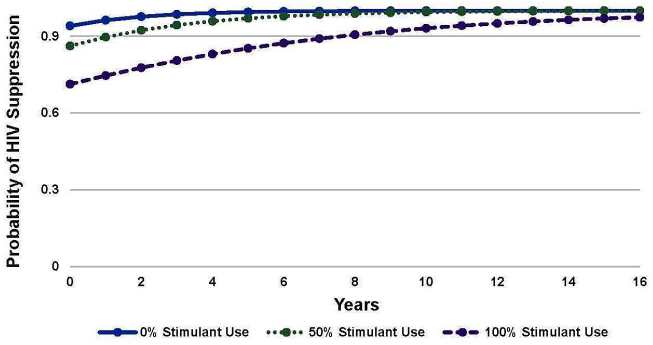
Background: HIV-positive persons who use stimulants (i.e., methamphetamine, powder cocaine, and crack-cocaine) experience difficulties navigating the HIV care continuum that undermine the clinical and public health benefits of anti-retroviral therapy (ART). However, stimulant users may be having more success with contemporary ART regimens that are less burdensome and more forgiving of non-adherence.

Methods: Study of the Consequences of the Protease Inhibitor Era (SCOPE) is a prospective, clinical cohort following HIV-positive persons on ART with assessments every six months. The exposure was the cumulative, time-varying proportion of assessments with any self-reported use of stimulants. HIV suppression (i.e., viral load less than 200 copies/mL), measured at SCOPE assessments or extracted from the clinical record at San Francisco General Hospital, was the time-varying outcome. We utilized multilevel modeling to examine whether the odds of HIV suppression among those receiving ART changed over time as a function of stimulant use.

Results: From 2000-2016, 1,637 HIV-positive participants on ART (57% Caucasian; 78% men who have sex with men) with a median CD4+ T-cell count of 475 cells/mm^3 at enrollment contributed 17,610 person-visits over an average of 21.2 follow-up assessments. Approximately 42% of participants reported any stimulant use over follow-up. We observed a significant interaction of cumulative, time-varying stimulant use by time (Unstandardized Beta = -0.32; 95% CI = -0.50 – -0.13; p = 0.001) such that stimulant users were slower to achieve the 90% target for HIV suppression (see Figure). Time was significantly and positively associated with greater odds of HIV suppression across all levels of stimulant use: 0% cumulative stimulant use (Odds Ratio [OR] = 1.62 95% CI=1.44 – 1.83); 50% cumulative stimulant use (OR = 1.39; 95% CI=1.25 – 1.54); and 100% cumulative stimulant use (OR=1.18; 95% CI = 1.01 – 1.39).

Conclusion: Despite the fact that they achieved HIV suppression at slower rates compared to non-users, stimulant users benefit substantially from ART. Novel approaches are needed to optimize the clinical and public health benefits of ART with HIV-positive stimulant users.

Figure. Predicted probability of HIV suppression from 2000-2016 as a function of stimulant use



520 FUNCTION OF CD4 RECOVERY AND DECREASING IMMUNE ACTIVATION OF A CHINESE HERB: TWHF

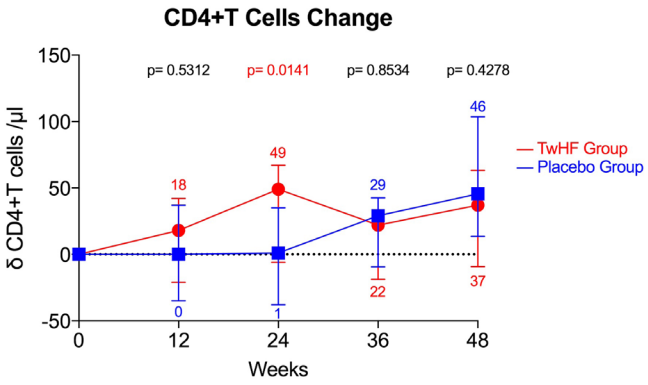
Wei Lu, Yuchao Liu, Yang Han, Zhifeng Qin, Xiaojing Song, Taisheng Li
Peking Union Medical College Hospital, Beijing, China

Background: Chronically enhanced T-cell activation is believed to cause poor recovery in CD4+ T cells in HIV immune non-responders (INRs) after successful antiretroviral therapy (ART). Extracts of Tripterygium wilfordii Hook F (TwHF, known as "lei gong teng") have been used as an anti-inflammatory agent to treat rheumatoid arthritis, lupus and nephritic syndrome in China for decades. Our previous pilot study demonstrated that use of TwHF was associated with a reduction in T-cell activation and improved CD4 recovery.

Methods: In a multi-centered, double-blinded clinical trial, we enrolled 115 HIV individuals with suboptimal CD4+ T cell recovery (<350/ul) on cART for over 24 months with suppressed viral load (<40 copies/ml) for over 18 months. They were randomly assigned to TwHF group (10mg, tid, n=58) and placebo group (n=57) for 24 weeks with continuous ART. The placebo group was uncovered at week 24 and continued to take TwHF until 48 weeks. T-cell subsets with activation markers and inflammation cytokines were evaluated at baseline, week 12, 24 and 48.

Results: Totally 107 patients finished 48 weeks' follow-up with good tolerance and safety profile. There was significant difference in the mean increase of total and memory CD4+ T cell counts and CD4/CD8 ratio in the TwHF group at week 12, 24 and 48 weeks compared to baseline value. There was no change in CD4+ T cell count in the placebo group during the first 24 weeks, but a significant increase of CD4+ T cell count was seen after transferring the placebo group to TwHF regimen. Interestingly, we demonstrated a significant decrease in IP-10, MCP-1, IFN-α and IFN-γ at week 24 compared to baseline between two groups. There was no similar significant difference seen in sCD14, IL-6, TNF-a, CD38, HLA-DR in either groups.

Conclusion: Our data showed that extracts of TwHF is helpful in CD4+ T cells recovery and also could dampen inflammation and immune activation for HIV INR individuals. The possible mechanisms of type I interferon signaling needs to be further explored. It could be a potential strategy combined with antiretroviral therapy to reduce immune activation and inflammation for HIV patients.



521 METABOLIC SHUT DOWN OF CD4 T CELL ACTIVITY AND FUNCTION INDUCED BY HAART

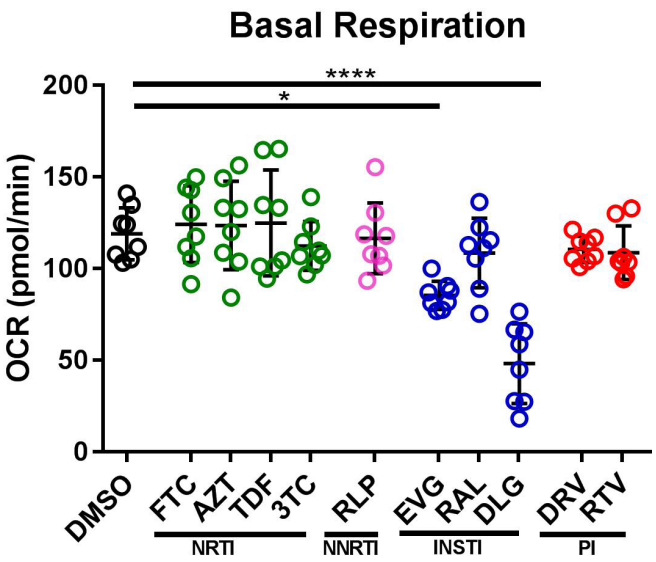
Marek Korencak[1], Enrico Richter[1], Eva Eilers[1], Bruce T. Schultz[1], Patrick Juszczak[1], Stefan Esser[2], **Hendrik Streeck**[1]
[1]Institute for HIV Research, Essen, Germany, [2]University Hospital Essen, Essen, Germany

Background: Metabolism plays a pivotal role in a cell's ability to maintain their viability and fulfil their effector functions. It has been shown that cells in chronically HIV-infected individuals become exhausted and undergo a progressive loss of hierarchical functions, but the changes in their cellular metabolism remain unclear. In this study we evaluate the impact of HIV infection and individual HAART regimens on two major metabolic pathways – oxidative phosphorylation and glycolysis as well as on cellular function.

Methods: Different cell types were isolated from PBMC of HIV-infected treatment-naïve and treated individuals as well as from healthy donors. Cells were stimulated in the presence of different ART regimens and their metabolic profiles were analysed by the extracellular flux analyser Seahorse XFp. We used multicolour flow cytometry to study the function and phenotype of PBMC of each individual and determined changes in ROS production as well as mtDNA content by qPCR.

Results: NK cells, B cells, CD4 and CD8 T cells from HIV infected treatment-naïve individuals displayed significantly reduced basal and maximal respiration compared to healthy controls. The metabolic capacity strongly correlated with the expression of the inhibitory receptor PD-1 ($p<0.0001$) and immune activation level (defined as HLA-DR+ CD38+ expression; $p<0.0001$). Interestingly, while long-term HAART treatment robustly restored the bioenergetic profile of NK cells, B cells and CD8 T cells, it had a negative effect on CD4 T cells, particularly in Dolutegravir (DLG) containing regimens. We therefore assessed the impact of individual antiretrovirals on CD4 T cell metabolism. Strikingly, the integrase strand transfer inhibitors (INSTI) Elvitegravir (EVG) and DLG, but not Raltegravir (RAL), shut down the basal and maximal respiration of CD4 T cells. This significantly altered the functional profiles of the cells by driving them from a balanced polyfunctional response to a TNFα-dominated 'stress' immune response. Analysis of mitochondrial ROS and mtDNA quantities revealed increased mitochondrial toxicity, but not general cytotoxicity, in the presence of these drugs.

Conclusion: Taken together, our data demonstrate a substantial disruption in the metabolic activity of lymphocytes during chronic HIV infection that is restored through antiretroviral therapy. However, two INSTI, DLG and EVG, diminish the metabolic activity in CD4 T cells, leading to a switch in functionality and impairment of overall function.



522 NATURAL CONTROL OF HIV INFECTION IN A COHORT OF YOUNG WOMEN IN SOUTH AFRICA: HPTN 068

Mariya V. Sivay[1], Yinfeng Zhang[1], Jing Wang[2], Jessica M. Fogel[1], Estelle Piwowar-Manning[1], William Clarke[1], Erica Hamilton[3], Kathleen Kahn[4], Amanda Selin[5], Xavier Gomez-Olive[4], Catherine MacPhail[6], James P. Hughes[7], Audrey Pettifor[5], Susan H. Eshleman[1]
[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Statistical Center for HIV/AIDS Research and Prevention, Seattle, WA, USA, [3]FHI 360, Durham, NC, USA, [4]University of the Witwatersrand, Johannesburg, South Africa, [5]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [6]University of Wollongong, Wollongong, Australia, [7]University of Washington, Seattle, WA, USA

Background: HIV controllers are able to suppress viral replication to low levels without antiretroviral (ARV) therapy. The HIV Prevention Trials Network (HPTN) 068 trial was conducted in a rural area in South Africa and evaluated the impact on HIV incidence of a cash transfer conditional on high school attendance (study period: 2011-2015). The trial enrolled 81 HIV-infected and 2,448 HIV-uninfected women who were followed annually until their expected graduation date; some women had a post-graduation follow-up visit 1-2 years later. Overall, 164 women acquired HIV infection (seroconverters). We evaluated the frequency of HIV controllers in this cohort.

Methods: HIV viral load (VL) testing was performed using the RealTime HIV-1 Viral Load assay (limit of quantification: 40 copies/mL). ARV drug testing was performed using a qualitative assay that detects 20 ARV drugs in 5 drug classes. HIV genotyping was performed for samples with VLs >400 copies/mL using the Viroseq HIV-1 Genotyping System, v2.8. Women were classified as viremic controllers if they had a VL ≤ 2,000 copies/mL at study enrollment or their first HIV-positive visit (for seroconverters), and maintained this level of viral suppression for at least 12 months in the absence of ARV drug use. Statistical analysis was performed using SAS software.

Results: Thirty-four (13.9%) of the 245 HIV-infected women had VLs ≤2,000 copies/mL at the first visit tested with no ARV drugs detected at that visit (12 at enrollment; 22 at their first HIV-positive visit; three seroconverters had VLs <40 copies/mL at this visit). Fifteen of the 34 women were followed for ≥12 months. Twelve of the 15 women were classified as viremic controllers (seven who were HIV-infected at enrollment; five who seroconverted during the study; one woman had a single VL value ≥2,000 copies/mL during follow-up; median follow-up: 20 months, range 13-42 months). These women had sustained viral suppression with no ARV drugs detected during follow-up. Only one of 12 viremic controllers had HIV drug resistance.

Conclusion: In this cohort of young women in rural South Africa, at least 5% were able to control viral replication to low levels in the absence of ARV drug use (8.6% of women who were HIV infected at enrollment and 3.1% of the seroconverters). These data may help inform future studies of HIV treatment and prevention in this high-incidence population.

523 PRETREATMENT HIV DRUG RESISTANCE SPREAD WITHIN TRANSMISSION CLUSTERS IN MEXICO CITY

Margarita Matías-Florentino[1], Antoine Chaillon[2], **Santiago Avila-Rios**[1], Verónica Ruiz[3], Silvia del Arenal[1], Manuel A. Becerril-Rodríguez[1], Alicia Piñeirúa[3], Florentino Badial Hernandez[3], Andrea Gonzalez Rodriguez[3], Sanjay R. Mehta[2], Gustavo Reyes-Terán[1]

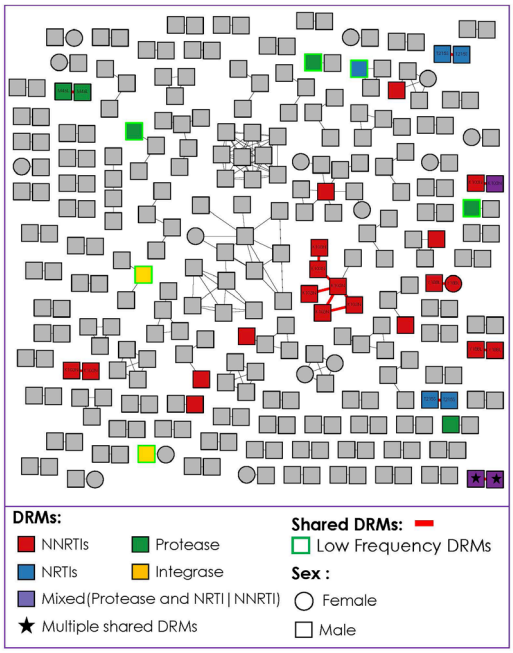
[1]National Institute of Respiratory Diseases, Mexico City, Mexico, [2]University of California San Diego, San Diego, CA, USA, [3]Clinica Especializada Condesa, Mexico City, Mexico

Background: Baseline screening for HIV drug resistance mutations (DRM) for all individuals starting antiretroviral treatment (ART) has been proposed as a public health action in Mexico in response to rising non-nucleoside reverse transcriptase inhibitor (NNRTI) pretreatment drug resistance (PDR). Here we performed full-length pol deep sequencing (MiSeq, Illumina) for DRM screening in all persons diagnosed at Clinica Especializada Condesa (CEC), the largest HIV clinic in Mexico, to estimate prevalence and transmission of PDR.

Methods: All individuals diagnosed with HIV at CEC from April 2016 to July 2017 who agreed to participate in the study were enrolled, and blood was obtained for sequencing. Sequences were assembled using HyDRA (Public Health Agency of Canada). ART resistance was defined as presence of any surveillance DRM at a sensitivity threshold 5%. Genetic network analyses were performed to infer relationships between HIV sequences (<1.5% genetic distance), and we looked for DRM shared between genetically linked sequences.

Results: Full-length pol sequences were generated from 987 individuals. The median read coverage for DRM sites was 1,620 (IQR 944-2548). Using the 5% sensitivity threshold, 14.9% (147/987) of sequences contained surveillance DRM to any antiretroviral, 11.3% (74/987) to NNRTI, 4.3% (42/987), to nucleoside RT inhibitors (NRTI), 4.9% to protease inhibitors (PI) (48/987), and 0.7% (6/987) to integrase strand transfer inhibitors (INSTI). K103N was the most frequent surveillance DRM (5.3%). A total of 295/987 (31.5%) sequences had a putative linkage with at least one other sequence forming 109 clusters (range: 2-14 individuals, 28 non-dyad clusters). 36 sequences within clusters had DRMs. From these, 22/36 (61.1%) shared the same DRM with a linked sequence in 9 distinct clusters, including one cluster of 7 individuals in which 6/7 sequences shared K103N (Figure). The most frequently transmitted DRMs were K103N (10/22 individuals sharing DRMs, 3 clusters), T215S (6/22, 3 clusters), Y188L (4/22, 2 clusters and M46L (4/22, 2 clusters). None of 6 low-frequency DRMs (<20% sensitivity threshold) were shared between genetically linked individuals.

Conclusion: Network analysis demonstrated frequent cases of shared DRMs among linked individuals, especially K103N, revealing the potential for spread of pretreatment DRM. No cases of transmission of low-frequency DRMs were observed. These results highlight the need to obtain and rapidly deliver HIV DR results to treating clinicians in Mexico.



524 SPREAD OF HIV-1 PRE-TREATMENT DRUG RESISTANCE IN THE COLOGNE-BONN REGION, GERMANY

Melanie Stecher[1], Martin Hoenigl[2], Anna-Maria Eis-Huebinger[3], Clara Lehmann[1], Gerd Fätkenheuer[1], Jan-Christian Wasmuth[3], Rolf Kaiser[1], Sanjay R. Mehta[2], Joerg Janne Vehreschild[1], Antoine Chaillon[2]

[1]Cologne University Hospital, Cologne, Germany, [2]University of California San Diego, San Diego, CA, USA, [3]Bonn University Hospital, Bonn, Germany

Background: In Germany, the prevalence of HIV-1 drug resistance mutations (DRM) remains high, affecting treatment failure and the choice of antiretroviral therapy (ART). We sought to understand the molecular epidemiology of HIV and DRM transmission in the metropolitan region of Cologne-Bonn, one of the regions with the highest rate of new infections, using a combined phylogenetic and geospatial approach.

Methods: We included 714 HIV-1 infected ART naïve individuals, followed at the University Hospital Cologne (n=558;78.2%) and Bonn (n=156;21.9%) between 1999 and 2016. Phylogenetic and network analyses were performed to infer putative relationships between HIV partial pol sequences obtained by routine genotype testing. Sociodemographic and geographic data were used to characterize transmission clusters. Geospatial dispersal of the clusters was determined by calculating the average distance between reported residence (centroids of 3-digit zipcode, ArcGIS®). Transmission of DRM was estimated between genetically linked individuals.

Results: HIV-1 infected participants were predominantly male (81.9%) and had a median age of 39 years (IQR: 31-47). Drug resistance screening found 7% and 13.6% of sequences contained nucleoside or non-nucleoside reverse transcriptase inhibitor (NRTI/NNRTI) DRM. Putative transmission links were inferred in 177/714 (24.8%) sequences forming a total of 63 clusters (size ranging from 2-8, Figure). Clustering individuals were significantly younger (median age 36 vs 39, p=0.0014), men (92.1% vs 78.5%, p<0.001) reporting sex with men (MSM) as main risk factor (69.5% vs 53.1%, p<0.001). DRM frequency was comparable in clustering and not clustering individuals (18.1% vs 17.1%, p=0.91). Most clustering individuals were found in the city center of Cologne 43/177 (47.5%). The distance between centroids was significantly lower for genetically linked- than non-linked sequences (18.6km [IQR 11.7-30.7] vs 36.2km [IQR 22.5-53.8]; p<0.001). Of the 51 putative links including sequences harboring any DRM, 20 (39%) were shared by genetically-linked partners (Figure, red edges), suggesting DRM transmission among ART Naïve individuals.

Conclusion: In our study sample, we found evidence of transmitted DRM located especially in the city center of Cologne, well known for its districts with strong gay community. Phylogenetic and geospatial characterization of HIV revealed close/dense hotspots of HIV transmission that could help identifying targets for treatment and interventions.

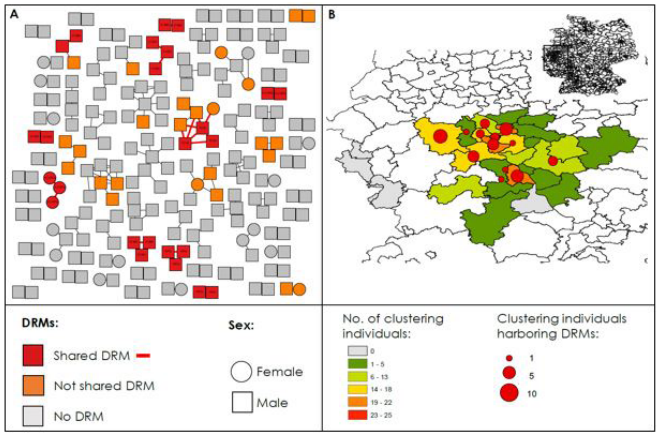


Figure. Local HIV pre-treatment drug resistance transmission network in the city of Cologne, Germany. **A)** All edges represent a genetic distance of ≤1.5% separatinnodes. Color indicates the absence (in grey) or presence of shared (in red) or not shared DRM (in orange). Edges in bold red indicate individuals who shared DRMs. Only shared DRM are labeled with each nodes. N|NRTIs indicate ≥1 nucleoside or non-nucleoside reverse transcriptase inhibitor resistances. **B)** Map of the Cologne-Bonn region of the sample population, plotted by using the first three digits of the zip code of residency. Number of clustering individuals and clustering individuals harboring DRMs, mostly located in the city center of cologne, are displayed.

525 IMPACT OF TRANSMITTED RESISTANCE ON CLINICAL OUTCOMES IN THE VMVN TRIAL IN VIETNAM

Vu P. Thao[1], Cuong D. Do Duy[2], Thanh Thuy Pham Thi[2], Duong T. Hao[3], Bui T. That[1], Donn Colby[4], Todd Pollack[3], Thuy Le[1]
[1]Oxford University Clinical Research Unit in Vietnam, Ho Chi Minh, Vietnam, [2]Bach Mai Hospital, Hanoi, Vietnam, [3]Beth Israel Deaconess Medical Center, Boston, MA, USA, [4]SEARCH, Bangkok, Thailand

Background: Transmitted drug resistance (TDR) has been shown to impair treatment outcomes. Baseline drug resistance testing is recommended to guide therapy in resource-rich countries. However, drug resistance screening is expensive, is not widely available, and its impact on treatment outcomes in resource-limited countries remains unclear.
Methods: We investigated TDR mutations and their clinical impact in antiretroviral-naïve patients initiating first-line ART in the VMVN study, a randomized controlled trial of routine virological monitoring versus targeted virological monitoring at Bach Mai Hospital in Vietnam between April 2011 and May 2017. TDR mutations were identified by Sanger sequencing of the partial pol gene and were defined based on the 2009 WHO surveillance drug resistance mutation list. The association of TDR and virological failure (defined as confirmed HIV RNA >200 copies/mL) or death over 36 months was investigated using Logistic regression analyses.
Results: Among 650 patients enrolled in the trial, 603 patients were ART-naïve, successful sequencing was obtained for 564 patients. The median age was 33; 65% were male; the median CD4 count was 119 (IQR: 29-273) cells/mm^3. TDR mutations were identified in 32 (5.6%) patients: 15 (46.9%) patients harbor mutations conferring resistance to NRTIs, 10 (31.3%) to NNRTIs, 11 (34.4%) to PIs, 4 (12.5%) to both NRTIs and NNRTIs. Complete outcome data were available for 500 patients. 50 (10%) patients died after a median of 4.9 (IQR: 2.2-14.8) months. In both univariable and multiple variable analyses (with routine versus targeted virological monitoring as a covariable), the risks of virological failure or death at 36 months were higher in patients who had TDR; however, the differences in risk were not statistically significant, univariable OR=1.30, 95% CI: 0.37-3.52, P=0.664 and adjusted OR=1.30, 95% CI: 0.37-3.54, P=0.641, respectively. ···
Conclusion: TDR remains stable at <10% despite over 10 years of ART scale up in Vietnam and does not increase the risk of virological failure or death over 36 months of follow up. Our data do not support baseline drug resistance testing in Vietnam.

526 PREVALENCE OF HIV-1 ANTIRETROVIRAL DRUG RESISTANCE IN FLORIDA, 2015-2016

Karalee Poschman[1], Emma C. Spencer[2]
[1]CDC, Atlanta, GA, USA, [2]Florida Department of Health, Tallahassee, FL, USA

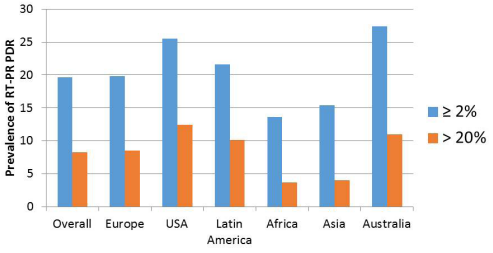
Background: Antiretroviral (ARV) use is pivotal in the treatment and prevention of the spread of HIV and has significantly reduced the morbidity of those living with HIV. Continued use of ARV drugs has led to resistance to certain drug classes as the HIV-1 virus mutates, reducing drug efficacy for patients to achieve viral load suppression (<200 copies/ml). Determining baseline drug resistance using nucleotide genotyping on treatment-naïve patients is recommended to ascertain appropriate therapies to use in the presence of resistance. Surveillance of HIV-1 ARV drug resistance in Florida's population is essential for the development of local and statewide treatment and prevention programs.
Methods: HIV-1 nucleotide genotype sequences and epidemiological data reported to the Florida Department of Health HIV/AIDS surveillance system were analyzed for persons whose HIV was diagnosed in Florida with a sequence obtained within three months of diagnosis in 2015 (n=2071) and 2016 (n=1952). ARV drug resistance was determined using the Stanford HIV Drug Resistance Database.
Results: From sequences obtained for persons whose HIV was diagnosed in 2015 and 2016, transmitted drug resistance (TDR) to any drug class was identified in 11.9% (10.9-13.0% CL). For specific drug classes, TDR for non-nucleoside reverse transcriptase inhibitors (NNRTIs) was identified in 9.1% (8.2-10.0% CL), 1.4% (1.1-1.9% CL) for nucleoside reverse transcriptase inhibitors (NRTIs), 0.9% (0.6-1.2% CL) for protease inhibitors (PI), and 1.8% (1.4-2.3% CL) for integrase inhibitors (IN). From 2015 to 2016, resistance to NNRTIs decreased (p=0.006), and resistance to IN increased (p=0.033). Among persons whose HIV was diagnosed in 2016, resistance to multiple drug classes occurred more frequently in women (p=0.002) and persons with HIV attributable to heterosexual contact (p=0.034). Furthermore, a baseline genotype was indicative of being retained in care (two HIV-related labs or medical visits at least three months apart) (p<0.001) and virally suppressed (p=0.004). Resistance to any drug class was associated with a decreased likelihood of viral suppression (p=0.048).
Conclusion: HIV-1 ARV drug resistance within a population is dynamic in nature and should be monitored closely to inform treatment and prevention programs, especially as new drug regimens are brought to market. A baseline genotype should be conducted as an initial point of care service to validate future treatment and care plans and reduce the transmission of HIV.

527 PRETREATMENT HIV DRUG RESISTANCE IN THE START STUDY USING NEXT GENERATION SEQUENCING

John D. Baxter[1], David Dunn[2], Rasmus L. Marvig[3], Marc Bennedbaek[4], Alessandro Cozzi-Lepri[2], Shweta Sharma[5], Anna Tostevin[2], Michael Kozal[6], Mark Gompels[7], Angie N. Pinto[8], Jens D. Lundgren[4]
[1]Cooper University Hospital, Camden, NJ, USA, [2]University College London, London, UK, [3]Rigshospitalet, Copenhagen, Denmark, [4]Copenhagen HIV Program, Copenhagen, Denmark, [5]University of Minnesota, Minneapolis, MN, USA, [6]Yale University, New Haven, CT, USA, [7]North Bristol NHS Trust, Bristol, UK, [8]University of New South Wales, Sydney, NSW, Australia

Background: In START, an international trial of immediate verses deferred ART initiation among ART-naïve HIV-infected persons with CD4 counts >500 cells/µL, study entry HIV-1 was characterized by next generation sequencing (NGS); a sensitive assay capable of detecting low-frequency variants associated with pre-treatment HIV-1 drug resistance (PDR).
Methods: Stored plasma specimens from participants with study entry HIV RNA >1,000 copies/ml were analyzed by NGS (Ilumina MiSeq). PDR was based on the WHO 2009 surveillance definition with the addition of reverse transcriptase (RT) mutations T215N and E138K, and integrase inhibitor (INI) mutations (Stanford HIVdb). Drug resistance mutations (DRMs) detected at two thresholds are reported, ≥2% verses >20% of the viral population (the latter comparable to the detection threshold for Sanger sequencing).
Results: Between 2009-2013, the START trial enrolled 4,684 ART-naïve individuals in 35 countries. Baseline NGS data at study entry was available for 3,365 participants; median CD4 count 642 cells/µL, median HIV RNA 19,800 copies/mL, and median time since diagnosis was 0.9 years. The overall prevalence of PDR in START using a detection threshold of ≥2%/>20% was 19.7/8.3% for RT-protease (PR) DRMs (6.1/2.7% for NRTIs, 7.0/4.3% NNRTIs, 9.0/2.1% PIs) and 0.9/<0.1% for INI DRMs. The prevalence of RT-PR PDR was highest in Australia and the USA, while lowest in Africa (figure). Prevalence of NNRTI PDR using the ≥2%/>20% thresholds by region was: USA 11.7/9.4%, Latin America 7.7/5.8%, Europe 6.8/3.3%, Asia 5.7/2.2%, Australia 5.5/2.7%, and Africa 4.1/2.2%. Using the ≥2% detection threshold, the six individual DRMs with the highest prevalence were: RT K103N 2.9/2.7%, M41L 1.6/1.2%, G190E 1.3/0.1%, PR M46I 3.1/0.4%, M46L 1.3/0.5%, and D30N 1.3/0.2% at the ≥2%/>20% thresholds. RT M184I 0.4/0%, D67G 0.1/0%, L74V 0.1/0%, and Y188C 0.1/0% were only detected as minor variants. The most frequently detected INI DRMs were Y143H 0.2/0%, T66I 0.1/<0.1%, and Y143C 0.1/0%.
Conclusion: The START trial represents one of the largest global cohorts with NGS characterization of PDR. Overall prevalence of PDR using the ≥2% detection threshold was 19.7% for RT-PR DRMs, while only 8.3% using the 20% threshold and varied by region. INI DRMs were detected in 0.9% of the study cohort primarily as minor variants. NGS would be expected to detect a substantially higher prevalence of PDR than traditional Sanger sequencing, particularly for DRMs occurring predominately as minor variants.

Figure. Prevalence of RT-PR PDR in the START population at ≥2% and >20% detection thresholds, overall and by geographic region.



528 DECLINE IN CLINICALLY RELEVANT RESISTANCE TO FIRST-LINE ARV REGIMENS IN SPAIN

Marta Alvarez[1], José Ángel Fernández-Caballero[1], Ana B. Perez[1], Nuria Espinosa[2], Silvia García-Bujalance[3], Maria Jesus Perez-Elias[4], Rafael Delgado[5], José A. Iribarren[6], Isabel Viciana[7], David Dalmau[8], Antonio Aguilera[9], Mar Masia[10], Victoria Hernando[11], **Federico García**[1]

[1]Hospital Universitario San Cecilio, Granada, Spain, [2]Hospital Universitario Virgen del Rocio, Sevilla, Spain, [3]La Paz University Hospital, Madrid, Spain, [4]Hospital Ramon y Cajal, Madrid, Spain, [5]Hospital Universitario 12 de Octubre, Madrid, Spain, [6]Hospital Donostia, San Sebastián, Spain, [7]Hospital Virgen de la Victoria, Málaga, Spain, [8]Hospital Universitari Mútua de Terrassa, Terrassa, Spain, [9]Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain, [10]Hospital General Universitario de Elche, Elche, Spain, [11]Institute de Salud Carlos III, Majadahonda, Spain

Background: Transmitted drug resistance (TDR) is currently evaluated on single mutations. As initial regimens currently recommended by treatment guidelines include high genetic barrier antiretrovirals (ARVs), evaluating the clinically relevant resistance may be of interest. Here we present data on clinically relevant transmitted drug resistance to ARVs recommended for first line treatment in Spain during the period 2007-2017.

Methods: We analysed 5484 RT & Pro Fasta sequences from CoRIS, the HIV ARV naïve cohort of the Spanish AIDS Research Network. As Integrase resistance is not part of routine testing in naïve patients in Spain, we run a surveillance programme (2012-2017) and tested 576 patients with samples available at the RIS Biobank. We evaluated the prevalence of TDR mutations using the WHO list 2009 update (Bennet et al) and the 2017 IAS list (Wensing et al) for Integrase mutations. Clinically relevant TDR was investigated using Stanford v 8.4 Algorithm. As recommended, potential low-level resistance was pooled into the susceptible category. First line regimens for each study period were those recommended by the Spanish treatment guidelines (GESIDA).

Results: Overall, TDR mutations using the WHO list was 7.9% (3.6% NRTIs, 3.7% NNRTIs, 2.0% PIs), and 2,7 % INSTIs (IAS list), and no significant change during the study period was observed. Clinically Relevant resistance to recommended 1st line regimens showed a slow decline from 2007-2012, and peaked in 2013-2014 due to the inclusion of Rilpivirine for 1st line in the Spanish recommendations. Detailed results for 2007-2017 are shown in the table below:

Conclusion: TDR remained stable in Spain through 2007-2017 when individual mutations were evaluated. However, clinically relevant TDR to approved first line regimens showed a slow decline from 2007 to 2017. Resistance to INSTIs remains at very low levels even in 2017 in Spain. These findings, together with the very low prevalence of resistance to first line NRTIs in 2015-2017 may question the need for baseline resistance prior to starting an INSTI based first line regimen in Spain.

Period	Overall % (IQR)	NRTIs (%)	NNRTIs (%)	PIs (%)	INsTIs (%)
2007 (n=482)	8,5 [6.2-11.4]	3,3 [1.9-5.3]	5,6 [3.7-8.0]	1,4 [0.5-2.9]	*
2008-2009 (n= 1169)	6,8 [5.4-8.4]	3,5 [2.5-4.7]	4,3 [3.2-5.6]	0,6 [0.2-1.2]	*
2010-2011 (n=1298)	6,2 [4.9-7.6]	1,6 [1.0-2.4]	4,5 [3.4-5.8]	0,6 [0.3-1.2]	*
2012 (n=555)	6,7 [4.8-9.1]	2,5 [1.4-4.2]	4,7 [3.1-6.8]	1,1 [0.4-2.4]	0,7 [0.01-4.0] (n=134)
2013 (n=577)	9,5 [7.2-12.2]	1,2 [0.5-2.5]	8,1 [6.0-10.6]	0,9 [0.3-2.1]	0 (n=60)
2014 (n=582)	11,8 [9.3-14.7]	1,7 [0.8-3.1]	10,1 [7.8-12.8]	1,4 [0.6-2.7]	0 (n=103)
2015-2017 (n=821)	2,2 [1.3-3.4]	2,1 [1.2-3..3]	*	*	0,7 [0.1-2.5] (n=279)

*ARVs not recommended for 1st line

529 HIGH PREVALENCE OF NNRTI AND INI-RESISTANT POLYMORPHIC VIRUS IN PRIMARY HIV INFECTION

Marie-Laure Chaix Baudier[1], Maxime Grudé[2], Heloise M. Delagreverie[1], Catherine Roussel[3], Helene Pere[4], Helene Le Guillou-Guillemette[5], Julia Dina[6], Anne Signori-Schmuck[7], Marie-Josee Carles[8], Laurence Morand-Joubert[9], Jacques Izopet[10], Laurence Meyer[11], Lambert Assoumou[2], Diane Descamps[12]

[1]Hôpital Saint-Louis, Paris, France, [2]INSERM, Paris, France, [3]CHU de Amiens, Amiens, France, [4]Georges Pompidou European Hospital, Paris, France, [5]CHU de Angers, Angers, France, [6]CHU de Caen, Caen, France, [7]CHU de Grenoble, Grenoble, France, [8]CHU de Nimes, Nimes, France, [9]Saint-Antoine Hospital, Paris, France, [10]Toulouse University Hospital, Toulouse, France, [11]INSERM, Le Kremlin-Bicetre, France, [12]Bichat–Claude Bernard Hospital, Paris, France

Background: According to the French ANRS program for HIV-1 resistance surveillance, we estimated the prevalence of transmitted drug resistance associated mutations (TDRAMs) in primary infected patients (PHI) diagnosed in France in 2014-2016.

Methods: TDRAMs were sought in plasma samples from 373 patients in 2014, 388 in 2015 and 375 in 2016 (n=1136), from 46 clinical centers. Protease and reverse-transcriptase TDRAMs were identified from the 2009 Stanford Resistance Surveillance list; etravirine, rilpivirine and integrase mutations from the IAS and ANRS lists. Doravirine-associated mutations identified in vitro and defining DOR resistance in this study were: V106A, V106M, V108I, H221Y, F227L, F227C, F227V, M230I, L234I, P236L. The HIV envelope gene was sequenced and tropism was determined using the Geno2Pheno algorithm (FPR 10%). HIV-1 subtype was determined from the RT sequence.

Results: Patients were mainly men (90%), having sex with men (73%), living in the Paris area (41%). At inclusion, the median CD4 cell count and plasma HIV-1 RNA were 480/µL (IQR: 330–637) and 5.5 $\log_{10}$ cp/mL (IQR: 4.7–6.4), respectively. By the Stanford list, the prevalence of virus with PR or RT RAMs was 10.6% (CI95% [8.92;12.59]). Prevalence of PI and NRTI resistance was 2.8% (CI95% [1.93;3.95]) and 5.1% [3.90;6.55]; prevalence of NNRTI resistance was 4.0% [2.90;5.26] or 10.2% [8.51;12.12] including etravirine and rilpivirine RAMs. INI RAMs were observed in 5.3% of samples [3.96;6.97]: L74M n=9, E92Q/G n=2, T97A n=14, E138K n=3, E157Q n=18, S230R n=2, R263K n=2. The double mutant E92Q+T97A was observed in 1 patient. The overall prevalence of sequences with at least 1 DOR associated mutation was 0.9% [0.42; 1.61]. The frequency of TDRAMs to NRTI, NNRTI, PI and INI was stable over time (Figure). At enrolment, 81/523 (15.5%) of samples harbored a X4/DM tropic virus. In a multivariate analysis, age (>30 years) was the only factor significantly associated with TDRAMs while baseline characteristics such as gender, transmission route, CD4 count, viral load, subtype and year of inclusion were not. The prevalence of non-B subtype increased from 37.1% in 2014 to 50.2% in 2016 (p<0.0027).

Conclusion: In France in the 2014/2016 period, the overall prevalence of TDRAMs was 10.6%, similarly to the previous surveys (going back to 1996 for PI and NRTI.) However, we describe a high level of NNRTI resistance (10.2%) including ETR and RPV (only 0.9% of resistance to doravirine) and a high prevalence of INI RAMs.

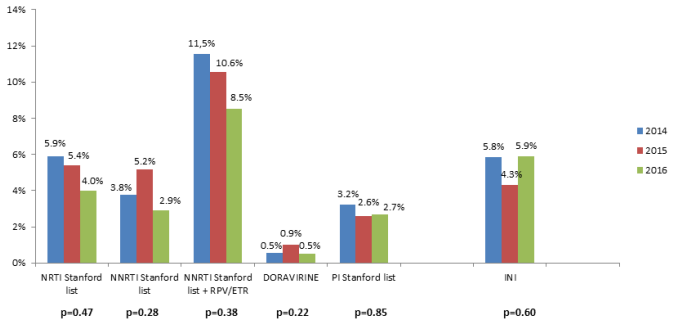


Figure: Frequency of transmitted drug resistant mutations to NRTI, NNRTI, PI and INI according to the year of inclusion

530 HIV DRUG RESISTANCE AS A SIGNIFICANT DRIVER OF FIRST-LINE TREATMENT FAILURE IN UGANDA

Suzanne McCluskey[1], Nicholas Musinguzi[2], Kimia Kamelian[3], Guinevere Q. Lee[1], Yap Boum[4], Bosco M. Bwana[2], Conrad Muzoora[2], Jeffrey N. Martin[5], Peter W. Hunt[5], Vincent C. Marconi[6], David R. Bangsberg[7], Jessica E. Haberer[1], P. Richard Harrigan[3], Mark J. Siedner[1]

[1]Massachusetts General Hospital, Boston, MA, USA, [2]Mbarara University of Science and Technology, Mbarara, Uganda, [3]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, [4]Epicentre, Mbarara, Uganda, [5]University of California San Francisco, San Francisco, CA, USA, [6]Emory University, Atlanta, GA, USA, [7]Oregon Health and Sciences University, Portland, OR, USA

Background: The World Health Organization recommends a change to second line antiretroviral therapy (ART) after two HIV RNA results >1,000 copies/mL with interval adherence support. We have previously shown that adherence does not predict resuppression following failure with HIV RNA >1,000 copies/mL. Herein, we seek to evaluate the effect of HIV drug resistance (HIVDR) at first line failure on rates of resuppression.

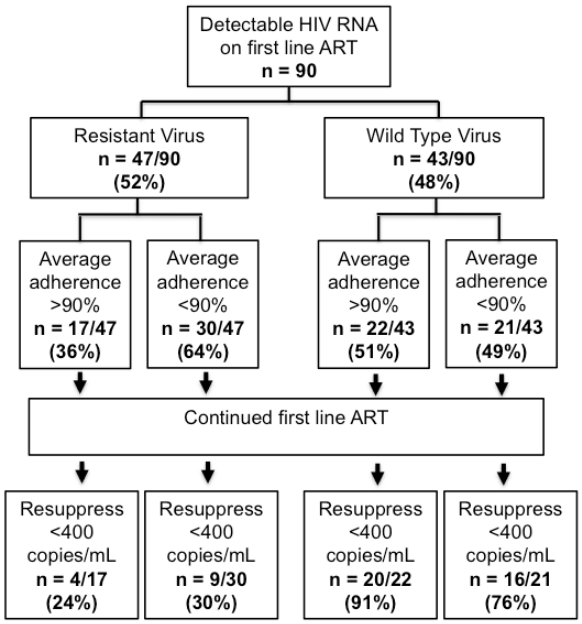
Methods: We analyzed data from the Uganda AIDS Rural Treatment Outcomes study, which followed adults with HIV initiating ART with objective adherence monitoring (2005-2015). Participants underwent quarterly HIV RNA tests

and genotypic resistance tests (GRTs) for episodes of detectable viremia. In this analysis, we included episodes of detectable HIV RNA with paired GRTs after at least four months on ART, after which participants remained on the same regimen until a subsequent HIV RNA test. Our aim was to identify relationships between HIVDR, adherence and resuppression. We defined HIVDR as intermediate or high-level resistance to any drug in the first line regimen using Stanford susceptibility scores. We calculated resuppression rates by HIVDR status, stratified by average adherence. We fit logistic regression models with robust standard errors with resuppression as the outcome and HIVDR as the predictor of interest, adjusting for sex, age, HIV RNA at first failure, average adherence, and regimen.

Results: We analyzed 90 episodes of viremia. Median ART duration was 0.84 years, and 100% were on non-nucleoside reverse transcriptase inhibitors (NNRTI). Median log HIV RNA at first failure was 3.56 copies/mL. Median time between HIV RNA tests was 84 days. Forty-seven (52%) participants had HIVDR, with NNRTI mutations most common. 49/90 (54%) achieved resuppression, but the rate was significantly lower in those with versus without HIVDR (28% vs. 84%, P<0.001). When stratified by adherence, results were not significantly different (Figure). HIVDR remained a strong negative predictor of resuppression in a logistic regression model, adjusted for sex, age, HIV RNA at first failure, adherence, and regimen (OR 0.06, 95% CI 0.02 – 0.20, P<0.001). Adherence was not correlated with resuppression, and there was no significant interaction with HIVDR.

Conclusion: HIVDR is an important driver of persistent virologic failure on first line ART. Current guidelines that focus on those with HIV RNA >1,000 copies/mL and adherence support may fail to address this primary driver of treatment failure in the region.

Figure. Genotypic Resistance and Viral Resuppression



531 EFFECT OF 12-WEEK RALTEGRAVIR INTENSIFICATION OF FIRST-LINE ART ON HIV RESISTANCE

Cissy Kityo[1], Sarah Walker[2], Immaculate Nankya[1], Moira J. Spyer[2], Eva Nabulime[1], Mutsa Bwakura-Dangarembizi[3], Linda Mipando[4], Simon Wachira[5], Anthony Etyang[6], Godfrey Musoro[3], Esther Nambi[1], Kusum Nathoo[3], Sarah Pett[2], Diana Gibb[2]

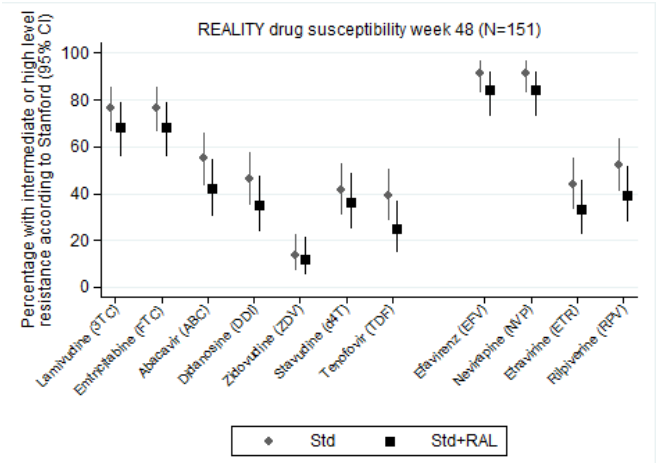
[1]Joint Clinical Research Centre, Kampala, Uganda, [2]University College London, London, UK, [3]University of Zimbabwe, Harare, Zimbabwe, [4]University of Malawi, Blantyre, Malawi, [5]Moi University, Eldoret, Kenya, [6]KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya

Background: The REALITY trial (ISRCTN43622374) showed that 12-week raltegravir (RAL)-intensified ART (Std+RAL) was well tolerated, reduced VL faster through 24 weeks, but did not affect mortality or WHO 3/4 events through 48 weeks compared to standard 2NRTI+NNRTI (Std) ART in ART-naïve HIV-infected adults/children ≥5y with CD4<100 cells/ul. The impact of RAL intensification on HIV resistance in those initiating ART with low CD4 and high VL is unknown.

Methods: Integrase (INT) was sequenced from Std+RAL samples with VL>1000 c/ml at week 12 , and reverse transcriptase (RT) sequenced in samples >1000 c/ml from both groups at week 48. INT/RT resistance was predicted using Stanford.

Results: 1550 eligible patients were from Kenya, Uganda and Zimbabwe (Malawi samples not available) and randomized to Std+RAL (n=775) vs Std (n=775). Median baseline CD4 was 36 cells/ul and VL 275,700 c/ml (76%≥100,000 c/ml). At week 12, VL was <50 c/ml in 470/667 (69%) Std+RAL vs 334/685 (49%) Std (p<0.001). 45(7%) Std+RAL had VL>1000 c/ml, of whom INT genotypes were obtained in 30(67%) (median 55680 c/ml). The primary/major accessory mutations R263K, T97A, L74M or N155H were found in 5, 5, 1, 1 respectively, translating into 1 with intermediate (T97A+R263K) and 1 with high-level (N155H) RAL resistance (7% of sequenced at week 12; 0.4% of randomized) (week-48 VL 22976 and <50 c/ml respectively). No patient had intermediate/high-level dolutegravir resistance. At 48 weeks, VL was <50 c/ml in 527/654 (81%) Std+RAL vs 495/642 (77%) Std (p=0.12) and >1000 c/ml in 76(12%) vs 90(14%) respectively (p=0.20). RT genotypes were obtained in 69(91%) Std+RAL vs 82(91%) Std. K219E/Q (p=0.005), M41L (p=0.053), K101E/P (p=0.04) and P225H (p=0.008) were less common in Std+RAL. However, there was no evidence of differences between Std+RAL vs Std in intermediate/high-level resistance to 3TC (overall 73%,p=0.23), ABC (49%,p=0.12), ZDV (13%,p=0.74), EFV/NVP (88%,p=0.16), RPV (46%,p=0.10) or ETR (39%,p=0.18), whereas there was marginally less intermediate/high-level resistance with Std+RAL to TDF (25% vs 39% Std, p=0.06).

Conclusion: 12 week RAL intensification had no clinical benefit and did not substantially protect against developing clinically meaningful NRTI/NNRTI resistance. Major INT mutations potentially compromising RAL, but not dolutegravir, occurred in very small numbers of those receiving 12 week RAL; whether this was transmitted or emergent is uncertain, as baseline INT sequencing was not performed.



532 POOLED WEEK 48 EFFICACY AND BASELINE RESISTANCE: B/F/TAF IN TREATMENT-NAIVE PATIENTS

Kirsten L. White, Rima Kulkarni, Madeleine Willkom, Ross Martin, Silvia Chang, Xuelian Wei, William Garner, Devi SenGupta, Hal Martin, Erin Quirk, Andrew Cheng

Gilead Sciences, Inc, Foster City, CA, USA

Background: Two phase 3, randomized, blinded, studies showed HIV-1 treatment with bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) had no emergent resistance and was non-inferior to abacavir/dolutegravir/lamivudine (ABC/DTG/3TC, Study 1489) and DTG+F/TAF (Study 1490) in treatment-naïve subjects. Here, pooled efficacy analyses through W48 and the effect of baseline resistance on treatment response are described.

Methods: Population sequencing of HIV-1 protease and reverse transcriptase was done at screening; resistance to study NRTIs was excluded. Baseline retrospective next generation sequencing of integrase (all randomized,

N=1274) was correlated with prespecified pooled virologic outcomes from the 2 studies. Virologic failures with HIV-1 RNA ≥200 c/mL had resistance analyses at confirmed failure or last visit.

Results: High levels of virologic suppression of HIV-1 RNA to <50 c/mL at W48 was achieved: 91% (576/634) in the pooled B/F/TAF groups and 93% of subjects in both the DTG/ABC/3TC (293/315) and DTG+F/TAF (302/325) groups, respectively. There was rapid suppression to HIV-1 RNA <50 c/mL at W4: 76% (477/625) in the B/F/TAF group, 76% (236/311) in the DTG/ABC/3TC group, and 80% (258/324) in the DTG+F/TAF group by the Missing=Excluded approach. HIV-1 subtype B was present in 89% of patients. 92% (1048/1138) B subtype and 90% (123/136) non-B subtype had HIV-1 RNA <50 c/mL at W48. Pre-existing primary resistance mutations (-R) to any drug class were found in 18% (224/1274) of patients overall and consisted of NRTI-R in 2%, NNRTI-R in 13.2%, PI-R in 2.9%, and INSTI-R in 1.3%. One subject in the B/F/TAF group had Q148H+G140S at baseline and was suppressed with HIV-1 RNA <50 c/mL at W48. HIV-1 RNA <50 c/mL at W48 was similar with or without pre-existing resistance mutations (92%; 205/224 vs 92%; 966/1050, respectively). Through W48, 17 patients qualified for resistance testing (1.3% (8/634) B/F/TAF; 1.3% (4/315) ABC/DTG/3TC; 1.5% (5/325) DTG+F/TAF); none had emergent resistance to study drugs.

Conclusion: Treatment with B/F/TAF, ABC/DTG/3TC, or DTG+F/TAF rapidly achieved and maintained high rates of virologic suppression in HIV-1 treatment-naïve subjects. The presence of pre-existing resistance mutations did not affect treatment outcomes. Development of primary drug resistance mutations to study drug was not observed through W48.

533 HIV DRUG RESISTANCE WITH EARLY VS DELAYED ANTIRETROVIRAL TREATMENT (HPTN 052)

Philip J. Palumbo[1], Jessica M. Fogel[1], Ethan A. Wilson[2], Sarah E. Hudelson[1], Stephen Hart[3], Laura Hovind[3], Estelle Piwowar-Manning[1], Maria Papathanasopoulos[4], Mariza Morgado[5], Shanmugam Saravanan[6], Srikanth Tripathy[7], Ying Q. Chen[2], Myron S. Cohen[8], Susan H. Eshleman[1]
[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [4]University of the Witwatersrand, Johannesburg, South Africa, [5]Oswaldo Cruz Foundation - Fiocruz, Rio de Janeiro, Brazil, [6]YR Gaitonde Center for AIDS Research and Education, Chennai, India, [7]National Institute for Research in TB, Chennai, India, [8]University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: HIV Prevention Trials Network (HPTN) 052 was a multi-national, clinical trial that demonstrated reduced HIV transmission and health benefits of early antiretroviral treatment (ART). The study enrolled 1,763 serodiscordant couples and followed them for up to 10 years (2005-2015). At enrollment, HIV-infected index participants were randomized to the early ART arm (CD4: 350-550 cells/mm^3 at ART initiation) or the delayed ART arm (CD4: ≤250 cells/mm^3 at ART initiation). All index participants were offered ART at any CD4 cell count after the release of interim study results in May 2011. The rate of virologic failure was similar in the two study arms. We evaluated factors associated with HIV drug resistance in HPTN 052 participants with virologic failure.

Methods: Virologic failure was defined as two consecutive viral load measures >1,000 copies/mL after 24 weeks on ART. HIV drug resistance was evaluated at ART initiation (baseline) and virologic failure using the ViroSeq HIV-1 Genotyping System and the Resistance Calculator Program at Frontier Science Foundation (Stanford v7.0 algorithm). Factors associated with HIV drug resistance were analyzed using Chi-square, t-tests, and logistical regression models using SAS software.

Results: HIV genotyping results were obtained at the time of ART initiation (baseline) and at virologic failure for 211 (84.7%) of 249 participants (128 early arm; 83 delayed arm [22 started ART before May 2011]). Overall, 4.7% of participants had resistance at baseline and 35.5% had new resistance at failure. The frequency of new resistance at failure was lower among participants in the early arm compared to all participants in the delayed arm (30.5% vs. 43.4%, p=0.06), and compared to the subset of participants in the delayed arm who started ART before May 2011 (54.5%, p=0.032). The frequency of new resistance at failure was lower among participants with higher baseline CD4 cell counts (p=0.047) and lower baseline viral loads (p=0.0001), and was higher among those receiving a regimen of efavirenz, lamivudine, and zidovudine compared to other ART regimens (p=0.0074). In a multivariate model, new resistance at failure was associated with baseline viral load (p=0.0008) and drug regimen (p=0.024).

Conclusion: The frequency of new drug resistance at virologic failure was lower in adults with early ART initiation. The main factor associated with reduced drug resistance with early ART was lower baseline (pre-ART) viral load.

534 DEFINING CLINICALLY RELEVANT THRESHOLD FOR ULTRASENSITIVE HIV RESISTANCE TESTING

Seth C. Inzaule[1], Raph L. Hamers[1], Marc Noguera-Julian[2], Maria Casadella[2], Mariona Parera[2], Bonaventura Clotet[2], Tobias F. Rinke de Wit[1], Roger Paredes[2]
[1]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands, [2]IrsiCaixa Institute for AIDS Research, Badalona, Spain

Background: Current HIV drug resistance tests, mainly based on Sanger-sequencing, have 20% detection thresholds that fail to detect minority variants (MVs). Ultrasensitive next-generation sequencing (NGS) offers potential as alternative lower-cost tests, but the clinical relevance of MVs is uncertain. Using data from a multi-country cohort study, we assessed which resistance threshold, including MVs, optimally predict an increased risk of virological failure (VF) on first-line NNRTI-based antiretroviral treatment (ART).

Methods: Case-control study in the PanAfrican Studies to Evaluate Resistance cohort (PASER-M) in 12 sites in five countries. Cases were defined as those who had VF (viral-load (VL) ≥400 cps/ml) at 12 months or switched to second-line ART, and controls as those with VL<400 cps/ml on first-line ART at month 12, matched by country, age, pre-ART VL and CD4 cell counts. PDR was assessed by Illumina MiSeq next-generation sequencing of HIV-1 from pre-ART plasma samples, using the International Antiviral Society-USA 2017 drug resistance mutation list. We used logistic regression to assess the odds of VF at different PDR mutant detection thresholds (1% to 20%), compared with the cut-off used for major circulating variants in Sanger sequencing (≥20%). We calculated the relevant measures of diagnostic accuracy, summarized in Table.

Results: We included 403 samples from 158 cases and 249 controls. Lowering the thresholds improved the sensitivity to identify cases, i.e. 12%, 13%, 16% and 18% at the 20%, 10%, 5% and 1% thresholds respectively. This came with a limited reduction in specificity (i.e. correctly identifying controls) of 98%, 96%, 96% at 20%, 10%, 5%, respectively, but a larger reduction to 92% at 1% threshold. DOR was 5.4, 4.0, 4.0 and 2.4 at the 20%, 10%, 5% and 1% thresholds, respectively. The OR of VF for the presence of PDR was 12.9, 8.3, 10.0 and 3.6 at 20%, 10%, 5% and 1%, respectively. NNT was 3, 4, 3 and 8 at 20%, 10%, 5% and 1% thresholds, respectively. A sensitivity analysis that excluded major variants (≥20%) showed that MVs at the 5% threshold were still significantly associated with VF (OR 7.6, 95%CI 1.1-53.4).

Conclusion: Ultrasensitive resistance testing improves prediction of VF relative to the conventional 20% threshold. A 5% MV detection threshold could be an adequate cutoff for operationalization of ultrasensitive assays, although the marginal gain over 20% is small.

	NGS sensitivity cut-off			
	20%	10%	5%	1%
Sensitivity (%, 95%CI)	12 (8-18)	13 (8-19)	16 (11-22)	18 (12-24)
False-negative (%, 95%CI)	88 (82-93)	87 (81-92)	84 (78-90)	83 (76-88)
Specificity (%, 95%CI)	98 (95-99)	96 (93-98)	96 (92-98)	92 (88-95)
False-positive (%, 95%CI)	2 (1-5)	4 (2-7)	4 (2-8)	8 (5-12)
DOR (95%)	5.4 (2.1-13.8)	4.0 (1.8-9.0)	4.0 (1.9-8.4)	2.4 (1.3-4.5)
Odds Ratio for VF (95%)	12.9 (3.2-43.8)	8.3 (2.8-28.0)	10.0 (3.2-30.8)	3.6 (1.6-8.2)
NNT	3	4	3	8
**MVs Odds Ratio for VF (95%)	_	2.7 (0.3-25.4)	7.6 (1.1-53.4)	1.5 (0.5-4.7)

Summary table of diagnostic accuracy measures to assess clinical relevance of detection thresholds for ultrasensitive resistance testing

DOR, a measure of the effectiveness of diagnostic tests; the odds of having PDR among cases relative to having PDR among controls: [(sensitivity*specificity)/(1-sensitivity)*(1- specificity)]; NNT, number of patients detected as having PDR at the specific threshold that need to be treated (NNT) with a fully-active ART regimen to prevent one case of VF

** Sensitivity analysis- included only 351 patients; 135 cases with 216 controls and excluded cases and controls with resistant variants ≥20%

535 PROVIRAL DRUG RESISTANCE ACQUIRED DURING EARLY THERAPY PREDICTS VIROLOGICAL OUTCOME

Bindu P. Gopalan[1], Reena Dsouza[1], Karthika Arumugam[1], Niharika Rajnala[1], Udaykumar Ranga[2], Anita Shet[3]
[1]St John's Research Institute, Bangalore, India, [2]Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, India, [3]Johns Hopkins University, Baltimore, MD, USA

Background: The extent of viral evolution during early ART impacting virological outcome is unknown in HIV-1 infected children. We hypothesised that acquisition of treatment relevant drug resistance mutations (TRDRMs) in the proviral compartment of children at six months of ART predicts virological failure (VF).
Methods: Children ≤ 16 years initiated on ART (2 NRTI + 1NNRTI) from 2012 to 2015 were included in a nested case-control study. Six monthly CD4 counts HIV-1 RNA load and adherence was assessed. 'Cases' were VFs (VL ≥200 copies/ml at 2 years of ART) and 'controls' were viremia suppressors (VL<200 copies/ml during the 2-year period). Genotyping of proviral DNA from whole blood was performed by next-generation sequencing (NGS) in the partial pol gene of HIV-1 RT (amino acid 40 to 240) prior to (baseline) and at six months of ART by a paired-end protocol (Illumina). Plasma virus was genotyped by Sanger method at baseline and at VF. Mutations were identified and categorized using HIVdb (v8.4) and IAS-USA 2017 list. Groups were compared by the Mann Whitney U test and predictors for VF were assessed by the conditional logistic regression model (CLR).
Results: Among 67 children (30 cases and 37 age-matched controls; median 8 years; 51% male) infected with HIV-1 Subtype C, baseline viral load was 5.4 log copies/ml and CD4 18.5%. NNRTI started was nevirapine in 70% of cases and 81% of controls. No significant differences were observed at baseline between the two groups (p=>0.05). At VF 86.6% (26/30) had DRMs in plasma virus. In CLR univariate model adherence (OR=6.4, 95%CI= 1.3 to 32.5, p=0.02) detection of at least one DRM (OR=6.2, 95%CI= 2.1 to 18.4, p=0.001), TRDRM (OR=9.1, 95%CI =2.5 to 31.9, p=0.001) and NNRTI DRMs (OR=4.9, 95%CI=1.6 to 14.6, p=0.004) showed association with an increased risk of VF. TRDRMs or TRNNRTI DRMs absent at baseline and detected at month six increased the risk of early VF (OR=15.6, 95%CI=3.2 to 75.5, p=0.001, OR=7.1, 95%CI=1.8 to 27.9, p=0.005 respectively). In the multivariable model, adherence (OR=9.7, 95%CI 1.6-55.8, p=0.011) and TRDRMs acquired at month six of ART (OR=11.4, 95%CI 3.1-42.3 p=0.001) were independently associated with VF.
Conclusion: These data highlight the extent of viral evolution in the cellular compartment under ART jeopardizing the therapeutic outcome. Paired sequencing of the proviral compartment for TRDRMs prior to and at six months of ART by NGS may be explored for assessing the virological outcome in children initiating 1st line NNRTI based ART.

536 RARE HIV VARIANTS WITH LINKED DUAL-CLASS RESISTANCE ARE ASSOCIATED WITH ART FAILURE

Valerie F. Boltz[1], Wei Shao[2], Elias K. Halvas[3], James A. McIntyre[4], Robert T. Schooley[5], Shahin Lockman[6], Judith S. Currier[7], Fredrick Sawe[8], Evelyn Hogg[9], Michael D. Hughes[10], Mary F. Kearney[1], John M. Coffin[11], John W. Mellors[3]
[1]National Cancer Institute, Frederick, MD, USA, [2]Leidos Biomedical Research, Inc, Frederick, MD, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA, [4]Anova Health Institute, Johannesburg, South Africa, [5]University of California San Diego, La Jolla, CA, USA, [6]Brigham and Women's Hospital, Boston, MA, USA, [7]University of California Los Angeles, Los Angeles, CA, USA, [8]Kenya Medical Research Institute, Kisumu, Kenya, [9]Social &Scientific Systems, Silver Spring, MD, USA, [10]Harvard University, Cambridge, MA, USA, [11]Tufts University, Boston, MA, USA

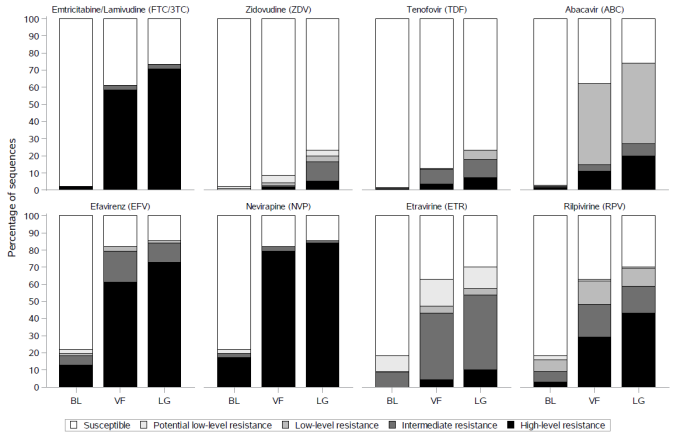
Background: The clinical significance of low frequency HIV-1 drug-resistant variants is controversial. We hypothesized that variants encoding both NRTI and NNRTI resistance mutations, but not single class resistance mutations, would be associated with virological failure of ART. To test this hypothesis, we developed an ultrasensitive, NGS-based single viral genome sequencing assay (uSGS) (Boltz, Retrovirology 2016) that can detect rare variants with linked drug resistance mutations (DRMs).
Methods: Pre-ART plasma samples were obtained from the NVP/FTC/TDF arm of the ACTG A5208/OCTANE trial (Lockman, NEJM 2010) for women who had received (Trial 1 [T1]) or had not received (Trial 2 [T2]) single dose nevirapine (sdNVP) within 6-24 months of entry. HIV-1 RNA-derived cDNA libraries were generated with primer IDs for paired-end next-generation uSGS of RT codons 58-217. We compared the frequency of linked, single- and dual-class (NRTI and NNRTI) DRMs conferring resistance to >1 component of NVP/FTC/TDF ART (Stanford db v.8.4) in pre-ART samples from women with and without subsequent virological failure of ART.
Results: A total of 1,344,024 single-genome sequences were obtained from pre-ART plasma samples from 122 women: 61 women from T1 (prior sdNVP), 27 with ART failure; and 61 from T2 (no prior sdNVP), 13 with ART failure. Overall, linked DRMs were found in more women in T1 than T2: 15/61 (25%) vs 3/61 (5%) p=0.004. Importantly, linked dual-class DRMs were found in more women in T1 with ART failure than in T1 without failure: 8/27 (30%) vs 2/34 (6%); p=0.017. In addition, linked dual-class DRMs were found in more women in T1 with failure than in T2 with failure although the difference did not reach statistical significance: 8/27 (30%) vs. 1/13 (8%) p=0.23. Linked single-class DRMs were not associated with failure in either trial.
Conclusion: This study shows for the first time that rare HIV variants with linked resistance mutations to 2 drug classes (NRTI and NNRTI) are significantly associated with ART failure, whereas variants with linked single-class resistance mutations are not. Transient exposure to a single ARV (e.g., single dose nevirapine) can increase the frequency of dual-class resistance and the risk of ART failure as a consequence of stochastic mutations occurring in a virus population that had already expanded through selection for resistance to the first ARV.

Trial	Outcome	sdNVP	# PIDs	# Linked Dual Class DRMs	P value	# Linked Single Class DRMs	P value
T1	ART Failure	Yes	27	8 (30%)	0.017	4 (15%)	0.69
T1	ART Success	Yes	34	2 (6%)		3 (9%)	
T1	ART Failure	Yes	27	8 (30%)	0.23	4 (15%)	1.0
T2	ART Failure	No	13	1 (8%)		2 (15%)	

537 ACCUMULATION OF HIV DRUG RESISTANCE ON FAILING FIRST-LINE ART IN LUSAKA, ZAMBIA

Parker Hudson[1], Lloyd Mulenga[2], Andrew Westfall[3], Ranjit Warrier[4], Aggrey Mweemba[2], Michael Saag[3], Jeffrey S. Stringer[5], Joseph J. Eron[5], Benjamin H. Chi[5]
[1]University of Texas at Austin, Austin, TX, USA, [2]University of Zambia, Lusaka, Zambia, [3]University of Alabama at Birmingham, Birmingham, AL, USA, [4]Center for Infectious Disease Research in Zambia, Lusaka, Zambia, [5]University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: In many high-burden settings, access to routine HIV viral load (VL) and resistance testing is limited; as a result, individuals with virologic failure (VF) to first-line anti-retroviral therapy (ART) may remain on their regimen for prolonged periods.
Methods: We analyzed data from a cluster-randomized trial of VL monitoring in Lusaka, Zambia. From 2006 to 2011, 12 randomized sites provided either routine VL monitoring at 3mo, 6mo, and every 6mo after ART initiation (intervention) or immunologic and clinical monitoring with discretionary VL testing (control). Stored specimens in the controls were tested for VF at study completion. VF was defined as the first of two consecutive plasma VLs > 400 copies/mL at least 4 weeks apart. For those with VF, HIV genotyping was performed retrospectively at baseline (BL) and on all subsequent specimens on first-line ART until participants changed to second-line ART or were censored (study completion, withdrawal, death). We used the 2016 Stanford HIV Resistance Database to predict drug susceptibilities (v8.2).
Results: Of 1,973 enrolled participants, 165 (8.4%) developed VF over 4,446 person years of follow up. Among those with VF, ART regimens included ZDV (51%), d4T (32%), TDF (16%), NVP (84%), and EFV (16%). 464 genotype results were available, including 132 (80%) at BL and 116 (70%) at VF. 125 (76%) had at least one result between VF and censoring, for a cumulative 191 person-years on failing first-line ART. At BL, 23% had a major NNRTI mutation, which did not affect median time to VF in a Kaplan-Meier survival analysis (p=0.4). At VF, 82% had a major NRTI/NNRTI mutation; this increased to a cumulative 89% at last genotype (LG). M184 mutations increased from 2% (BL) to 59% (VF) to 71% (LG). K65R mutations increased from 2% (BL) to 11% (VF) to 13% (LG); among those on a failing TDF-based regimen, TDF resistance increased from 42% (8/19, VF) to 58% (15/26, LG). 70% developed resistance to second generation NNRTIs. The majority of resistance occurred by the time VF was detected (figure).
Conclusion: In this sub-study, over half who failed first line therapy with TDF developed TDF resistance. Incremental increases in HIV drug resistance accumulated after VF on failing first-line ART. These data highlight the urgent need for effective adherence strategies and earlier detection of VF if we are to reach the ambitious 90-90-90 goals set forth by international agencies and local governments.



538 IMPACT OF FIRST-LINE ART CHOICE AND DURATION OF VIRAL FAILURE ON SECOND-LINE OPTIONS

Seema T. Meloni[1], Chika K. Onwuamah[2], Oche Agbaji[3], Beth Chaplin[1], David O. Olaleye[4], Rosemary Audu[2], Ezechi C. Oliver[2], Godwin Imade[3], Adesola Z. Musa[2], Georgina N. Odaibo[4], Holly Rawizza[5], Prosper Okonkwo[6], Emmanuel O. Idigbe[2], Phyllis J. Kanki[1]

[1]Harvard University, Boston, MA, USA, [2]Nigerian Institute of Medical Research, Lagos, Nigeria, [3]Jos University Teaching Hospital, Jos, Nigeria, [4]University of Ibadan, Ibadan, Nigeria, [5]Brigham and Women's Hospital, Boston, MA, USA, [6]AIDS Prevention Initiative In Nigeria, Abuja, Nigeria

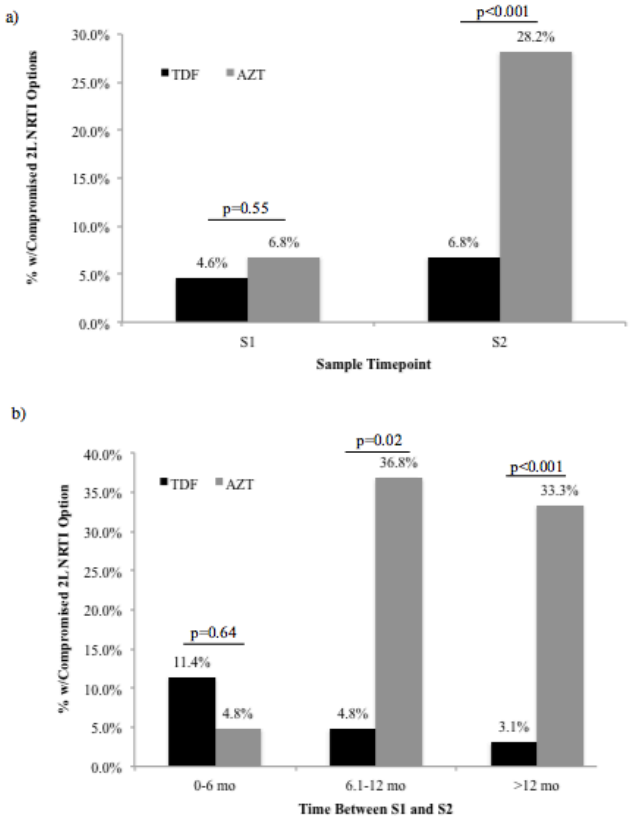
Background: The WHO recommends a simplified approach to second-line (2L) nucleoside reverse transcriptase inhibitor (NRTI) options in resource-limited settings (RLS); if zidovudine (AZT) was used in first-line (1L), then tenofovir (TDF) should be prescribed for 2L and vice versa. As AZT is commonly used for 1L in many RLS and data regarding impact of regimen choice and duration of virologic failure (VF) on accumulation of mutations in the context of current viral load (VL) monitoring guidelines remain sparse, this study was designed to compare the patterns of drug resistance mutations (DRM) for patients failing AZT- versus TDF-containing 1L ART to examine the potential impact on 2L NRTI options.

Methods: Paired samples from patients that met the criteria for VF and were switched from 1L to 2L ART at three medical institutions in the APIN/Harvard PEPFAR Nigeria Program were retrospectively identified. Genotyping was performed on the first sample with VL≥1000 copies/mL (S1) and the second from time nearest switch to 2L (S2). For each sample, the HIV-1 polymerase gene was sequenced. DRM were analyzed and genotype susceptibility score (GSS) calculated using reports from Stanford University's HIVdb Program.

Results: In total, 191 patients were included, of whom 88 (46%) were on a TDF- and 103 (54%) on an AZT-containing 1L regimen. At S1, there was no difference in percentage of patients that were resistant to 2L NRTI option (p=0.6), but at S2, we found that 28.2% of patients with 1L AZT versus 6.8% of patients with TDF had DRM compromising the recommended 2L NRTI backbone (p<0.001). Controlling for time between the paired samples, patients with <6 months between S1 and S2 had no difference in proportion with compromised 2L, whereas for those with 6-12 months between S1 and S2, 4.8% of those on 1L TDF versus 36.8% of patients on AZT were compromised to their 2L NRTI option (p=0.02). The median rate of decrease of GSS from S1 to S2 for those on TDF was 0.00 (IQR: 0.00-0.45) drug/year as compared to 0.50 (IQR: 0.00-1.00) drug/year for the AZT group. In a multivariate analysis, patients on 1L AZT had 9.90 times higher odds of having a compromised 2L NRTI option than patients on 1L TDF.

Conclusion: This study revealed differences in the accumulation of DRM by 1L ART regimen resulting in compromised recommended 2L NRTI options in a time-dependent manner. Our findings have implications for regimen-specific recommendations on VL monitoring scheduling for people with elevated VL following initiation of ART.

Figure 1. Percent of patients with a compromised 2L NRTI option by 1L NRTI: a) By sample time point; and, b) By time between S1 and S2 samples.



539 GENOTYPIC RESISTANCE PROFILES IN HIV-INFECTED CHILDREN WITH TREATMENT FAILURE

Birkneh T. Tadesse[1], Byron A. Foster[2], Degu Jerene[3], Kyle Cobarrubias[4], Bemuluyigza Baraki[4], Natalie Kinloch[4], Mark Brockman[4], Eyasu Makonnen[3], Eleni Aklillu[5], Zabrina Brumme[4]

[1]Hawassa University, Hawassa, Ethiopia, [2]Oregon Health and Sciences University, Portland, OR, USA, [3]Addis Ababa University, Addis Ababa, Ethiopia, [4]Simon Fraser University, Burnaby, BC, Canada, [5]Karolinska Institute, Stockholm, Sweden

Background: Due to the lifelong nature of cART, treatment failure remains a major concern, particularly for pediatric patients in settings where cART options are limited. Access to drug resistance genotyping is limited in Southern Ethiopia and international shipping of frozen plasma is not feasible. We characterized HIV drug resistance among children experiencing virologic treatment failure on first-line cART in Hawassa, Ethiopia, using proviral DNA amplified from dried blood spots.

Methods: EPHIC is a prospective pediatric HIV first-line treatment cohort with 788 children currently enrolled, with pVL and CD4 counts monitored semiannually. Dried blood spots were collected from 94 EPHIC participants experiencing WHO-defined virologic treatment failure with pVL ≥ 2500 copies/ml. HIV DNA was extracted using commercial spin-column kits and protease, and a minimum of codons 1-240 of RT were amplified by nested PCR and sequenced using subtype C-optimized primers. Four primer sets (1 primary, 3 backup) were used to maximize PCR success. Resistance interpretation was performed using the Stanford HIV drug resistance database.

Results: Participants were a mean of 11.4 (standard deviation [SD] 3.3) years old and had been on first line cART for a mean of 3.8 (SD 2.8) years. Eighty six (91.5%) children had WHO stage 1 or 2 disease; the remaining 8 (8.5%) had WHO stage 3 or 4 disease. Only 4(4.2%) participants had taken ART for prevention of mother to child transmission. Genotyping was successful for 93/94 (98.9%) participants, though 6 sequences were hypermutated and one contained a 23-base deletion, consistent with high proportions of defective proviruses in chronic HIV infection. All sequences were subtype C. Of the 86 intact sequences,

16 (18.6%) harbored no major resistance mutations, 11 (12.8%) harbored NNRTI resistance only, 1 (1.1%) harbored NRTI resistance only and 58 (67.4%) harbored both NRTI and NNRTI resistance. PI resistance was not observed. The most prevalent mutations were M184V (59.3%), K103N (31.4%),Y181C/V (26.7%) and G190A/S (N=24.4%).

Conclusion: Dried-blood spot-based genotyping offers an alternative to plasma HIV RNA genotyping where the latter is not feasible. While nearly 70% of pediatric treatment failures in this Southern Ethiopian cohort occur with major NRTI and NNRTI resistance mutations, 30% occur with no resistance, or resistance to one drug class only. Enhanced access to resistance testing would greatly facilitate clinical-decision making capacity in this priority setting.

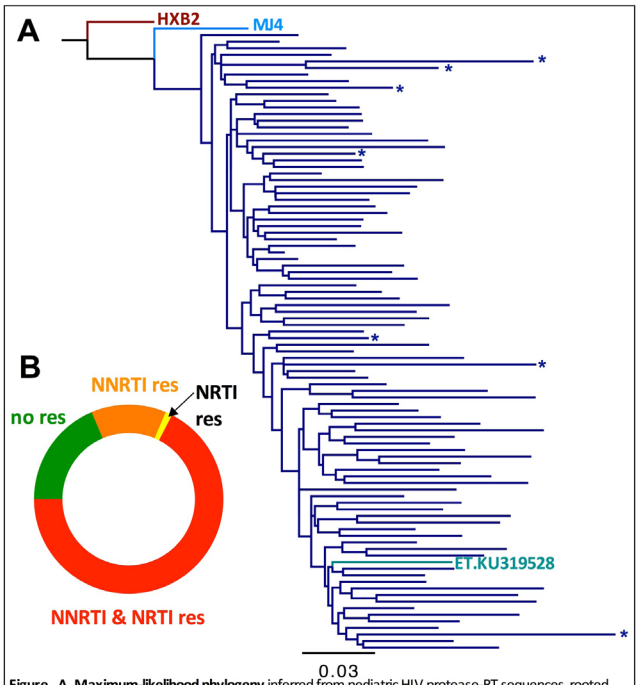


Figure. A. Maximum-likelihood phylogeny inferred from pediatric HIV protease-RT sequences, rooted on subtype B reference strain HXB2. Subtype C ref strain MJ4 (botswana) and Ethiopian sequence KU319528 also included. Asterisks denote hyper-mutated or defective sequences. Scale in nucleotide substitutions per site. **B. Resistance profiles.** 70% of sequences harbor NNRTI and NRTI resistance mutations, but 30% retain susceptibility to one or both of these classes. Increased accessibility to resistance testing would greatly enhance clinical decision making in this priority population.

540 FIRST-LINE HIV TREATMENT FAILURE IN NON-B SUBTYPES AND RECOMBINANTS IN UGANDA

Art Poon[1], Emmanuel Ndashimye[1], **Mariano Avino**[1], Richard Gibson[1], Fred Kyeyune[2], Immaculate Nankya[2], Miguel E. Quinones-Nateu[3], Eric Arts[1]
[1]Western University, London, ON, Canada, [2]Joint Clinical Research Centre, Kampala, Uganda, [3]Case Western Reserve University, Cleveland, OH, USA

Background: The enormous genetic diversity of HIV-1 subtypes has been a persistent concern for antiretroviral treatment (ART). HIV-1 infections in Uganda are predominated by subtypes A and D. While there is evidence for associations between HIV-1 subtypes and pathogenesis, finding associations with ART failure has been limited by sample population sizes in resource-limited settings. To maximize statistical power, we have combined HIV genotype and clinical data associated with first-line treatment failures across multiple cohorts and clinical sites in Uganda (Table 1).

Methods: First-line treatment failures (FTFs, *n*=1,724) were defined by HIV genotype records with sample collection dates after the ART start dates in the database. We used a rules-based record linkage algorithm to associate genotype and clinical data (including plasma viral load, CD4 cell count, and first-line ART regimen). These data were combined with ART-naive records in the combined Uganda database (*n*=968) and location-time matched records in the Stanford HIVdb database (*n*=1,462) for a total of 4,134 records. Genotypic resistance predictions were generated with the Stanford HIVdb algorithm (version 8.1.1). HIV subtype predictions and recombination detection was performed with HyPhy SCUEAL on a local computing cluster.

Results: FTFs and subtype D were independently associated with lower genotypic susceptibility scores ($P<10^{-12}$ and $P=0.02$), which measures resistance to individual ART regimens. A/D recombinants were significantly less frequent in FTFs (odds ratio=0.53, $P=7.8\times10^{-7}$). No associations were observed for the other subtypes, implying that ART is uniformly effective in this setting. Power analysis estimated that our database conferred 80% power to detect an association between FTF and a subtype with an odds ratio of about 1.2. The number of inferred recombination breakpoints was negatively associated with FTFs, both within A/D recombinants (binomial generalized linear model, $P=4.7\times10^{-3}$) and all recombinants ($P=2.9\times10^{-5}$).

Conclusion: This is the largest database of FTFs in Uganda to date, with a predicted statistical power to detect odds ratios as low as 1.2. Our findings support the hypothesis that variation in rates of disease progression among subtypes does not have a major impact on response to ART, and suggest that inter-subtype recombination may on average represent a burden on viral fitness.

Source	*Baseline*	*Failures*	*A*	*D*	*A/D*	*C*
JCRC	160	1194	44%	29%	5%	3%
EARNEST	0	356	43%	32%	5%	2%
HIV-1 Genital Shedding study	81	0	43%	28%	11%	4%
MARCH	209	103	50%	28%	6%	2%
PASER	518	71	44%	31%	8%	2%
Stanford HIVdb	1462	0	40%	32%	9%	3%
Total	**2430**	**1724**	**43%**	**30%**	**7%**	**3%**

541 HIGH LEVELS OF HIV DRUG RESISTANCE AMONG ADULTS FAILING SECOND-LINE ART IN NAMIBIA

Michael R. Jordan[1], Ndapewa Hamunime[2], Souleymane Sawadogo[3], Simon Agolory[3], Andreas Shiningawamwe[4], Taffa Negussie[3], Christa L. Fischer Walker[3], Elliot G. Raizes[3], Nicholus Mutenda[2], Christian Hunter[5], Natalie Dean[6], Kim Steegen[7], Vibha Kana[7], Chunfu Yang[3], Steven Y. Hong[1]
[1]Tufts University, Boston, MA, USA, [2]Ministry of Health and Social Services, Windhoek, Namibia, [3]CDC, Atlanta, GA, USA, [4]Namibia Institute of Pathology, Windhoek, Namibia, [5]University of Namibia, Windhoek, Namibia, [6]University of Florida, Gainesville, FL, USA, [7]University of the Witwatersrand, Johannesburg, South Africa

Background: Global HIV drug resistance (HIVDR) surveillance efforts have largely focused on descriptions of HIVDR prior to treatment initiation or at time of first-line antiretroviral therapy (ART) failure. Data regarding the prevalence of HIVDR in people failing second-line ritonavir-boosted protease inhibitor (PI)-based ART in sub-Saharan Africa are limited and no data are available from Namibia. As of the end of 2015, Namibia had 136,324 people on first-line non-nucleoside reverse transcriptase inhibitor (NNRTI) based ART and 3,884 people on PI-based second-line regimens in its public health sector. We investigated the prevalence of HIVDR at second-line failure in Namibia.

Methods: Between August 2016 and February 2017, HIV-infected people ≥15 years who failed PI-based second-line ART (2 consecutive HIV RNA tests >1000 copies/ml) were identified at 15 ART clinics in Namibia. The population on second-line ART at the 15 participating ART sites represented >70% of the total population on second-line in the country. At time of confirmed virological failure, dried blood spot specimens were collected for genotypic testing for drug resistance. HIV-1 Pol sequences were obtained using RT-PCR and Sanger sequencing. Sequences with low-, intermediate- or high-level HIVDR by the Stanford HIVdb were classified as resistant.

Results: A total of 238 individuals were enrolled; 56.7% were female. The median age and duration on PI-based ART at time of failure were 37 years (IQR = 21 to 46) and 3.4 years (IQR 1.82 to 5.1), respectively. 237 individuals received lopinavir/ritonavir-based regimens; one received an atazanavir/ritonavir-based regimen. 160 (67.2%) individuals had sequencing data available. HIVDR prevalence data are presented in Table 1. No difference in the prevalence of HIVDR to any drug class by gender was observed.

Conclusion: In this first study of HIVDR amongst patients failing PI/r-based ART in Namibia, significant levels of resistance are observed, suggesting prolonged virological failure and moderate to high levels of adherence. Nonetheless, up to 87% may achieve virological suppression with intensive strategies to improve adherence on current PI/r regimens. Drug resistance testing is needed to reduce unnecessary switches to more costly regimens

among this group. For the 13% with PI resistance, accessible and effective agents should be considered.

Table 1. Prevalence of HIV drug resistance amongst second-line ART failures in Namibia; n= 160

Resistance	Any HIVDR	Any NRTI	Any NNRTI	Any PI	ZDV	XTC	ABC	TDF	NVP or EFV	LPV/r or ATV/r	DRV/r
Prevalence %; (95% CI)	70.0%; (62.8-77.2%)	50.6%; (42.7-58.4%)	63.1%; (55.6-70.7%)	13.1%; (7.8%-18.4%)	31.3%; (24.0-38.5%)	43.1%; (35.4-50.9%)	45.0%; (37.2-52.8%)	23.8%; (17.1-30.4%)	61.2%; 38.6-53.6%)	13.1%; (8.3-19.1%)	6.9%; (2.9-10.8%)

NRTI resistance is defined as resistance to any nucleoside reverse transcriptase inhibitor. Any NNRTI resistance is defined as resistance to nevirapine (NVP), efavirenz (EFV), rilpivirine (RPV) or etravirine (ETR). Any PI resistance is defined as resistance to lopinavir/ritonavir (LPV/r), atazanavir/r (ATV/r), darunavir/r (DRV/r). Any HIVDR is defined as resistance to NVP/EFV, any NRTI, ATV/r, LPV/r or DRV/r.

542 LOW PREVALENCE OF INTEGRASE STRAND TRANSFER INHIBITORS RESISTANCE ACROSS BOTSWANA

Simani Gaseitsiwe[1], Sikhulile Moyo[1], Melissa Zahralban-Steele[2], Dorcas Maruapula[1], Baitshepi Mokaleng[1], Terence Mohammed[1], Shenaaz El-Halabi[3], Elliot G. Raizes[4], Tendani Gaolathe[1], Shahin Lockman[2], Max Essex[2], Vlad Novitsky[2]
[1]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [2]Harvard University, Cambridge, MA, USA, [3]Botswana Ministry of Health, Gaborone, Botswana, [4]CDC, Atlanta, GA, USA

Background: The use of dolutegravir (DTG)-based first-line combination antiretroviral therapy (cART) is now recommended by the WHO HIV treatment guidelines. The Botswana national HIV treatment program started using DTG-based first-line cART in June 2016. As the previous HIV salvage regimen in Botswana has used raltegravir, a first generation integrase strand transfer inhibitor (INSTI), it is important to monitor the population prevalence of INSTI resistance mutations.

Methods: Blood samples were collected from HIV-positive participants in the Botswana Combination Prevention Project (BCPP) residing in 25 communities representing southern, northern, and eastern Botswana in 20132015. A long-range HIV genotyping protocol was applied. INSTI resistance mutations were analyzed according to the IAS-USA 2017 list with the addition of H51Y and G118R mutations described recently. All viral sequences were screened for hypermutations (HM). Mutations in sequences with adjusted HM rate >=2% were considered to be generated by HM, and were not counted toward drug-resistant INSTI.

Results: After adjusting for HMs, a total of 2,342 (979 southern, 916 eastern and 447 northern) unique sequences, were included in analysis of INSTI resistance mutations. Among 2,241 individuals with ART data available, 1,583 (71%; 95% CI 6973%) were receiving cART and 1,520 of them (96%; 95% CI 9597%) had HIV-1 RNA 400 copies/mL. The overall prevalence of INSTI resistance mutations was 2.0% (47 of 2,342; 95% CI 1.52.7%). Prevalence of INSTI mutations was similar across the country regions1.8%, 2.2% and 2.0% in the South, East, and North, respectively. Among a subset of 16 communities with genotyping density 10%, median (IQR) prevalence of INSTI was 2% (1.1% to 2.7%) ranging from 0 to 3.8%. The table demonstrates the prevalence of identified INSTI mutations among the analyzed 2,342 BCPP participants.

Conclusion: This is the first large-scale study of HIV-1C mutations associated with INSTI resistance in Africa. A low prevalence of INSTI resistance mutations at 2% across the country suggests minimal impact of population exposure to raltegravir and provides a strong rationale for use of DTG as the first-line cART regimen. Monitoring of the prevalence of INSTI resistance mutations is warranted to ensure effectiveness of the first line cART regimen.

Table 1: Frequency of INSTI Mutations in Botswana (n=2342)

INSTI mutation	Prevalence, %	95% CI, %
H51Y	0.044%	0.001 - 0.25%
L74M	0.36%	0.15 - 0.70%
E92Q/G	0.13%	0.03 - 0.39%
T97A	0.27%	0.1 - 0.58%
G118	0.044%	0.001 - 0.25%
E138K	0.53%	0.27 - 0.92%
Q148R	0.044%	0.001 - 0.25%
R263K	0.73%	0.42 - 1.16%

543 HIGH LEVEL RESISTANCE TO DOLUTEGRAVIR (DTG) AFTER EMERGENCE OF T97A MUTATION

Safia S. Kuriakose[1], Jomy M. George[2], Nicola Dee[1], Pam Stoll[2], Brian K. Agan[3], Robin L. Dewar[1], Alice K. Pau[2], Frank Maldarelli[4]
[1]Leidos Biomedical Research, Inc, Frederick, MD, USA, [2]NIH, Bethesda, MD, USA, [3]Uniformed Services University of the Health Sciences, Bethesda, MD, USA, [4]National Cancer Institute, Frederick, MD, USA

Background: The IN mutation T97A is a major accessory mutation that may emerge with viral rebound during DTG salvage therapy, often with additional drug resistance mutations (DRMs). The contribution of T97A alone to in vivo emergence of INSTI resistance, especially DTG, is not well described. We report 2 patients with extensive ARV resistance who had INSTI DRMs (including G140S, Q148H) prior to switching to DTG. Both had emergence of the T97A mutation as the sole new DRM, leading to >10-fold increases in phenotypic resistance to DTG.

Methods: Both patients were enrolled in a clinical study investigating ART failure (NCT 01976715). Samples were analyzed using commercial phenotyping (Monogram) and genotyping (TRUGENE) assays, and in-house genotyping. Selected samples were subjected to next generation sequencing (NGS, Illumina) with limit of detection of DRM of c. 1%. HIV sequences were analyzed (Stanford/ANRS algorithms); phenotyping analyses (PhenoSense Integrase GT™) and coreceptor tropicity (Monogram) were performed.

Results: Pt 1 - 51 yr-old man diagnosed with HIV in 1989, with extensive prior ART including RAL. At enrollment, he was on LPV/r+ATV+TDF/FTC with HIV-VL 136,476 c/mL. Genotypic testing revealed INSTI DRMs (G140S, Q148H). NGS did not detect other INSTI DRMs. Phenotypic testing showed partial sensitivity to DTG (4.61-fold change (FC) of IC50 from reference range) and R5-tropic HIV. Within 3 months of ART change to DTG 50mg bid+DRV/r+TDF/FTC+MVC, VL was <50 c/ml. After 6 months, however, VL rebounded to 1,638 c/mL despite ARV levels consistently within therapeutic range. Resistance testing revealed high-level phenotypic resistance to DTG (inc. from 4.61 to 66 FC). T97A was the only new DRM (Table 1). Pt 2 - 52 yr-old man diagnosed with HIV in 1993, with extensive prior ART including INSTIs. Resistance testing revealed partial sensitivity to DTG (6.7 FC) and INSTI DRMs (E138T, G140S, Q148H). NGS did not detect other INSTI DRMs. After restarting a regimen of DTG/ABC/3TC+TDF for 2 months, VL was 44,186 copies/mL. Resistance testing revealed high-level phenotypic resistance to DTG (inc. from 6.7 to 119 FC). T97A was the only new DRM (Table 1).

Conclusion: Isolated emergence of the T97A mutation led to high level DTG resistance in these 2 patients with prior INSTI resistance. Rebound viremia, even after suppression, with > 10 fold increases in DTG IC50 may emerge with T97A in patients with reduced INSTI susceptibility and Q148H + G140S containing genotypes.

Table 1: Timeline of Genotypic and Phenotypic DTG Analyses

	ART	INSTI DRMs	Genotype Interpretation to DTG	Phenotype Fold Change to DTG	Phenotype Interpretation to DTG
PATIENT 1					
Aug 2014	LPV/r + ATV + TDF/FTC	G140S, Q148H	Intermediate Resistance	4.61	Partially Sensitive
Apr 2015	DTG + DRV/R + TDF/FTC + MVC	G140S, Q148H, T97A	High Level Resistance	66	Resistant
PATIENT 2					
Nov 2014	RAL + ETR + TPV/r + FTC	E138T, G140S, Q148H	Partially sensitive	6.71	Partially Sensitive
Jan 2017	DTG/ABC/3TC + TDF	E138T, G140S, Q148H, T97A	High Level Resistance	119	Resistant

544 UNINTEGRATED VIRAL DNA INVOLVED IN DOLUTEGRAVIR RESISTANCE

Isabelle Malet[1], Frédéric Subra[2], Hervé Leh[2], Charlotte Charpentier[3], Gilles Collin[3], Diane Descamps[3], Eric Deprez[2], Vincent Calvez[1], Anne-Geneviève Marcelin[1], **Olivier Delelis**[2]

[1]Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France, [2]Ecole Normale Supérieure de CachanEcole Normale Supérieure de CachanEcole Normale Supérieure de CachanEcole Normale Supérieur, Cachan, France, [3]Bichat–Claude Bernard Hospital, Paris, France

Background: Dolutegravir (DTG), belonging to the strand-transfer inhibitor (STI) family, shows a high genetic barrier. Contrary to the first generation of STI, raltegravir and elvitegravir, no pathway of resistance has been yet described in DTG treated individuals. We previously selected a virus resistant to DTG without mutation in the integrase (IN) gene but with mutations in the 3' poly-purine tract (PPT). In this study, we characterize the original replication mechanism of this mutant virus.

Methods: Previously, a virus highly resistant to DTG was obtained by in-vitro selection. We infected MT4 cells with this virus in the presence or absence of a high DTG, RAL or EVG concentration (500 nM). We compared the replication of the mutant to the WT in the same conditions by quantitative PCR measuring all viral DNA forms (integrated, 2-LTR and 1-LTR circles DNA, linear DNA). We also sequenced integrated viral DNA sites in all conditions. Infections with these settings were also performed in Rev-GFP cells allowing quantification of late viral DNA expression by flow cytometry analysis.

Results: We found that the replication of the mutant was important and similar with or without STI, highlighting the resistance of the mutant to all approved STI. As expected, the replication of the WT virus was totally impaired in the presence of STI. Interestingly, no integrated DNA has been detected for the mutant under STI treatment neither with qPCR nor with viral integrated DNA sequencing methods. Quantifications of episomal viral DNA show no accumulation of 2-LTR circles, normally observed when integration is inhibited, but an important amount of 1-LTR circles. Results obtained by infection of Rev-GFP cells show that expression of unintegrated viral DNA from the mutant is much more important than the one reported from unintegrated viral DNA from WT infection under STI treatment.

Conclusion: For the first time, we describe the replication of a mutant resistant to all used STI without mutation in the integrase but which is supported by unintegrated viral DNA. Importantly, replication of the mutant under STI treatment, without integration, is due to the higher expression level of its unintegrated viral DNA compared to unintegrated viral DNA from the WT. This study highlights the role of unintegrated viral DNA in HIV-1 replication as a way to escape to IN inhibitors. These data are important to understand why some patients fail to STI inhibitors treatment without mutations in the integrase gene.

545 PREVALENCE AND CLINICAL IMPACT OF MINORITY RESISTANT VARIANTS TO INTEGRASE INHIBITORS

Thuy T. Nguyen[1], Djeneba Bocar Fofana[1], Charlotte Charpentier[2], Sidonie Lambert[1], Laurence Morand-Joubert[1], Diane Descamps[2], Marc Wirden[1], Christine Katlama[1], Minh Le[2], Gilles Peytavin[2], Philippe Flandre[1], Vincent Calvez[1], Eve Todesco[1], Anne-Geneviève Marcelin[1]

[1]Pierre and Marie Curie University, Paris, France, [2]Bichat–Claude Bernard Hospital, Paris, France

Background: Integrase inhibitors (INIs) including raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG) now play a key role in antiretroviral therapy. Studies evaluating selection of drug resistance-associated mutations (DRAMs) in patients failing INI-based regimen are often performed by Sanger sequencing and may underestimate the prevalence of DRAMs. Moreover, few studies using ultra-deep sequencing (UDS) have been conducted to evaluate impact of pre-existing DRAMs on virological failure to INI treatment. Therefore, in this study, we aimed at evaluating the prevalence of DRAMs at failure and also the clinical impact of baseline DRAMs on INI response by UDS.

Methods: Sanger and UDS were performed on samples at failure of 134 patients failing an INI-based regimen (65, 49, and 20 patients failed RAL, DTG, and EVG respectively) to study the prevalence of DRAMs. Samples at baseline of 34 patients with virological failure (VF) and of 31 with virological success (VS) under INIs were also sequenced by UDS to evaluate the clinical impact of pre-existing DRAMs on INI response. UDS data were analyzed by Smartgene platform and resistance was interpreted following the ANRS resistance algorithm V26.

Results: At failure, the prevalence of at least one INI DRAM was 39.6% (53/134) by Sanger, 47% (63/134) by UDS at 5% detection threshold, and 57.5% (77/134) at 1% detection threshold. Among 53 patients harbouring at least 1 DRAM detected by both techniques, the most dominant DRAMs are the N155H, Q148H/K/R, and T97A observed in 24 (45.2%), 12 (22.6%), and 10 (18.9%) patients respectively whereas the Y143C was detected in 6 (11.3%) patients. UDS detected additionally DRAMs such as T66A/I (n=7), E92Q (n=3), T97A (n=2), E138K (n=3), G140S (n=1), Y143C/H (4), S147G (n=2), Q148R (n=2), N155H (n=3), S230G/R (n=2), and R263K (n=2). Overall, the presence of DRAMs detected only by UDS has led to changes in resistance interpretation to INI class in 13% (17/134) of patients at 1% of detection threshold. There was no difference in prevalence (14.7% vs 12.9%, p value = 0.817) of baseline DRAMs between patients with VF and those with VS under INI regimen. DRAMs found at baseline by UDS in patients with VF were not detected at failure either in majority or in minority.

Conclusion: In this study, UDS was more sensitive than Sanger to detect minority DRAMs to INIs at failure. However, minority DRAMs identified at baseline did not emerge at failure and had no significant impact on the virological response to INI-based regimen.

546 INTEGRASE INHIBITOR RESISTANCE SELECTIONS INITIATED WITH DRUG RESISTANT HIV-1

Kristen Andreatta, Silvia Chang, Ross Martin, Madeleine Willkom, Kirsten L. White

Gilead Sciences, Inc, Foster City, CA, USA

Background: The integrase strand transfer inhibitors (INSTIs) raltegravir (RAL) and elvitegravir (EVG) have overlapping resistance pathways that develop during treatment failure while dolutegravir (DTG) and bictegravir (BIC) retain antiviral efficacy against many HIV-1 isolates with primary INSTI resistance (-R) substitutions in vitro. Here, the emergence of drug resistance in wild-type (WT) and mutant HIV-1 was assessed in parallel under in vitro selective pressure by the four INSTIs to compare viral evolution from preexisting drug resistant mutants.

Methods: The INSTI-R substitutions E92Q, Q148R, N155H, and R263K in integrase (IN) and the common reverse transcriptase (RT) resistance substitution M184V (RT-M184V) were introduced into HIV-1 as single site-directed mutants. In vitro dose-escalation resistance selections were performed starting with these mutants or WT viruses using RAL, EVG, DTG, BIC, and emtricitabine (FTC). Viral supernatants were genotyped by population and deep sequencing. Site-directed mutants representing the final viral genotypes observed in the selections were phenotyped for drug resistance.

Results: In selections initiated with WT HIV-1 IN (± RT-M184V), S153F/Y or R263K substitutions developed in the presence of BIC, S153Y or N144D developed in the presence of DTG, and Q148K/R and/or T66I developed in the presence of RAL and EVG (Table 1). In selections initiated with IN mutants (E92Q, Q148R, N155H, R263K), many had no further accumulation of INSTI-R substitutions: EVG and RAL selections were stopped after 16-26 weeks due to high levels of resistance while BIC and DTG selections continued for ~30 weeks with growth curves similar to the WT selections. In the presence of DTG, Q148R added the secondary INSTI-R substitution E138K, E92Q added the primary INSTI-R substitution S147G, and N155H added S147N. In the presence

of BIC, E92Q added G140E while Q148R, N155H, and R263K did not add any substitutions at positions associated with INSTI-R. WT and IN mutants, including R263K, developed M184V/I substitutions in RT under FTC pressure. All IN mutants showed higher phenotypic resistance to RAL and EVG than to DTG and BIC.

Conclusion: DTG and BIC selected similar substitutions in WT IN with little to no phenotypic resistance to either drug. Development of additional resistance substitutions was infrequent in selections starting with mutant IN. These results support potential utility and investigation of BIC (in addition to DTG) in patients with preexisting INSTI-R.

Table 1. Genotypes of Wild-type and Mutant HIV-1 after Resistance Selection Experiments

Initial Viral Genotype	Gene	Substitutions Present at Final Time-points of Resistance Selections[1]					
		BIC	DTG	EVG	RAL	FTC	No drug control
WT	RT	None	R211K	None	None	M184V	None
	IN	**S153F**	**S153Y** L234F	**Q148K/R T66I/T E138K/E**	**Q148K**	None	None
RT-M184V	RT	M184V	M184V	M184V	None	NA	M184V
	IN	**S153Y**[2] V72I[2] **R263K**[2]	**S153Y**[3] N144D[3]	**T66I**	**G140A Q148R**		None
E92Q	RT	None	D237E	None	None	M184V/I	None
	IN	**E92Q** G140G/E M154M/I	**E92Q S147S/G**[4]	**E92Q**	**E92Q G140A**/G	**E92Q**	**E92Q**
Q148R	RT	None	None	None	None	M184V/I	None
	IN	**Q148R**	**Q148R E138K**	**Q148R**	**Q148R**	**Q148Q/R**	None
N155H	RT	None	None	V8I/V	None	M184V	None
	IN	**N155H** L45Q	**N155H** S147S/N	**N155H V72A** G140G/E	**N155H** S24G D253E	**N155H** D207D/E	**N155N/H**
R263K	RT	None	None	K219N/K	None	M184V	None
	IN	**R263K**	**R263K**	**R263K T66I**	**R263K**	**R263K**	**R263K**/R

[1] Substitutions present at frequencies >20% are shown, except where noted. Substitution frequencies <80% are shown as mixtures. Known INSTI resistance substitutions are in bold.
[2] V72I/S153Y and R263K developed on separate viral genomes in 2 independent selection experiments with BIC.
[3] S153Y and N144D developed on separate viral genomes in 2 independent selection experiments with DTG.
[4] Primary INSTI resistance substitution S147G present at 5% frequency.
BIC = bictegravir; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; IN = integrase; INSTI = IN strand transfer inhibitor; NA = not applicable; RAL = raltegravir; RT = reverse transcriptase; WT = wild-type

547 157Q INTEGRASE POLYMORPHISM: IN VITRO PHENOTYPIC IMPACT AND IN VIVO VIROLOGIC OUTCOME

Charlotte Charpentier[1], Isabelle Malet[2], Audrey Rodallec[3], Laurence Bocket[4], Corinne Amiel[5], Laurence Morand-Joubert[6], Pantxika Bellecave[7], Thuy T. Nguyen[2], Anne Maillard[8], Brigitte Montes[9], Marie Leoz[10], Constance Delaugerre[11], Vincent Calvez[2], Anne-Geneviève Marcelin[2], Diane Descamps[1]
[1]Bichat–Claude Bernard Hospital, Paris, France, [2]Pitié-Salpêtrière Hospital, Paris, France, [3]CHU de Nantes, Nantes, France, [4]CHU de Lille, Lille, France, [5]Tenon Hospital, Paris, France, [6]Saint-Antoine Hospital, Paris, France, [7]CHU de Bordeaux, Bordeaux, France, [8]CHU de Rennes, Rennes, France, [9]CHU de Montpellier, Montpellier, France, [10]Rouen University Hospital, Rouen, France, [11]St. Louis Hospital, Paris, France

Background: We assessed prevalence of E157Q integrase (IN) polymorphism across HIV-1 subtypes, in vitro phenotypic susceptibility to the different IN inhibitors (INI) of E157Q site-directed mutants and virological outcome at W48 in patients harboring E157Q virus initiating INI-based regimen.

Methods: We analyzed, in a multi-center study, all available IN sequences issued from INI-naïve patients among 17 French ANRS network HIV clinical centers. IN sequencing was performed by Sanger technology using ANRS procedures. E157Q mutation was introduced by site-directed mutagenesis into pNL4.3 and CRF02_AG contexts and assessed in recombinant phenotypic assay using HeLa-P4 cells.

Results: 8528 IN sequences from INI-naïve patients were analyzed: 56% subtype B, 23% CRF02_AG and 21% various "Non-B" subtypes. Overall prevalence of E157Q polymorphism was 2.7% and its distribution among subtypes was 1.7%, 5.6% and 2.2% in B, CRF02_AG and "Non-B" subtypes, respectively. 39 INI-naïve patients with E157Q virus initiated INI-based regimen (19 RAL, 10 EVG and 10 DTG). Among them, 15 patients had VL <50 c/mL at initiation of INI-based regimen and virological suppression was maintained during the follow-up in all but 2 exhibiting viral blip at W48. 24 patients initiated INI-based regimen with a detectable VL (median=4.9 log c/mL): 8 in first-line (5 EVG, 2 RAL, 1 DTG) and 16 ARV-experienced in virological failure with resistant viruses (10 RAL, 3, EVG, 3 DTG). They experienced different virological outcomes depicted in Table 1, not related to the genotypic susceptibility score. INI-discontinuation occurred between W24 and W48 in 3/8 patients in first-line and in 5/16 ARV-experienced patients. Phenotypic analyses showed fold-change of 0.6, 0.9 and 1.9 for RAL, DTG and EVG, respectively in subtype B pNL4.3 context and of 1.1, 1.9 and 2.4 for RAL, DTG and EVG, respectively in CRF02_AG context.

Conclusion: Among this large set of IN sequences, overall prevalence of E157Q was 2.7% with heterogeneity among HIV-1 subtypes. Focusing on ARV-naïve patients receiving a first-line INI-based regimen, two out of the five patients receiving EVG did not reach undetectability at W24, despite baseline VL below 5 log c/mL. Phenotypic analyses showed that the highest E157Q fold-change was observed for EVG in CRF02_AG context, borderline to the 2.5 Phenosense© cut-off. These findings highlight the need to better understand the role of E157Q polymorphism and of potential associated genotypic determinants

Patients initiating INI with VL >50 c/mL	VL <50 c/mL at W24 and W48	VL decrease <2 $\log_{10}$ c/mL at W24 and W48	VL decrease >2.5 log c/mL but VL >50 c/mL	Viral blip	INI stop after W24 with VL <50 c/mL
First-line (n=8)	5 (EVG n=2, DTG n=1, RAL n=2)	0	2 (EVG n=2, 2 stopped EVG after W24)	0	1 (EVG)
ARV-experienced (n=16)	4 (RAL n=3, DTG n=1)	4 (RAL n=2, EVG n=2, 2 stopped RAL after W24)	4 (RAL n=2, EVG n=1, DTG n=1, 1 stopped RAL after W24)	2 (W48, RAL n=2)	2 (DTG n=1, RAL n=1)

548 CHARACTERIZATION OF THE DOLUTEGRAVIR MONOTHERAPY-ACQUIRED S230R RESISTANCE MUTATION

Hanh T. Pham[1], Ingeborg Wijting[2], Lydia Labrie[1], Said Hassounah[1], Ineke van der Ende[2], Bluma G. Brenner[1], Bonnie Spira[1], Charles Boucher[2], Bart Rijnders[2], Jeroen J. van Kampen[2], Thibault Mesplede[1], Mark A. Wainberg[1]
[1]McGill University, Montreal, QC, Canada, [2]Erasmus University Medical Center, Rotterdam, Netherlands

Background: Dolutegravir (DTG) is a potent and well tolerated integrase strand-transfer inhibitor (INSTI) with a high barrier to resistance, which makes it a suitable candidate for antiretroviral maintenance monotherapy and simplified regimens. Here, we report the emergence of a S230R substitution in two patients who experienced virological failure after switching to DTG monotherapy from triple therapy and have characterized the effects of S230R on integrase (IN) enzyme activity, viral infectivity and drug resistance.

Methods: IN-resistance associated mutations were evaluated by sequencing both prior to and at the time of virologic failure. The pET15b-IN overexpression and pNL4.3 proviral vectors containing S230R were generated by site-directed mutagenesis. Biochemical strand-transfer and tissue culture assays were performed to characterize enzyme activity, viral infectivity and to measure resistance to DTG and other INSTIs.

Results: The first case of S230R was found in the context of the DOMONO study (NCT02401828) in a patient who experienced virologic failure at week 30 (HIV-1 RNA was 1570 copies/mL). The patient had a CD4 nadir of 330 cells/mm^3 and had been virologically suppressed on EFV/TDF/FTC for 25 months before switching to DTG 50 mg once daily. A second case involved a patient who had been virologically suppressed on DTG/ABC/3TC for 8 months before switching to DTG monotherapy. Viral load (VL) remained <20 copies/mL but increased to 700 copies/mL with the presence of S230R in IN at week 29. The results of cell-free assays showed that, compared to the WT-IN (Km = 8.8 ± 0.95), the S230R-IN had a modest 2.22-fold increase in Km (19.9 ± 2.3). In the presence of DTG, yielding a 2.6- fold decrease in DTG susceptibility. The infectivity of S230R virus was also impaired by about 1.26-fold compared to WT. The relevance of the S230R substitution was confirmed in a recent study, where DTG monotherapy failed to durably suppress HIV viremia in humanized mice.

Conclusion: In conclusion, virological failure involving DTG monotherapy can occur due to replication of a virus containing a novel S230R substitution that confers modest-level resistance to DTG and other INSTIs.

549 IN VITRO SELECTED RESISTANCE TO NEW INTEGRASE INHIBITORS BY B & NON-B SUBTYPE VIRUSES

Bluma G. Brenner, Maureen Oliveira, Ruxandra-Ilinca Ibanescu, Bonnie Spira, Thibault Mesplede, Jean-Pierre Routy
McGill University, Montreal, QC, Canada

Background: The integrase strand transfer inhibitors (INSTIs) bictegravir (BIC), dolutegravir (DTG), and cabotegravir (CAB) have improved resistance profiles when compared to raltegravir and elvitegravir (EVG), with few reported cases of resistance in the clinic. This study used in vitro drug selections with primary HIV-1 isolates to examine potential pathways for resistance to EVG and DTG and the investigational drugs BIC and CAB.

Methods: Subtype B (n=7) and non-B subtypes (n=5) strains were amplified from PBMCs of primary HIV infections through co-culture in cord blood mononuclear cells (CBMCs). CBMCs were serially passaged in escalating concentrations of DTG, EVG, BIC, and/or CAB for 36-46 weeks. Sanger and ultradeep sequencing ascertained the acquisition of resistance mutations under selective drug pressure at weeks 8-9, 16, 24-30, and 43-46.
Results: Parallel in vitro selections found resistance mutations in more strains for EVG (12/12), followed by CAB (8/12), and BIC and DTG (6/12 each). For EVG, T66I (n=8), E92 G/V/Q (n=3) or R263K (n=1) were followed by the accumulation of mutations leading to viral escape and high-level resistance (bold). With CAB, at the final passages, 8/12 selections resulted in R263K (n=3), Q148K, S153Y, or S147G with acquisition of Q148R/K in two strains leading to viral escape. For DTG and BIC at the final passages, 6/12 strains had singleton mutations R263K, S153Y or H51Y which conferred low-level (<3-fold) resistance and reduced replicative fitness, precluding escalations in DTG and BIC beyond 5-25 nM.
Conclusion: There is a high genetic barrier to resistance to BIC and DTG compared to CAB and EVG. Emergent resistance mutations by singleton mutations, R263K or S153Y confers <1.5-3 resistance retaining antiviral activity to DTG and BIC, whereas more complicated patterns of high-level resistance were selected by CAB and EVG. Ongoing studies will deduce resistance to INSTIs in larger panel of viral strains.

Virus	Clade	Acquired mutations at week 43-46 (Final Passages)			
		DTG	BIC	CAB	EVG
3 isolates	B	none	none	none	T66I (2); E92Q (1)
C050.64	B	none	none	H51HY	T66I
C185.09	B	R263K	R263K	R263K	**T66I, E157Q, R263K**
C185.15	B	R263K	R263K	R263K, S153A	**T66I, E138EK, S147G, Q148R**
196.02	B	H51H/Y	S153Y	**L74M, G140S, S147G, Q148K**	**R263K, S153A**
4742	C	None	None	R263K	E92EG, R263KR
CAE 11.12	AE	None	None	None	H51HY, T66I
96USSN20	AG	R263K	S153FS, E157EK	**L74I, E138K, Q148R, R263**K	**T66I, Q146R, S147G, Q195K**
CAE 13.01	AE	R263K	S153Y	S153Y, G163R	**T66I, R263K**
CC002.02	C	R263K	R263K	S147G	**E92V, R263K**

550 ARV DRUG USE AND HIV DRUG RESISTANCE AMONG MSM IN SUB-SAHARAN AFRICA (HPTN 075)

Yinfeng Zhang[1], Jessica M. Fogel[1], Xu Guo[2], William Clarke[1], Autumn Breaud[1], Vanessa Cummings[1], Erica Hamilton[3], Arthur Ogendo[4], Noel Kayange[5], Ravindre Panchia[6], Karen Dominguez[7], Ying Q. Chen[2], Theodorus Sandfort[8], Susan H. Eshleman[1]
[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]FHI 360, Durham, NC, USA, [4]Kenya Medical Research Institute, Kisumu, Kenya, [5]Malawi Coll of Med–Johns Hopkins Univ Rsr Proj, Blantyre, Malawi, [6]University of the Witwatersrand, Soweto, South Africa, [7]University of Cape Town, Cape Town, South Africa, [8]Columbia University, New York, NY, USA

Background: African men who have sex with men (MSM) are at increased risk of HIV infection and may have limited access to quality health care because of social discrimination, stigmatization or criminalization. The HIV Prevention Trials Network (HPTN) 075 evaluated the feasibility of recruiting and retaining MSM in sub-Saharan Africa, in preparation for HIV prevention trials. The study enrolled HIV-infected and HIV-uninfected men at four sites in Kenya, Malawi, and South Africa. We analyzed antiretroviral (ARV) drug use and HIV drug resistance among HIV-infected men screened for participation in HPTN 075.
Methods: Laboratory testing was performed using plasma samples collected at the screening visit. ARV drug testing was performed using an assay that detects 20 ARV drugs in 5 drug classes. HIV viral load was measured for men who had ARV drugs detected. Viral suppression was defined as a viral load <400 copies/mL. HIV drug resistance testing was performed using the ViroSeq HIV-1 Genotyping Assay v3.0 for men who had ARV drugs detected with a viral load ≥400 copies/mL. Men who reported knowledge of their HIV status were asked if they were in care and if they had been prescribed ARV drugs for HIV treatment.
Results: ARV drugs were detected in samples from 63 (34.4%) of 183 HIV-infected men at screening. In 57 (90.5%) of the 63 cases, the drugs detected were consistent with ARV treatment (ART; unusual combinations of drugs were detected in two of the 57 cases; efavirenz alone was detected in the remaining six cases). Eleven (17.5%) of the 63 men with ARV drugs detected were not virally suppressed; 6 of those men had drug-resistant HIV (4 NNRTI+NRTI resistance; 1 NNRTI resistance alone; 1 NRTI resistance alone). In multivariate logistic regression, detection of ARV drugs was more frequent among older men (26-44 years; compared to 18-25 years p=0.019), men from Kisumu, Kenya (compared to Blantyre, Malawi [p=0.003], Cape Town, South Africa [p=0.022], and Soweto, South Africa [p=0.016]), and men who reported that they were engaged in HIV care with current or prior ARV drug use (p<0.001).
Conclusion: Most of the HIV-infected men screened for participation in HPTN 075 were not on ART at the screening visit, and many of those on ART were not virally suppressed. Among those who were taking ARV drugs and were not virally suppressed, more than half had drug-resistant HIV and many were at risk of acquiring additional resistance. These findings underscore the importance of improving HIV care for African MSM.

551 ARV DRUG USE AND HIV DRUG RESISTANCE AMONG YOUNG WOMEN IN SOUTH AFRICA (HPTN 068)

Yinfeng Zhang[1], Mariya V. Sivay[1], Sarah E. Hudelson[1], Jing Wang[2], Yaw Agyei[1], William Clarke[1], Autumn Breaud[1], Erica Hamilton[3], Kathleen Kahn[4], Xavier Gomez-Olive[4], Catherine MacPhail[5], James P. Hughes[6], Audrey Pettifor[7], Susan H. Eshleman[1]
[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Statistical Center for HIV/AIDS Research and Prevention, Seattle, WA, USA, [3]FHI 360, Durham, NC, USA, [4]University of the Witwatersrand, Johannesburg, South Africa, [5]University of Wollongong, Wollongong, Australia, [6]University of Washington, Seattle, WA, USA, [7]University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: Antiretroviral (ARV) drugs are widely used for HIV treatment and prevention, and may be used for other reasons in some populations. We analyzed ARV drug use and HIV drug resistance among young women enrolled in the HIV Prevention Trials Network (HPTN) 068 study. HPTN 068 was conducted in rural northeast South Africa and evaluated the impact of cash transfer on HIV incidence conditional on high school attendance (study period: 2011-2015).
Methods: In the main study, young women were enrolled in high school and were tested for HIV infection annually until their expected graduation date. Some women had a post-graduation follow-up visit 1-2 years later. ARV drug testing was performed using a qualitative assay based on high resolution mass spectroscopy that detects 20 ARV drugs in five drug classes. HIV genotyping was performed using the ViroSeq HIV-1 Genotyping System v2.8.
Results: We analyzed two sample sets: (1) enrollment samples (2,526 women: 80 infected; 2,446 uninfected), and (2) samples from the first HIV-positive visit (162 seroconverters; 107 in the main study, 55 in the follow-up study). ARV drugs were detected in enrollment samples from 10 (12.5%) of 80 HIV-infected women (six had 1 NNRTI with 1 or 2 NRTIs; three had 1 NNRTI alone; one had 1 NRTI alone). ARV drugs were also detected in samples from 16 (9.9%) of 162 seroconverters (14 had 1 NNRTI with 1 or 2 NRTIs; two had 1 NNRTI alone). None of 2,446 HIV-uninfected women had ARV drugs detected. Among the 242 HIV-infected women (80 infected at enrollment; 162 seroconverters), 211 (87.2%) had viral loads >400 copies/mL. HIV genotyping results were obtained for 198 of the 211 women (67 infected at enrollment; 131 seroconverters); this included 7 (26.9%) of the 26 women who had ARV drugs detected. Eighteen (9.1%) of the 198 women had NNRTI resistance, including 9 (13.4%) of 67 women infected at enrollment and 9 (6.9%) of 131 seroconverters; five of the 18 women also had NRTI resistance.
Conclusion: In this cohort, 12.5% of the women who were HIV infected at enrollment and 9.9% of the women with new HIV infection were taking ARV drugs. ARV drugs were not detected in >2,400 HIV-uninfected women. Among women who were not virally suppressed, 9.1% had NNRTI resistance and 2.5% had multi-class resistance. This study provides novel information about ARV drug use and HIV drug resistance among young women in rural South Africa. These findings may help inform future studies using ARV drugs for HIV prevention and treatment in this population.

552 PREVALENCE OF NRTI, NNRTI AND PI MUTATIONS ACROSS BOTSWANA IN 2013 – 2015

Sikhulile Moyo[1], Simani Gaseitsiwe[1], Melissa Zahralban-Steele[1], Dorcas Maruapula[1], Baitshepi Mokaleng[1], Terence Mohammed[1], Erik van Widenfelt[1], Madisa Mine[2], Elliot G. Raizes[3], Etienne Kadima[1], Tendani Gaolathe[1], Joseph Makhema[1], Shahin Lockman[1], Max Essex[1], Vlad Novitsky[4]
[1]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [2]Ministry of Health, Gaborone, Botswana, [3]CDC, Atlanta, GA, USA, [4]Harvard University, Cambridge, MA, USA

Background: In the context of antiretroviral therapy (ART) scale-up and treat-all strategy, population-level monitoring of HIV drug resistance is critical. This study aimed to survey the prevalence of HIV-1 mutations associated with

resistance to nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) from a population-based study conducted across Botswana communities.

Methods: Blood samples were collected from 2343 HIV-positive individuals residing in 25 communities across Botswana (South, East and North) who participated in the Botswana Combination Prevention Project (BCPP) in 2013-2015. HIV sequences were obtained by a long-range HIV genotyping. NRTI, NNRTI and PI resistance mutations were analyzed according to the WHO 2009 and IAS-USA 2015 lists. Viral sequences were screened for G-to-A hypermutations (HM). Mutations in sequences with adjusted HM rate above 2% were considered to be generated by HM, and were not counted toward drug-resistant mutations (DRMs). Viral suppression was considered at HIV-1 RNA less than or equal to 400 copies/mL.

Results: Among analyzed 2343 participants, prevalence of mutations associated with NRTI-, NNRTI- and PI-drug resistance was 2.9%, 3.2% and 1.2%, respectively. Prevalence of drug resistance to any drug class (NRTI, NNRTI or PI) was 5.8% (95% CI: 4.9–6.8%), and did not differ between 3 major regions of Botswana: North (4.7%), East (5.7%) and South (6.4%). ART status was documented for 2225 (95%) participants. Among individuals on ART (n=1583), 96% were virologically suppressed and had prevalence of NRTI-, NNRTI- and PI-associated mutation at 2.0 %, 2.6% and 1.3%, respectively. Among individuals on ART who were not suppressed (n=63), NRTI-, NNRTI- and PI-associated mutation were found in 22%, 24% and 0%, respectively. Among HIV-infected individuals not on ART (n=642), NRTI-, NNRTI- and PI-associated mutation were found in 3.3%, 2.0% and 0.9%, respectively. The overall distribution of specific mutations to 3 classes of drugs is presented in Table 1.

Conclusion: Low prevalence of NRTI-, NNRTI- and PI-drug-resistant mutations was found among residents of 25 communities across Botswana. However, individuals on ART with detectable virus had prevalence of NRTI and NNRTI mutations above 20%. Monitoring of HIV mutations associated with drug-resistance is important during broad scale-up of the treat-all national policy in Botswana.

NRTI mutations		NNRTI mutations		PI mutations	
M41L	0.48%	K101E/P	0.53%	D30N	0.17%
K65R	0.31%	K103N/S	1.68%	M46I/L	0.56%
D67N	0.31%	V106M	0.31%	F53Y	0.04%
K70R/E	0.26%	Y181C/I/V	0.66%	G73S	0.35%
L74I	0.04%	Y188L/C	0.18%	V82A/S	0.30%
V75M/S	0.13%	G190A	0.79%	I85V	0.04%
Y115F	0.04%			N88S	0.04%
M184V/I	2.12%				
T215Y/F/S/D	0.35%				
K219E/R	0.22%				
Any NRTI	**2.90%**	**Any NNRTI**	**3.20%**	**Any PI**	**1.20%**

553 ARV RESISTANCE AND CO-RECEPTOR TROPISM IN HIV+ DECEASED ORGAN DONORS IN THE US

Gilad Bismut[1], Christine Durand[2], Diane M. Brown[2], Brianna Doby[3], Shanti Seaman[2], Michael Seisa[4], Christos Petropoulos[4], Reinaldo Fernandez[2], Dorry Segev[1], Aaron Tobian[1], Andrew D. Redd[5]

[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Johns Hopkins University, Baltimore, MD, USA, [3]Positive Rhetoric, LLC, Denver, CO, USA, [4]Monogram BioSciences, San Francisco, CA, USA, [5]NIH, Bethesda, MD, USA

Background: In HIV+ to HIV+ organ transplantation, there is a theoretical risk of transmitting ART-resistant or CXCR4-tropic virus from HIV-infected deceased donors (HIVDD). Furthermore, the time required for a laboratory to definitively test for these risk factors by obtaining viral genotypes and phenotypes is substantially greater than the window period for transplantation. Examining HIVDD for risk factors associated with ART-resistance and CXCR4 tropism may allow physicians to more accurately predict resistance in potential donors.

Methods: Blood from potential HIVDD were obtained from 11 distinct organ procurement organizations throughout the United States. Demographic, virologic, and serology data were evaluated in two groups, subjects whose organs were used for transplantation and those who were not used. ART-resistance and viral co-receptor tropism were determined in viremic individuals using the Genosure Prime and standard Trofile assays; and in virally suppressed individuals using the Genosure Archive and Trofile DNA assays (Monogram Biosciences).

Results: Of 36 potential HIVDD with sufficient blood collected for the study, five provided organs for HIV+ to HIV+ transplants (T group). The remaining were evaluated as research only (RO group). Differences in age were seen among the groups with the T group being younger (mean age=30.2 vs 48.1). Thirty-one subjects were successfully genotyped for ART-resistance. In the T group, 80.0% of subjects (n=4) had successful genotyping with only one HIVDD showing drug resistance to NRTIs (Table 1). 60% (n=3) of the T group yielded tropism results with 100% using CCR5. In the RO group (n=27), seven subjects (25.9%) had resistance to one or more ARVs (Table 1). 71% (n=22) of the RO group were successfully phenotypes for co-receptor tropism with 45.5% (n=10) using CCR5 exclusively, and 54.5% (n=12) being mixed or dual-tropic (CCR5 and CXCR4).

Conclusion: This is the first report classifying the preliminary levels of ART-resistance and viral tropism in the HIVDD pool in the US. Levels of ART-resistance and CXCR4-tropism were comparable to levels reported in the general population. With the passage of the HIV Organ Policy Equity (HOPE) Act, and the first successful HIV+ to HIV+ kidney and liver transplants occurring in the US, it is important to better understand the underlying risk within this unique donor population.

Table: Genotype ART resistance profiles for all donors with detectable resistance

Donor ID	ART resistance	Class	Mutation
Transplant Group			
Donor 4*	ABC, ddI, FTC, 3TC, ZDV	NRTI	V118I, M41L, M184V
Research Only Group			
Donor 12	NFV	PI	I62V, A71V, M36I, M46M/L, L10L/I, I203I/M
Donor 11	EFV, NVP	NNRTI	A71A/V, K103K/N, V118V/I, L10L/V
Donor 25	FTC, 3TC	NRTI	K20K/R, M36I, I33I/V, I13V, M184M/V
Donor 15	ABC, ddI, FTC, 3TC, EVG, RAL, ATV	NRTI; INI; PI	A62A/V, K65R, A71I, M184V, I203M; N155H; V82A, L33F, I50L
Donor 17	EFV, NVP	NNRTI	A71I, K103K/N, V151I
Donor 18	EFV, NVP	NNRTI	K103N, V90I, D60D/E, E35D
Donor 24	FTC, 3TC	NRTI	V118I, V90V/I, M184M/V

*-Recipients for Donor 4 were pre-screened to have ART options that allowed for possible resistance conferred by transplant with resistant donor strains.

554 IMPROVED CARE OF SOCIALLY DISADVANTAGED PATIENTS IS NEEDED TO REDUCE DRUG RESISTANCE

Irene A. Abela[1], **Alexandra Scherrer**[1], Jürg Böni[2], Sabine Yerly[3], Thomas Klimkait[4], Matthieu Perreau[5], Manuel Battegay[6], Hansjakob Furrer[7], Alexandra Calmy[3], Patrick Schmid[8], Matthias Cavassini[5], Enos Bernasconi[9], Huldrych F. Günthard[1]

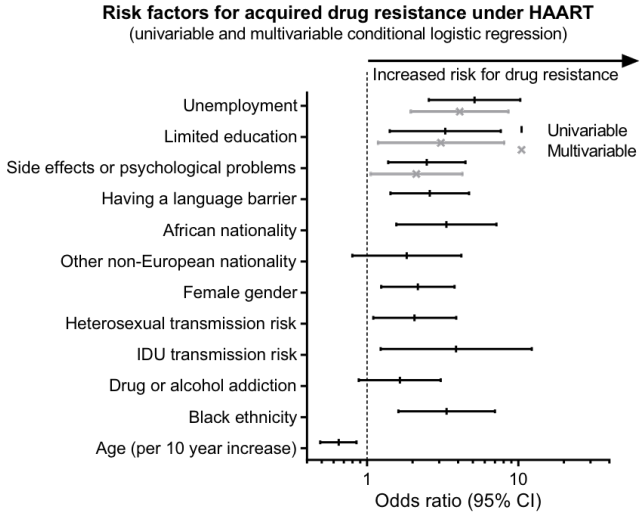
[1]University Hospital Zurich, Zurich, Switzerland, [2]University of Zurich, Zurich, Switzerland, [3]University Hospitals of Geneva, Geneva, Switzerland, [4]University of Basel, Basel, Switzerland, [5]Lausanne University Hospital, Lausanne, Switzerland, [6]University Hospital Basel, Basel, Switzerland, [7]University Hospital of Bern, Bern, Switzerland, [8]St. Gallen Cantonal Hospital, St. Gallen, Switzerland, [9]Servizio di Malattie Infettive, Lugano, Switzerland

Background: The rate of acquired HIV-1 drug resistance (ADR) has fallen dramatically over recent years since introduction of combined antiretroviral therapy (cART) in Switzerland (Scherrer, CID, 2016,15;62(10):1310). However, clinical experience indicates that there are still patient subgroups in which ADR remains a therapeutic challenge. Here, we aimed at characterizing risk factors for ADR, in order to improve patient care and prevent treatment failure.

Methods: We performed a case-control study to identify risk factors for ADR in all patients starting their first cART regimen in the Swiss HIV Cohort Study (SHCS) since 1996. Hundred-fifteen cases with ADR were randomly matched with 115 controls without ADR. Matching criteria were viral load, first year of cART initiation, transmitted drug resistance and SHCS center. Furthermore, we performed a systematic medical chart review to obtain more detailed information on 20 additional parameters not routinely collected in the SHCS, i.e. psychosocial characteristics (e.g. migratory background, language barrier), adherence, psychiatric disorders, and side effects. We performed univariable conditional logistic regressions and implemented a stepwise forward selection adding terms with $p<0.1$ in the multivariable model.

Results: Compared to controls, a high proportion of patients with ADR mutations were migrants (48% vs 27%), were in unstable job situations (67%

vs. 30%) and suffered more often from psychiatric problems such as depression (32% vs. 20%), mood swings (24% vs. 8%) and tiredness (14% vs. 4%). In the univariable models, several factors were associated with an increased risk for ADR (see figure): i.a. younger age, female gender, black ethnicity, having a language barrier, having any psychiatric problems or side effects, belonging to the heterosexual transmission group. In the multivariable model, unemployment (OR: 4.1, 95% CI: 1.9-8.6, p<0.001), limited education (OR 3.1, 95% CI 1.1-8.1, p=0.022) and psychiatric comorbidities or side effects (OR: 2.1, 95% CI: 1.1, 4.3, p=0.034) remained significantly associated with ADR. Patients with ADR and without any identified risk factor were rare (n=18).
Conclusion: Although, ADR has become very rare with cART, patients in socially challenging life situations or patients with psychiatric problems are at higher risk for drug resistance. Prompt identification and adequate support of these patients may prevent further drug resistance acquisition.



555 PASEQ: ONE-CLICK, CLOUD-BASED WEB SERVICE FOR NGS-BASED HIV GENOTYPING DATA ANALYSIS

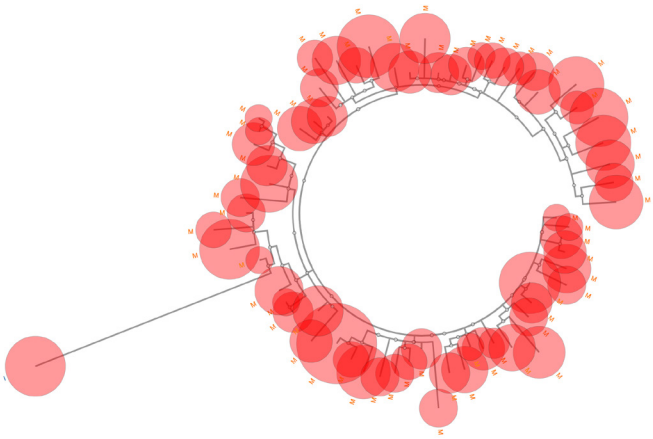
Jordi Herms[1], Cristina Rodriguez[2], Maria Casadella[2], Teresa Puig[2], Bonaventura Clotet[2], Roger Paredes[2], **Marc Noguera-Julian**[2]
[1]Fundació Lluita Contra la Sida, Badalona, Spain, [2]IrsiCaixa Institute for AIDS Research, Badalona, Spain

Background: Cost-effective HIV drug resistance testing is needed. Next Generation Sequencing (NGS) technologies produce high quality results at an optimized cost[1]. However, the need for bioinformatics analysis of large data volumes is one of the main bottlenecks for the adoption of NGS in HIV DR testing.
Methods: We developed an automatic analysis pipeline, PASeq: Polymorphism Analysis by Sequencing. Briefly, raw NGS data is quality&contamination filtered, aligned to a pre-defined reference (HXB2) and codon-level queried for amino acid variants. Mutations are programmatically used to query Stanford HIVdb for resistance interpretation. All results are interactively provided both through the web and a pdf report. PASeq runs on a computational cloud and can scale up to virtually an unlimited number of concurrent analyses with a <1 hour mean runtime. PASeq provides a one-click friendly user web interface, creates printable reports and streamlines data submission and interpretation. Additionally, PASeq stores results in a structured database that can be exploited for HIV epidemiology and is freely available at www.paseq.org. 26 HIV routinely genotyped plasma and 1 NL4.3 plasmid samples were sequenced using Illumina (MiSeq/Nextera-XT protocol). Illumina raw data was directly uploaded and analyzed through PASeq.org, with a 1% lower threshold. Protease and positions 1-335 in reverse transcriptase were compared
Results: High quality Sanger and Illumina NGS data was obtained for all samples. PASeq analysis took approximately 1h time. Median coverage for Illumina data was 7662(IQR:6325-9739). All except 8/11733 (<0.001%) amino acid Sanger calls were also detected by PASeq in Illumina data. Thorough re-inspection of these 8 discrepancies showed that 4 corresponded to low Sanger quality sequences, 3 within the same sample, while the other 4 discrepant readouts corresponded to dual mixes, a known technical limitation of Sanger Sequencing resolved by NGS clonal sequencing and codon variant calling. PASeq analysis also detected 186 additional amino acid mutations with median frequency of 3.420%(IQR:1.72-10.69%). Of these, none was found in the NL4.3 positive control and all PASeq detected mutations for this sample were also detected in Sanger Sequencing
Conclusion: PASeq.org combined with NGS is an effective alternative for HIV NGS data analysis that provides Sanger-like information with improved resolution and increased sensitivity, by overcoming technical and data throughput limitations.

556 SMRT SEQUENCING OF FULL-LENGTH POL AMPLICONS TO INVESTIGATE HIV-1 DRUG RESISTANCE

Sergio Ita, Caroline Ignacio, Sanjay Mohan, Venkatesh Kumar, Benjamin Murrell, Douglas D. Richman, Davey M. Smith, Gabriel A. Wagner
University of California San Diego, La Jolla, CA, USA

Background: Current HIV drug-resistance testing does not identify viral variants present at levels below 20% of the population and fails to simultaneously sequence the principal regions targeted by antiretroviral therapy (ART). Deep sequencing platforms have improved detection of minority drug resistant mutations (DRMs); however, these methods are limited by the relatively short length of the output reads (~150-400 base pairs). We used Pacific Biosciences single molecule real time (SMRT) sequencing to deep sequence en bloc the 3-kilobase pol gene among HIV-infected individuals, and monitor DRMs within full-length (FL) pol amplicons.
Methods: Viral RNA was isolated and cDNA generated from a participant of the San Diego Primary Infection Resource Consortium. We optimized amplification of a 3,338-bp pol product using subtype-B-specific primers spanning RT, PR, and IN (HXB2 1736 to 5074). Libraries of each FL pol amplicon were sequenced on the PacBio RS II platform. For sequence analysis, we adapted FLEA, a pipeline for processing full-length HIV env PacBio data. Populations were characterized using interactive browser-based visualizations of sequence alignments and phylogenies, highlighting DRMs from the Stanford HIV Drug Resistance Database.
Results: SMRT reads produced from a sample collected 385 days after the estimated date of infection and before initiation of ART (Figure 1) revealed a heterogeneous population with a single outlier variant (estimated frequency: 2.8%), which had APOBEC-induced mutations. Total pol nucleotide diversity (as measured by total tree span under a GTR model) was 2.35%, but reduced to 0.8% after excluding the APOBEC-mutated variant. M184I was observed in this APOBEC-mutated variant, along with 18 other APOBEC mutations and 9 premature stop codons, rendering this variant defective. M184I was not found on any other haplotype variants and no other DRMs were found within the viral population.
Conclusion: We showed that SMRT sequencing of plasma HIV-1 RNA: a) generated deep coverage of FL pol amplicons, b) detected DRMs within a defective variant, and c) did not reveal minority DRMs in FL reads, consistent with the local epidemic. Long-read deep sequence platforms, such as PacBio, provide a sensitive method for linkage analysis across the entire length of HIV-1 pol. Further studies could apply this methodology to detect co-evolution of DRMs.



557 POINT-OF-CARE HIV-1 GENOTYPIC RESISTANCE TESTING USING MELT-CURVE ANALYSIS

Dana S. Clutter[1], Gelareh Mazarei[2], Justen Manasa[3], Sara Bolouki[2], Ruma Sinha[2], Peter Kuimelis[2], Robert Kuimelis[2], Benjamin Pinsky[1], Gary Schoolnik[2], Arjang Hassibi[2], Robert Shafer[1]
[1]Stanford University, Stanford, CA, USA, [2]InSilixa, Inc, Sunnyvale, CA, USA, [3]African Institute of Biomedical Science and Technology, Harare, Zimbabwe

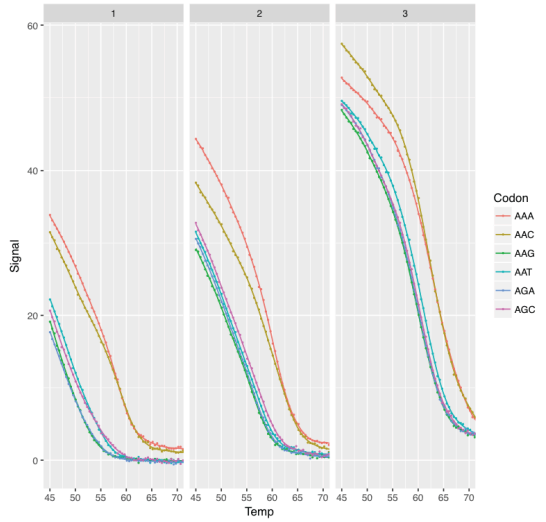
Background: An inexpensive point-of-care (POC) genotypic resistance test (GRT) would enable HIV-1 providers to make informed decisions for ARV-naïve patients starting therapy and for patients on therapy with virological failure. The main challenge in developing a POC GRT is the variability at and surrounding each drug-resistance mutation (DRM) position. We performed in silico and in vitro experiments to determine whether melt-curve analysis could distinguish between 6 different codon 103 variants despite surrounding sequence variability. In vitro experiments were performed using a developer platform for the HYDRA-1K CMOS biochip (InSilixa, Inc, Sunnyvale, CA).

Methods: We performed in silico thermodynamic modeling of 43,000 global RT sequences to design a probe set comprising 18 34-bp probes (6 codons x 3 flanking regions) predicted to discriminate the 6 most common codon 103 variants: AAA (K), AAG (K), AAC (N), AAT (N), AGA (R), AGC (S). We then printed each probe in the set onto silicon slides and performed 81 experiments using diverse fluorescently-labeled 80-bp targets. In each experiment, we added a single target or a mixture of AAA and AAC targets to a slide, which we then heated over 20 minutes while a fluorescent microscope captured serial images. The Tm (temperature at which 50% of the target was hybridized) was calculated for each probe and weighted by the initial signal intensity to reflect the degree of hybridization.

Results: In 54 experiments, we tested 18 targets (6 codons x 3 flanking regions) in triplicate. In 27 experiments, we tested mixtures of AAC/AAA targets with 3 different flanking regions at ratios of 50/50, 25/75, and 10/90 in triplicate. In the 54 experiments using single targets, a mean weighted ΔTm cutoff of 8.7°C was 100% sensitive and specific for correctly identifying single targets. A mean weighted ΔTm cutoff of 13.1 °C was 97% sensitive and 100% specific for identifying targets present at 25% or 50%. A mean weighted ΔTm cutoff of 16.3 °C was 90% sensitive and 89% specific for the detection of variants at 10% frequency.

Conclusion: Despite genetic variability surrounding the DRM position, multiple codons at a DRM position can be correctly identified in isolation or as part of a mixture when the frequency of both species is ≥25% using a solid-phase melt curve analysis platform. Future work will include additional DRM positions, minority variant detection, and transfer to the HYDRA-1K CMOS biochip.

Figure 1. Example of mixing experiment (1 of 27)



Targets bearing the AAA (75%) and AAC (25%) variants of codon 103 were added. Each of the 3 panels displays the melt curves generated by one set of probes. All probes within a set share the same flanking sequence (either flanking sequence 1, 2 or 3), but each of the 6 probes within a set bears a different codon 103 variant. The melt curves complementary to AAA (red) and AAC (gold) had the highest initial signal intensities – indicating the greatest degree of hybridization -- and highest T_ms. Although the initial signal intensities are lower in probe sets with flanking sequences 1 and 2 because of a greater degree of mismatch with the added targets (containing flanking sequence 3), the separation of melt curves was preserved.

558 PROTEASE, GAG AND GP41 MUTATIONS ASSOCIATED WITH VIROLOGICAL RESPONSE TO PI REGIMEN

Marine Perrier[1], Louise Castain[2], Eve Todesco[2], Roland Landman[1], Benoit Visseaux[1], Yazdan Yazdanpanah[1], Leslie Regad[3], Veronique Joly[1], Vincent Calvez[2], Anne-Geneviève Marcelin[2], Diane Descamps[1], **Charlotte Charpentier**[1]
[1]Bichat–Claude Bernard Hospital, Paris, France, [2]Pitié-Salpêtrière Hospital, Paris, France, [3]University Paris Diderot, Paris, France

Background: Protease (PR) resistance associated mutations are rarely observed in case of virological failure (VF) of a first-line PI-based regimen. The aim of this study was to assess the impact of baseline determinants in PR, but also in gag and gp41 regions, on virological response of a first-line PI-based regimen.

Methods: In an observational cohort we enrolled all ARV-naïve patients initiating a first cART including 2 NRTI associated with DRV/r (n=131) or with ATV/r (n=23) between January 2012 and March 2015, including 36 experiencing VF. Baseline ultra-deep sequencing of PR, gag and gp41 regions was performed using Illumina® technology. Supervised data mining analysis were performed to identify mutations associated with virological response. Statistical analyses were performed with Fisher's exact test and Bonferroni correction was applied. Structural analyses were performed to assess impact of mutations on PR conformation.

Results: Among 154 patients enrolled, HIV-1 sequences were successfully obtained in 127, 138 and 134 samples for PR, gag and gp41, respectively. 31% of samples were subtype B, 38% CRF02_AG and 31% others "non-B" subtypes. Overall in PR, 2 mutations were identified as associated with VF: T4A, S37T (p=0.02; p=0.05, respectively). Among CRF02_AG sequences, mutations I72M and E21D were associated with VF (p=0.03 for both). Structural modeling analysis showed that all these mutations induced some conformational changes of some PR side-chain residues located near mutated residues. In gag, mutations associated with VF were G62D, N315H and Y441S (p=0.05, p=0.07 and p=0.0003, respectively). All these mutations are localized outside gag cleavage site (G62D: matrix, N315H: capsid and Y441S: p1). In gp41, I270T mutation was associated with VF (p=0.003). This mutation is located in the cytoplasmic tail, a region whose impact on PI resistance has been recently showed. In addition, mutation I4L, localized in fusion peptide, was associated with virological success (p=0.004).

Conclusion: In this study, based on patients initiating a first-line DRV or ATV/r-based regimen, we identified baseline mutations associated with virological response as well inside as outside PR, in gag and gp41 regions. Further in vitro studies are needed to better characterize the impact of these new mutations on PI phenotypic susceptibility.

559 HIV-1 GAG REDUCES PI-SUSCEPTIBILITY IN THE ABSENCE OF PROTEASE RESISTANCE MUTATIONS

Oscar Blanch-Lombarte, José Ramón Santos, Ruth Penya, Alba Ruiz, Esther Jimenez-Moyano, Roger Paredes, Bonaventura Clotet, Julia G Prado
IrsiCaixa Institute for AIDS Research, Badalona, Spain

Background: The HIV-1 genetic determinants of virological failure (VF) to Protease inhibitors in the absence of protease mutations are poorly understood. However, their identification would be crucial in improving the actual genotypic tools to define VF to PIs in B and particularly, non-B clade HIV-1 subtypes.

Methods: We performed a retrospective review of 520 HIV-1 infected patients who started monotherapy with Protease inhibitors (PIs) LPV/r or DRV/r in our clinic. Eleven experienced VF and were further analysed. We amplified the HIV-1 Gag-Protease from 9 subjects at the time of VF. Signature mutations in the Gag-Protease region were identified by comparison with 2000 naïve B clade sequences from Los Alamos database using VESPA (www.hiv.lanl.gov). Also, we evaluated replicative capacity and drug susceptibility to LPV and DRV in Gag-Protease recombinant virus generated from plasma samples at VF.

Results: All study patients experienced VF to PIs in the absence of Protease resistance mutations. We observed a high frequency of mutations previously described outside Gag cleavage sites at positions R76K (55%), I389T (44%), E12K (33%), V370A (33%) and T81A (11%). VESPA analyses provided a signature pattern of mutations in Gag including residues K95R, E203D, V215M, R286K (p<0.01). Replicative capacity experiments demonstrated a preservation of viral fitness by direct comparison with the NL43 laboratory strain. Most virus did not show significant changes in drug susceptibility. However, a Gag-Protease recombinant virus from one patient harboring the K95R, R286K Gag mutations without Protease mutations revealed 8- to 10-fold reduction in

drug susceptibility to DRV, thus, demonstrating a direct linkage between Gag mutations and drug resistance to PIs.

Conclusion: These data define a novel set of Gag signature mutations involved in PIs resistance and identify Gag as a direct contributor to PI resistance in the absence of mutations in the Protease. These findings are crucial for the optimization of genotypic tools to identify VF to PIs in the absence of Protease mutations. Additional studies in non-B clade virus would be essential to extend our findings to other HIV-1 subtypes.

560 ACTIVITY OF TENOFOVIR ALAFENAMIDE IN HIV-1 WITH THYMIDINE ANALOG MUTATIONS AND M184V

Nicolas A. Margot, Renee R. Ram, Michael E. Abram, Richard Haubrich, Michael D. Miller, Christian Callebaut
Gilead Sciences, Inc, Foster City, CA, USA

Background: Tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are prodrugs of the HIV-1 nucleotide reverse transcriptase (RT) inhibitor tenofovir (TFV). In vivo, TAF achieves ~4-fold higher intracellular levels of TFV diphosphate (TFV-DP) compared to TDF. Thymidine analog mutations in HIV-1 (TAMs) confer incremental reduced susceptibility to TFV, and patients with TAM-containing HIV-1 may benefit from higher levels of TFV-DP delivered by TAF. Moreover, the presence of the M184V mutation increases susceptibility to TFV during TDF or TAF-based therapy. Virologic outcome of subjects harboring HIV with M184V/I are currently being studied clinically (GS-US-292-1824). Here, the in vitro activity of TAF was evaluated in a large set of TAM-containing HIV-1, with or without M184V.

Methods: Site-directed mutants (SDM) containing combinations of TAMs (M41L, D67N, K70R, L210W, T215Y, and/or K219Q) with or without M184V were generated. Antiviral drug susceptibilities (fold change [FC] EC50 relative to wild-type) were determined in MT-2 cells using either a 2-day Single-Cycle (SC; n=96) or 5-day Multi-Cycle (MC; n=96) PR-RT HIV assay. Patient-derived (PD; n=14) mutants with TAMs were tested using the MC assay. Comparison of TAF and TFV resistance profiles were further assessed in viral breakthrough (VB) experiments mimicking clinically relevant drug concentrations using TAM-containing viruses (SDM and PD).

Results: The presence of M184V in TAM-containing HIV-1 SDMs (n=48) significantly increased sensitivity to TAF in both SC and MC assays compared to TAM SDMs without M184V (n=48) (Table) (Mann-Whitney test: p-value of 0.005 and 0.003 for the SC and MC assays, respectively). The mean TAF FC for PD viruses (with or without M184V) was 3.8 (ranging from 1.4 to 14.6). FC resistance for TAF and TFV in MC assay showed a strong 1:1 correlation (r2=0.93). A total of 68 mutants (54 SDM and 14 PD) were assayed at physiological concentration in VB experiments, with 15 mutants breaking through under TFV treatment (average FC of 5.1; 3 to 6 TAMs ± M184V) and only 3 mutants breaking through under TAF treatment (average FC of 9.9; 5 TAMs without M184V).

Conclusion: In the presence of M184V, the antiviral activity of TAF was increased in HIV-1 mutants harboring TAMs, similarly to TFV. However, in VB assay mimicking the 4-fold higher intracellular levels of TFV-DP delivered by TAF compared to TDF in vivo, TAF inhibited viral breakthrough of TAMs-containing HIV-1 that were not inhibited by TFV.

Table. Susceptibility to TAF of TAM-Containing HIV-1 Mutants Without or With M184

Virus Type	Mutant Class (n)	Single-Cycle (SC) Assay TAF EC_{50} Fold-Change vs. WT			Multi-Cycle (MC) Assay TAF EC_{50} Fold-Change vs. WT			Viral Breakthrough (VB) Assay (#)	
		Without M184V	With M184V	M184V Effect*	Without M184V	With M184V	M184V Effect*	TFV	TAF
SDM (SC: n=96) (MC: n=96)	0 TAMs (n=1)	1.0	1.3	0.8	1.0	0.5	2.0	0	0
	1 TAMs (n=6)	1.4	1.3	1.0	0.8	0.4	2.1	0	0
	2 TAMs (n=15)	1.8	1.5	1.2	1.3	1.0	1.3	0	0
	3 TAMs (n=12)	2.3	1.3	1.7	2.1	1.3	1.6	0	0
	4 TAMs (n=7)	5.3	2.6	2.0	2.7	1.6	1.7	1	0
	5 TAMs (n=6)	4.9	2.5	1.9	2.9	1.7	1.7	3	0
	6 TAMs (n=1)	5.5	2.3	2.4	3.4	1.8	1.9	1	0
	Mean	2.9	1.7	1.7	1.9	1.2	1.6		
PD	3 TAMs (n=5)	nd	nd	nd	3.4	2.9	1.2	3	0
	4 TAMs (n=4)	nd	nd	nd	6.2	2.7	2.3	2	0
	5 TAMs (n=5)	nd	nd	nd	9.9	3.6	2.8	5	3
	Mean	na	na	na	6.5	3.1	2.1		

(*) M184V Effect is the Ratio of "Without M184V" to "With M184V".
WT: wild-type; SDM: site-directed mutants; PD: patient derived mutants; nd: not done; na: not applicable

561 IBALIZUMAB SUSCEPTIBILITY IN PATIENT HIV ISOLATES RESISTANT TO ANTIRETROVIRALS

Steven Weinheimer[1], Zvi Cohen[2], Christian Marsolais[2], Stanley Lewis[1]
[1]TaiMed Biologics USA, Irvine, CA, USA, [2]Theratechnologies, Inc, Montreal, QC, Canada

Background: Ibalizumab (IBA) is a long-acting humanized IgG4 monoclonal antibody that blocks HIV entry into CD4 cells while preserving normal immunological function. IBA binds to domain 2 of the CD4 receptor, away from the MHC II binding site. IBA susceptibility of patient isolates was determined at Baseline for a 24-week, Phase 3 clinical trial (TMB-301) conducted in 40 heavily treatment-experienced patients with multi-drug resistant HIV-1. Susceptibility was compared for isolates that were sensitive and resistant to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), enfuvirtide (ENF) and maraviroc (MVC).

Methods: Maximum Percent Inhibition (MPI) and ICHalfMax Fold Change (ICHMFC) from the dose-response curve were monitored as indicators of IBA susceptibility using the PhenoSense HIV Entry assay. MPI is the maximum level of inhibition achieved and ICHMFC occurs at the midpoint of the dose response curve.

Results: IBA susceptibility at Baseline was determined for 38 of 40 patient isolates. The mean IBA MPI at Baseline was 91±14 (median of 97). Twenty-seven samples had MPI values of 90-100%, 6 had MPI values of 80-90%, and 5 had MPI values <80%. The mean ICHMFC was 1.2 ± 0.9 (median of 0.9). The mean IBA MPI for patient HIV isolates with wild-type susceptibility to NRTIs, NNRTIs, PIs, or INIs, was 81%, 98%, 89%, and 91%, respectively; the mean ICHMFC was 1.3, 0.9, 1.1, and 1.0, respectively. For isolates that were resistant to all NRTIs, NNRTIs, PIs, or INIs, the mean IBA MPI was 94%, 91%, 91%, and 92%, respectively; the mean ICHMFC was 1.2, 1.2, 1.3, and 1.1, respectively. 6 patients had HIV with reduced susceptibility to ENF at screening. 5 of these had IBA MPI values 84-99% with ICHMFC values 0.7-1.4, while 1 had HIV with reduced IBA susceptibility (MPI = 41%, ICHMFC = 6.2). Two patient isolates exhibited CCR5-dependent replication with reduced susceptibility to MVC – one was CCR5 tropic with MVC MPI = 58% and one was dual-mixed (DM) tropic with MVC MPI <0 . Both isolates were susceptible to inhibition by IBA with MPI = 94% and 100%, respectively. The mean MPI for CCR5, DM, and CXCR4 tropic isolates was 89%, 91%, and 92%, respectively.

Conclusion: IBA is effective despite resistance to other antiretrovirals. The present in vitro IBA susceptibility results correlate with the efficacy observed in the Phase 3 trial 7 days after functional monotherapy.

562 RPV LA DOES NOT INHIBIT RESISTANT HIV TRANSMISSION OR SELECT SIGNIFICANT RESISTANCE

Zandrea Ambrose[1], Kevin Melody[1], Chris Kline[1], Mackenzie L. Cottrell[2], Brandon Keele[3], Angela Kashuba[2], Moses Bility[1]
[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [3]Leidos Biomedical Research, Inc, Frederick, MD, USA

Background: Long-acting rilpivirine (RPV LA) has been proposed for use as pre-exposure prophylaxis (PrEP) and the prevalence of transmitted RPV-resistant viruses can be relatively high in some populations. We studied how effectively RPV LA could inhibit vaginal transmission of WT HIV-1 as well as two RPV-resistant mutants.

Methods: Plasma and female genital tract (FGT) RPV pharmacokinetics were determined after a single dose of RPV LA in female humanized BLT mice. Vaginal virus challenges of WT, Y181C, and Y181V HIV-1 were performed in untreated animals and after RPV PrEP when plasma and FGT concentrations were either at biologically relevant (low) or 7- to 9-fold higher (high) concentrations (n=6-10 per group). Quantitative RT-PCR was used measure plasma viremia in the mice until 10 weeks post-challenge. Single-genome sequencing of the reverse transcriptase coding region was performed on plasma HIV-1 RNA in mice infected during PrEP treatment.

Results: Y181C HIV-1 conferred 2-fold resistance and Y181V HIV-1 conferred 30-fold resistance to RPV in vitro. High RPV concentrations delayed dissemination of a highly infectious WT HIV-1 clone (p>0.05) and completely inhibited Y181C HIV-1 (p=0.02). However, high RPV concentrations did not inhibit Y181V HIV-1. Biologically relevant RPV concentrations did not significantly inhibit vaginal transmission of WT or Y181C HIV-1. New mutations

associated with low-level RPV were detected in 25% of mice infected during RPV LA PrEP usually at frequencies of <5% of HIV-1 RNA genomes. E138K and mutations that do not confer RPV resistance (M184I and V179I) were also observed in some mice. E138K and M184I previously were shown to develop via APOBEC3-mediated hypermutation.
Conclusion: Biological concentrations of RPV in the genital tract and plasma were not sufficient to prevent vaginal transmission of a highly infectious HIV-1 molecular clone. While 8-fold higher RPV concentrations inhibited low RPV-resistant Y181C HIV-1, they were not sufficient to inhibit Y181V HIV-1, which has 30-fold resistance to RPV. Our data suggest that both level of resistance and infectivity affect the ability of HIV-1 to be transmitted during PrEP. HIV-1 did not develop high level or high frequency RPV resistance most mice infected during RPV LA PrEP. The impact of low frequency RPV-resistant viruses on virologic outcome during antiretroviral treatment remains to be determined.

563 FIELD EVALUATION OF A DUAL HIV/SYPHILIS TEST IN A COMMUNITY-BASED CLINIC, LOS ANGELES

Chrysovalantis Stafylis[1], Lauren J. Natoli[2], Katheryn Salow[2], Emma Davidson[2], Yancy Granados[2], Mark R. McGrath[2], Jeffrey D. Klausner[1]
[1]University of California Los Angeles, Los Angeles, CA, USA, [2]AIDS Healthcare Foundation, Los Angeles, CA, USA

Background: High rates of syphilis and HIV infection among high-risk populations in the United States call for strategies to identify and treat new cases early. Dual rapid assays offer a convenient way to screen simultaneously for both infections, but to date there is no FDA-approved device. The INSTI Multiplex HIV-1/HIV-2/Syphilis Antibody Test (BioLytical, Richmond, BC, Canada) is a single use, rapid flow-through in vitro qualitative immunoassay detecting IgG antibodies to HIV-1(gp41), HIV-2(gp36) and Treponema pallidum(p17, p47) in whole/fingerstick blood, serum or plasma. Laboratory evaluations on serum have proven the device highly sensitive and specific for both infections. The field performance of the Multiplex was evaluated in a community clinical setting.
Methods: The study was conducted between August 2016 and September 2017 among adult patients visiting two outpatient clinics of the AIDS Healthcare Foundation in Los Angeles, California; the Healthcare Center serves patients with HIV infection, while the Wellness clinic offers HIV/STD testing. Fingerstick whole blood was tested on the Multiplex and it was compared to serum tested in the laboratory for HIV and TP antibodies. Participant's infection status for HIV was determined using a 4th generation assay (Abbott Architect HIV Ag/Ab Combo, Abbott, IL). For syphilis, TP particle agglutination (Serodia TPPA, Fujirebio Inc, PA) with reflex to RPR and titer was performed. Sensitivity and specificity were calculated; sensitivity for syphilis is presented by RPR titer (Non-Reactive, 1:1-1:2, 1:4, ≥1:8). The exact binomial method was used to determine 95% confidence intervals (CI).
Results: In total, 156 patients participated in the evaluation; 55 patients had detectable HIV antibodies, 51 had antibodies for TP and 39 had a reactive RPR. There were no invalid tests. Sensitivity for HIV antibodies was 98.2%(90.3%,99.9%) and specificity was 100%(96.4%,100%). Among TPPA confirmed specimens, sensitivity was 8.3%(0.2%,38.5%) in those with a Non-Reactive RPR, 40%(21.1%,61.3%) for RPR titers 1:1 and 1:2, 60%(14.7%,94.7%) for RPR titer 1:4 and 100%(66.4%,100%) for RPR titer ≥1:8. Specificity was 97.1% (91.8% - 99.4%).
Conclusion: The INSTI Multiplex showed excellent performance for detection of HIV antibodies. The test is more sensitive in specimens with higher RPR antibody titers, when recent or active infection is more likely. Further research is required to evaluate its role in screening programs.

564 FIELD EVALUATION OF A DUAL ANTIBODY RAPID TEST FOR HIV/SYPHILIS INFECTION, VIETNAM

Keenan Withers[1], Minh D. Nguyen[2], Chrysovalantis Stafylis[1], Loc Pham[2], Le Minh Giang[2], Jeffrey D. Klausner[1]
[1]University of California Los Angeles, Los Angeles, CA, USA, [2]Hanoi Medical University, Hanoi, Vietnam

Background: Access to reliable, rapid and easy to use point-of-care (POC) tests for HIV and syphilis in Vietnam are limited. The SD BIOLINE HIV/Syphilis Duo rapid test (Standard Diagnostics, Inc, Gyeonggi-do, Republic of Korea) is a qualitative point-of-care, rapid immunoassay that detects antibodies (IgG, IgM, IgA) to HIV-specific antigens (HIV-1 gp41, sub O, HIV-2 gp36) and recombinant Treponema pallidum (TP) antigen (17 kDa) via fingerprick/whole blood, serum and plasma. This test has shown excellent performance in a number of field settings including Myanmar, Haiti, Kenya, and Ghana. However, data on its performance in Vietnam is currently unknown. We evaluated the field performance of the SD BIOLINE among two special populations in Hanoi, Vietnam -men who have sex with men (MSM) and pregnant women.
Methods: The study was conducted at a sexual health clinic for MSM and an antenatal care center. Participants who were 18 years and older and willing to return for counseling, testing and treatment were invited to participate in the study. We intentionally recruited a large proportion of MSM with known HIV and/or prior syphilis infection. Participant sera were obtained for reference testing of HIV and TP antibodies using SD BIOLINE HIV ½ 3.0 (Standard Diagnostics Inc., Republic of Korea) and Treponema pallidum particle agglutination (SERODIA-TPPA, Fujirebio Diagnostics, Japan) respectively. Sensitivity and specificity were calculated. The exact binomial method was used to calculate 95% confidence intervals (CI). Concordance between the SD BIOLINE Duo HIV/syphilis and reference tests were measured by Cohen's kappa statistic.
Results: Of 280 participants, 100 (35.7%) were MSM and 180 (64.3%) were pregnant women. The median age was 26 years, range 18 – 49. Of MSM, 17 (17.0%) were HIV-infected and 49 (49.0%) were TPPA-positive. All women were negative for both HIV and TP antibodies. Sensitivity and specificity were 100.0% (95% CI: 80.5% - 100.0%) and 100.0% (95% CI: 98.6% - 100.0%), respectively, for HIV antibodies with a kappa coefficient of 1.00 (95% CI, 1.00 - 1.00). For TP antibodies, the sensitivity and specificity were 83.1% (95% CI: 71.0% - 91.6%) and 100.0% (95% CI: 98.3% - 100.0%), respectively with a kappa coefficient of 0.89 (95% CI: 0.82 - 0.96).
Conclusion: The test performed well in this field setting. This rapid POC diagnostic dual test has the potential to help increase screening for both syphilis and HIV infections in resource-limited settings such as Vietnam.

565 TIME FROM HIV INFECTION TO EARLIEST DETECTION FOR 4 FDA-APPROVED POINT-OF-CARE TESTS

Kevin P. Delaney[1], Lauren Violette[2], George A. Ure[2], Andy M. Cornelius-Hudson[2], Lisa Niemann[2], Laura Wesolowski[1], Pollyanna Chavez[1], Steven Ethridge[1], Vanessa McMahan[2], Hollie Clark[1], David A. Katz[2], Joanne Stekler[2]
[1]CDC, Atlanta, GA, USA, [2]University of Washington, Seattle, WA, USA

Background: Estimates are available for time from HIV infection to first detection with FDA-approved rapid tests using plasma seroconversion panels. However, most point-of-care (POC) HIV tests that are critical for HIV screening programs and entry to HIV and PrEP care are performed on unprocessed whole blood, fingerstick blood, or oral fluid. We assessed seroconversion sensitivity for tests when using these unprocessed specimen types.
Methods: Participants were at high risk for HIV infection and seeking HIV testing or were referred to the study after diagnosis with early infection. Participants were tested with a panel of POC tests on up to 3 specimen types (Table). Those with discordant results were tested repeatedly with the test panel through seroconversion. Through 8/25/2017, there were 1,211 participants, including 43 newly identified as HIV infected; this analysis is limited to the 12 HIV-infected participants with discordant results and/or documented dates of last negative HIV test. All 12 initiated treatment a median of 2 days after enrollment (range: -10 to 37 days). We estimated the infection date based on changes in viral load, reported symptoms of acute HIV infection, and HIV risk history, and describe the distribution of time from infection to first detection with each test and specimen type combination.
Results: Estimated dates of infection ranged from 21 to 60 days before enrollment. Median time to first detection ranged between 33 and 43 days, and most tests were reactive in all participants by 90 days after estimated date of infection (Table). For 3 individuals, the time of first detection was delayed 1 study visit (3 to 7 days) for the same test performed on fingerstick compared to whole blood. For the 2 tests performed on oral fluid, there was a median delay of 2 and 4 days for oral fluid compared to whole blood. However, 3 participants who initiated treatment prior to peak viremia remained negative on ≥1 oral fluid test through day 90 of follow-up.
Conclusion: These are the first longitudinal data documenting seroconversion sensitivity of FDA-approved HIV tests performed on unprocessed specimens as intended for use in POC settings. These tests show a delay in earliest detection of 1 to 3 weeks when performed on these specimen types compared to previously published estimates using plasma. Because of the importance of POC tests, further improvements in seroconversion sensitivity and evaluations of new point-of-care tests using unprocessed specimens are warranted.

Table: Estimated time from infection to detection for 4 FDA-approved CLIA-waived rapid HIV tests

Test	Specimen type	Median days from infection to detection (Range)	%‡ Detected by 30 days post infection	45 days post infection	60 days post infection	90 days post infection
Determine HIV-1/ HIV-2 AG/AB Combo	Venous Whole blood	33 27–68	33%	75%	100%	
	Fingerstick blood	38 30–68	11%	89%	100%	
Insti HIV-1 /HIV-2	Venous Whole blood	35 28–68	33%	83%	100%	
	Fingerstick blood	42 30–68+	11%	67%	89%	100%
Oraquick HIV-1 /HIV-2 Advance	Venous Whole blood	38 30–70+	17%	75%	92%	100%
	Fingerstick blood	42 33–70+	0%	67%	89%	100%
	Oral fluid	42 32–90+	0%	75%	75%	83%
DPP HIV-1 /HIV-2	Venous Whole blood	38 30–68	17%	75%	100%	
	Fingerstick blood	42 33–68	0%	67%	100%	
	Oral fluid	43 32–90+	0%	75%	75%	75%

‡12 seroconverting participants were tested with whole blood and oral fluid samples. 9 with discordant results at the enrollment visit were also tested using EDTA whole blood, fingerstick blood, and oral fluid at 3, 7, 10, 14, 21, 28, 42, 56, 70, 90, 120, 180, 270 and 360 days past enrollment. Participants were followed until they tested positive on all HIV tests and specimen types. For this analysis follow-up was censored at 90 days the current recommended retesting window for POC rapid tests.
+3 participants remained negative on at least one test performed on oral fluid through 90 days of follow-up. All 3 had initiated antiretroviral therapy at or near study enrollment but were reactive on the blood and/or fingerstick version of the same test <70 days after estimated date of infection. 1 of these 3 exhibited seroreversion using the Insti test, testing positive at the first visit then negative for 4 study visits before again becoming positive for the remainder of follow-up.

566 UTILITY OF POC XPERT HIV-1 TESTS FOR DETECTION-QUANTIFICATION OF COMPLEX RECOMBINANTS

Marina Rubio Garrido[1], Adolphe Ndarabu[2], Gabriel Reina[3], David Barquín[4], Silvia Carlos[1], Africa Holguin[1]
[1]Hospital Ramon y Cajal, Madrid, Spain, [2]Centre Hospitalier Monkole, Kinshasa, Congo, Democratic Republic of, [3]Clínica Universidad de Navarra, Pamplona, Spain, [4]Universidad de Navarra, Pamplona, Spain

Background: Implementation of simple point-of-care (POC) molecular assays for early infant HIV diagnosis (EID) and viral load (VL) quantification for early treatment failure identification can improve HIV monitoring in settings with limited laboratory infrastructure. However, they should be evaluated in areas with extremely high diversity of HIV-1 variants. We analyzed the efficacy of two POC techniques for EID and VL (Cepheid Xpert HIV-1 Quali and Xpert HIV-1 VL) versus the non-POC Roche CAP/CTM Quantitative test v2.0 in dried blood samples (DBS) collected from children and adults in Kinshasa (Democratic Republic of Congo, DRC), the epicenter of the group M epidemic.
Methods: From April to November of 2016, 163 DBS were collected in Monkole Hospital (Kinshasa, DRC) from 84 children (60 HIV-, 18 HIV+, 6 HIV-exposed) and 76 HIV-infected adults (66 treated, 10 naïve). HIV diagnosis was firstly performed in DRC using rapid serological tests. Using one dot, we confirmed HIV status in children (mean age 9.6 years) using Xpert Quali. We compared viraemia with Xpert VL and Roche in all HIV+, providing RNA-HIV-1 copies per dot and per plasma milliliter after considering patient´s hematocrit. HIV-1 variant was characterized by phylogeny in partial pol sequences.
Results: HIV-1 infection was confirmed in 13 of 84 children by Xpert Qualy and in 71 (93.4%) of 76 adults by both Xpert VL and Roche VL, identifying false HIV+ diagnosis in DRC in 5 adults and in 5 children (range 12-158 months age), 4 of them under unnecessary ART during a mean time 35.6 months. Among the 84 HIV+ total samples, 80 (95.2%) could be detected by Xpert VL and 82 (97.6%) by Roche VL. Detectable viraemia with Xpert VL vs. Roche VL (>40 vs. >20 c/dot or >936-1078 vs. >468-539 c/ml plasma depending on hematocrit) was observed in 12 (92.3%) HIV+ children by both assays and in 53 (74.6%) or 52 (73.2%) HIV+ adults by Xpert or Roche, respectively. VL in 14/17 samples was below Xpert/ Roche detection limit. A high correlation was observed among both VL assays (R2=0.91) but showing significant differences [≥0.5log, range from -0.55 to 1.07] in 12 (15.4%) of 78 cases with VL above detection limit by both assays. Most (91.7%) of 24 obtained HIV-1 sequences were unique recombinant forms (URF), with >1000 c/ml by both VL tests in all but one sample.
Conclusion: POC Xpert HIV-1 assays can successfully detect and quantify URF using DBS, which can improve the EID in HIV and of ART failures in countries with highly recombinants HIV-1 strains.

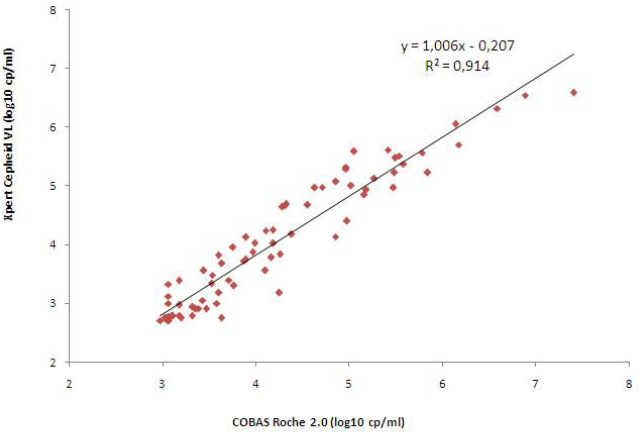


Fig. Correlation between Xpert VL and Roche VL assays in samples quantified by both techniques.

567 RELATIVE SENSITIVITIES OF 4TH AND 5TH GEN COMBO HIV AG/AB, P24 AND VIRAL LOAD ASSAYS

Mars Stone[1], John Bainbridge[2], Ana M. Sanchez[2], Andrea Pappas[2], Mark M. Manak[3], Robert Coombs[4], M Kathleen Shriver[5], Paul Contestable[6], Sangeetha Vijaysri Nair[7], David H. Wilson[8], Martin Stengelin[9], Gary Murphy[10], Indira Hewlett[11], Thomas M. Denny[2], Michael P. Busch[1]
[1]Blood Systems Research Institute, San Francisco, CA, USA, [2]Duke Human Vaccine Institute, Durham, NC, USA, [3]Walter Reed Army Institute of Research, Silver Spring, MD, USA, [4]University of Washington, Seattle, WA, USA, [5]Bio-Rad, Seattle, WA, USA, [6]Ortho Clinical Diagnostics, Rochester, NY, USA, [7]Hologic Corporation, Bedford, MA, USA, [8]Quanterix Corporation, Lexington, MA, USA, [9]Meso Scale Diagnostics, LLC, Rockville, MD, USA, [10]Public Health England, London, UK, [11]FDA, Silver Spring, MD, USA

Background: Detection of acute HIV infection is critical to HIV public health and diagnostics. HIV Ag/Ab combo (4th/5th gen) immunoassays have reduced the HIV diagnostic window period by enhancing detection of acute infection, but require ongoing evaluation with currently circulating diverse subtypes. Genetically and geographically diverse, well-characterized HIV clinical isolates assembled by the NIAID Supported EQAPOL (External Quality Assurance Program Oversight Laboratory) Viral Diversity Program were used for assessment of clinical HIV diagnostic and blood screening assays.
Methods: Blinded panels of 20 diverse recent HIV isolates in serial dilution (VL 106-102 virons/mL) were distributed to manufacturers and end user labs to assess relative analytic sensitivity of licensed and pre-licensed 4th/5th gen and stand-alone p24 Ag assays across diverse subtypes. Analysis of immunoassay sensitivity was benchmarked against confirmed VL measurement. Multivariable logistic regression modeling was used to estimate the limits of virus detection (LODs) for the different assays and subtypes relative to the $\log_{10}$ of viral loads determined on 2 FDA-approved VL assays.
Results: Qualitative assessment of 300 observations determined that the five Ag/Ab combo and stand-alone p24 assays performed similarly, with 20-40% of samples reactive. Ag/Ab combo and standard sensitivity p24 Ag assays performed within ½ log LOD of each other, illustrating similar diagnostic utility of these assays. MSD and Simoa ultrasensitive p24 Ag assays achieved dramatically increased sensitivities with 69%-99% of samples reactive. Alere and SD Bioline rapid assays performed poorly at all concentrations. Table 1 summarizes panel performance results. A single multivariable logistic regression analysis showed that the breadth of reactivity was similar among most diverse isolates with no evidence that any one FDA-approved platform performed significantly better in quantifying p24 across diverse HIV subtypes.

Conclusion: Blinded panels can assess the relative performance of HIV blood screening and diagnostic assays. We confirmed similar performance across subtypes between FDA-approved 4th/5th gen and p24 assays, enhanced sensitivity of next generation p24 platforms, and poor performance of POC assays. This diversity panel allows the evaluation of diagnostic assays to enable unbiased assessment of performance and is essential to validation of new diagnostic tools for identifying future recombinant strains of HIV.

568 INCREASING POSITIVITY FOR NON-PLASMA SAMPLES USING THE ABBOTT REALTIME HIV-1 ASSAY

Ming Chang, Junhui Wang, Jared Baeten, Andrew Mujugira, Robert Coombs
University of Washington, Seattle, WA, USA

Background: Measuring HIV-1 RNA levels in various biological compartments of infected patients provides insight to viral shedding, transmission, reservoirs, and pathological manifestations. Commercial HIV-1 RNA quantitative assays approved by the FDA for plasma samples are often used to quantify HIV-1 RNA in non-plasma specimens. Endocervical swabs, for example, contain bacterial and human byproducts which may affect PCR amplification of HIV-1 and subsequently generate false negative results. In this study, we retrospectively investigated endocervical swab results tested by the Abbott RealTime HIV-1 assay (Abbott).

Methods: Abbott assay-derived HIV RNA results, cycle numbers (CN), MaxRatios (MR), and amplification graphs for 762 endocervical swab samples collected from HIV-1 infected female individuals within the first year of ART in Kenya and Uganda were analyzed. Plasma assay reported a numerical HIV RNA copy, based on the CN at which the amplification curve crossed the defined HIV threshold (ΔRn=0.010), for samples with MR≥ 0.070; samples with MR< 0.070 yielded a "not detected" result. Amplification profiles of default "not detected" samples were visually evaluated one-by-one; if their curves crossing the threshold, CNs were estimated, otherwise samples' results were determined be HIV-1 negative.

Results: One hundred and fifty six endocervical swabs were detected to be HIV positive using the default cutoff and confirmed upon observation of the amplification curve crossing the threshold (Table 1). Among 606 default "not detected" endocervical swab samples, 188 (31%) swab samples were found to contain amplification curves crossing the threshold with MR ranging 0.011 to 0.068; 64 swab samples had HIV RNA ranging from 2.49 to 4.29 $\log_{10}$copies/swab, and 124 swab samples had < 2.39 $\log_{10}$copies/swab. PCR interfering agents may cause more flat amplification profiles for swab samples, resulting in lower MR values and failing the default criterion.

Conclusion: In addition to HIV RNA results, the Abbott HIV-1 assay provided MR values and amplification graphs useful for examining non-plasma sample results. Thus, in this study an additional 188 HIV positive endocervical swab were identified; HIV RNA positivity significantly increased from 20% (156/762) to 45% (344/762) in swabs collected from infected female individuals after initiation of ART, implying a greater rate of genital shedding than previously reported.

Table 1. The distribution of HIV-1 RNA levels and MR values by the Abbott HIV-1 assay for endocervical swab samples.

Default program for plasma samples		Adjusted criteria for endocervical swab samples	
The criterion for HIV-1 positivity: MR >=0.070		The criterion for HIV-1 positivity: confirmation of the amplification curve crossing the Threshold	
MR>=0.070	N=148 with quantifiable results Median: 3.91 Log_{10} copies/swab Range: 2.40-7.65 Log_{10} copies/swab	MR>=0.070	N=148 with quantifiable results Median: 3.91 Log_{10} copies/swab Range: 2.40-7.65 Log_{10} copies/swab
	N=8 with results <2.39 Log_{10} copies/swab		N=8 with results <2.39 Log_{10} copies/swab
MR<0.070	N=606 with HIV-1 not detected results	MR range: 0.011-0.068	N=64 with quantifiable results* Median: 2.94 Log_{10} copies/swab Range: 2.49 -4.29 Log_{10} copies/swab
			N=124 with results <2.39 Log_{10} copies/swab
		MR range: 0.002-0.013	N=418 with HIV-1 not detected results
HIV-1 RNA positivity	20% (156/762)	HIV-1 RNA positivity	45% (344/762)

*The cycle number at which the amplification curve crosses the Threshold was manually determined. Then the copy number was estimated using the established HIV-1 RNA calibration curve.

569 EVALUATION OF THE CDC/APHL HIV DIAGNOSTIC ALGORITHM WITH RECENTLY FDA-APPROVED ASSAYS

Wei Luo, William Fowler, Krystin A. Price, Vickie Sullivan, Timothy Granade, Steven Ethridge, Laura Wesolowski, Kevin P. Delaney, William M. Switzer, S. Michele Owen, **Silvina Masciotra**
CDC, Atlanta, GA, USA

Background: Two serologic assays, the BioPlex 2200 HIV Ag-Ab screening assay (BPC) that detects and differentiates p24 antigen (Ag) and HIV-1 and HIV-2 antibodies (Ab) and the Geenius™ HIV-1/2 supplemental assay (Geenius) that differentiates HIV-1 from HIV-2 Ab, were approved after the 2014 CDC/APHL laboratory HIV diagnostic algorithm was released. We evaluated the performance of these assays in HIV-1 seroconverters (SC) and HIV-2 infections in the context of the diagnostic algorithm.

Methods: 501 sequential plasma specimens (134 collected during antiretroviral therapy (ART)) from 49 U.S. HIV-1 SC and plasma from 100 HIV-2 Ab-positive persons (16 from the U.S. and 84 from Ivory Coast (IVC)) were tested with BPC and Geenius. Nucleic acid testing (NAT) was done with APTIMA HIV-1 RNA qualitative assay in 497 SC samples and with the Roche COBAS AmpliPrep/TaqMan HIV-1 v2.0 test in four. The algorithm was evaluated individually for each SC collection time.

Results: In SC, BPC was non-reactive (NR) in 91 samples, 67 of which were collected before the first NAT-reactive (R) and 24 were NAT-only R. After the first NAT-R, 407/434 (93.8%) were BPC-R and 27 were BPC-NR including four in a secondary negative diagnostic phase in three SC. Of 407 BPC-R, 315 (77.4%) were Geenius HIV-1-positive, 31 (7.6%) HIV-1-indeterminate, and 61 (15%) HIV-negative. All 41 BPC Ag-only R samples were Geenius HIV-negative. APTIMA resolved 88/92 (95.7%) Geenius HIV-negative or HIV-1-indeterminate samples. Overall, the algorithm detected 92.9% of early HIV-1 infections including 99.3% of samples during ART. Among 100 HIV-2 samples, 95 were BPC HIV-2 Ab-R (16 U.S., 79 IVC) and five from IVC were HIV-1/HIV-2 Ab-undifferentiated. Of 95 BPC HIV-2 Ab-R samples, 81 were Geenius HIV-2 positive (including 46 with HIV-1 cross-reactivity), 2 repeatedly HIV-2 indeterminate (gp36 reactivity only), 9 HIV untypable, 1 HIV indeterminate and 2 repeatedly HIV negative. Of 5 BPC HIV-2 undifferentiated from IVC, all were Geenius HIV-2 positive.

Conclusion: BPC performed well and detected Ag in early HIV-1 infections, but rarely a second negative diagnostic phase was observed. In the algorithm, BPC Ag-only R samples could be confirmed directly with NAT. BPC differentiated HIV-1 from HIV-2 Ab in most samples, but in combination with Geenius results, the possible final interpretations increased. These results provide important data for potential updates to the CDC/APHL recommendations for HIV diagnostics.

570 PERFORMANCE EVALUATION OF THE APTIMA HIV-1 QUANT ASSAY ON THE PANTHER SYSTEM

Silvina Masciotra[1], Wei Luo[1], Tara Smith[2], Vickie Sullivan[1], William Fowler[1], Steven Ethridge[1], Laura Wesolowski[1], Kevin P. Delaney[1], William M. Switzer[1], S. Michele Owen[1]
[1]CDC, Atlanta, GA, USA, [2]Oak Ridge Institute for Science and Education, Atlanta, GA, USA

Background: The APTIMA HIV-1 Quant Assay (APT-Quant) is FDA-approved for quantification of HIV-1 plasma RNA from 30-10^7 copies (cp)/ml. Outside the U.S. quantitative results can also be interpreted qualitatively. We evaluated the performance of APT-Quant for HIV-1 RNA quantification and for off-label diagnostic use.

Methods: One AccuSpan HIV-1 RNA linearity panel (LP) (n=30 or n=43 with two kit lots), U.S. samples from early HIV-1 infections collected from 46 seroconverters (n=420, subtype B), Cameroonian antibody-positive samples (n=113, non-B subtypes and Group O), and HIV-negative samples (n=478) were tested with APT-Quant on the Panther system. Volume permitting, samples were also tested with APTIMA HIV-1 RNA Qualitative (APT-Qual), Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test v2.0 (Roche viral load (VL)), and Abbott RealTi*me* HIV-1 (Abbott VL) assays. We analyzed agreement between APT-Quant and other FDA-approved VL assays by linear regression and concordance correlation coefficient, calculated specificity in APT-Qual-nonreactive/HIV-1 WB-negative (HIV-negative) specimens and evaluated test reproducibility (standard deviation) using two kit lots with LPs. We analyzed APT-Quant for diagnostic use by comparing to APT-Qual results (McNemar's paired test).

Results: Table shows agreement between APT-Quant and other VL assays. Using LPs, the standard deviation ranged from 0.021-0.113 (lot 1) and 0.015-0.489 (lot 2) with high variability at ~3 log(cp/ml). APT-Quant specificity was 99.79% [CI: 98.82- 99.96%]. APT-Quant detected virus in 34 more samples than APT-Qual in early stages of infection (n=417, p<0.0001) and in all 105 APT-Qual-reactive Cameroonian samples. Of 228 samples from seroconverters, APT-Quant detected virus in 180 samples, Roche VL in 163, and APT-Qual in 157. Both APT-Qual and Quant missed two infections with Roche VLs <20 cp/ml and one with 23 cp/ml. APT-Quant was nonreactive in two samples with VLs of 29 and 32 cp/ml. Controls failed in one run for LP and three panel members >7 log(cp/ml) were invalid needing 1:100 dilution (kit lot 2).

Conclusion: APT-Quant showed good agreement with Roche and Abbott VL assays in Group M and O specimens and with high sensitivity and specificity. APT-Quant performance exceeds APT-Qual for detecting infections with low VL in early stages of infection and established infections. The APT-Quant assay could also be used for diagnostics if properly validated in a laboratory or via an FDA diagnostic claim.

Table: Agreement between APTIMA Panther (APT-Quant) and FDA-approved viral load assays in different sample sets

	Linearity Panel kit lot 1*	Linearity Panel kit lot 2*	HIV-1 subtype B early infections	HIV -1 (Group O and non-B) established infections**
APTIMA Panther vs Roche				
Linear regression (R^2)	0.994	0.993	0.936	0.766
Concordance correlation coefficient (sample size)	0.9696 (4)	0.9857 (5)	0.9397 (150)	0.8348 (95)
95% Confidence interval	0.9233 - 0.9881	0.9423 - 0.9965	0.9203 - 0.9545	0.7703 - 0.8823
Pearson ρ (precision)	0.9972	0.9965	0.9674	0.8751
APTIMA Panther vs Abbott				
Linear regression (R^2)	0.999	0.996	0.881	0.869
Concordance correlation coefficient (sample size)	0.9483 (4)	0.9597 (5)	0.9245 (255)	0.9204 (98)
95% Confidence interval	0.7052 - 0.9919	0.8249 - 0.9912	0.9048 - 0.9402	0.8851 - 0.9452
Pearson ρ (precision)	0.9999	0.9978	0.9387	0.9324

*APT-Quant results are the mean of single results over 3 days; R^2 (linearity panels) for Roche vs Abbott was 0.987; **Established infections from Cameroon defined as antibody-positive by HIV-1 Western blot; Sample size depends on the number of samples tested with both assays and with quantifiable results; Except for the linearity panels, the analysis was done using singlet results and VL >7 log (cp/ml) was considered as 7.

571 EVALUATION OF THE APTIMA HIV-1 QUANT DX ASSAY FOR MONITORING OF HIV-1 VIRAL LOAD

Mónica García-Álvarez, Sagrario Zurita, Francisca Gutiérrez, Paula Aranguren[1], Samanta Aparicio, Rafael Delgado
Hospital Universitario 12 de Octubre, Madrid, Spain

Background: Viral load monitoring of HIV-1 is critical for effective HIV-infection management. This has led to the development of different HIV-1 quantitative assays. The Aptima HIV-1 Quant Dx is a quantitative assay based on real-time transcription mediated amplification and detection, run on the fully automated and random access Panther System instrument (Hologic). The objective of this study was to evaluate correlation, linearity, reproducibility and performance characteristics of the Aptima HIV-1 Quant Dx Assay (Aptima) in comparison to the reference method, Roche cobas 6800 System (c6800).

Methods: For clinical reactivity correlation, 120 retrospective and 300 prospective collected plasma samples were tested in parallel in Aptima in side-by-side testing to the reference method cobas® HIV-1 6800. Linearity and reproducibility were assessed by replicate testing of serial dilutions of well-characterized clinical samples (5 replicates of seven dilution levels spanning the assay dynamic range), and an external proficiency panel (AcroMetrix™ HIV-1 panel). Subtype reactivity was addressed in Aptima by testing an external panel (SeraCare HIV-1 Genotype). A workflow study was conducted to define the performance characteristics: protocols were designed to test different laboratory workflows when running HIV, HCV and HBV viral load assays on 3 different molecular diagnostics instruments (c6800, Veris and Panther).

Results: Correlation between Aptima and c6800 assays in a set of 100 clinical samples within the linear range of both techniques was 0.965. The Bland-Altman mean difference estimate between the two methods was 0.24 Log cp/mL. Both systems demonstrated linearity over the dilution range (0.997 for c6800 and 0.998 for Aptima). The intra-assay variability was 1.24% for c6800 and 1.76% for Aptima, and the mean coefficient of variation inter-assay was 1.52%. Specificity for Aptima on negative samples was 100%. Aptima allowed detection and quantification of all HIV-1 subtypes tested (A, AG, B, C, D, AE, F, G and H). Panther system allowed rapid and fully automated testing: average time to first result was 161 minutes and turn around time was the shortest at different scenarios.

Conclusion: The Aptima HIV-1 Quant Dx is a sensitive and reproducibility assay for monitoring of HIV-1 viral load. Random access, large capacity and improved time to result make the Aptima HIV-1 Quant Dx Assay run on the Panther System a good candidate for measuring HIV-1 viral load in HIV-1 infected patients.

572 CEPHEID XPERT HIV-1 VIRAL LOAD ASSAY PERFORMANCE EVALUATION

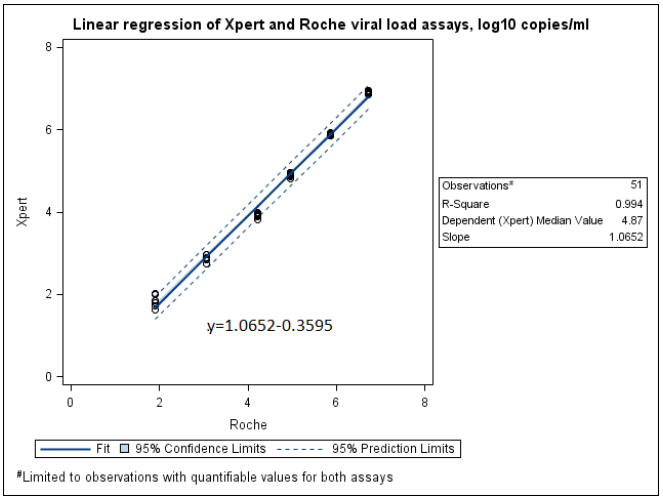
Laura Wesolowski[1], William Fowler[1], Wei Luo[1], Silvina Masciotra[1], Kevin P. Delaney[1], Emeka Oraka[2], Pollyanna Chavez[1], Steven Ethridge[1], William M. Switzer[1], S. Michele Owen[1]
[1]CDC, Atlanta, GA, USA, [2]ICF International, Atlanta, GA, USA

Background: The performance of the Cepheid Xpert HIV-1 Viral Load (Xpert VL) has not been extensively evaluated. This new, simplified, automated single-use quantitative VL assay uses 1-1.2mL of plasma on the Cepheid GeneXpert System with a reported limit of detection of 40 copies/ml and 100% specificity 95% CI (96.7–100%).

Methods: Using an HIV-1 RNA linearity panel (AccuSpan) previously tested with Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Version 2.0 (Roche VL), we examined agreement between both VL assays by plotting the log VL of each concentration, fitting a regression line and calculating the correlation. We compared the proportion of 221 commercial plasma seroconverter specimens detected using Xpert VL and Roche VL. Among seroconverters, we calculated the proportion of specimens with an Xpert $\log_{10}$ value ≥2.3 (threshold for virologic failure) and ≥3.0 (threshold for resistance testing) when the $\log_{10}$ Roche VL was at least 2.3 and 3.0, respectively. We also tested 497 archived, uninfected plasma specimens with Xpert VL to measure assay specificity.

Results: Roche and Xpert VLs were highly correlated (R^2=0.994) (Figure 1). There were 6 (2.7%) Xpert VL errors among seroconverters, indicating that the assay was aborted. There was an invalid (HIV-1 RNA presence or absence could not be determined). These specimens lacked volume for repeat testing. Of 153 seroconverter specimens with virus detected by Roche VL, 145 (94.8%) were detected by Xpert VL. Seroconverter specimens detected by Roche VL but missed by Xpert VL were detectable but not quantifiable (n=2) or had $\log_{10}$ VLs between 1.37 and 1.62 copies/mL (n=6). Of 61 seroconverter specimens not detected by Roche VL, 59 (96.7%) were not detected and 2 (3.3%) were

detectable but not quantifiable by Xpert VL. Most had concordant results at the log_{10} 2.3 threshold except one had a log_{10} VL <2.3 by Roche VL but ≥2.3 by Xpert VL while 9 specimens with a log_{10} VL ≥2.3 using Roche VL were <2.3 with Xpert VL. Results were similar at the log_{10} 3.0 cut-off. Among uninfected specimens there were 8 errors (1.6%) using Xpert VL; 5 had insufficient volume to repeat. Specificity was 491/492 (99.8%; 95% CI 98.87%-99.99%).
Conclusion: Xpert VL results were highly correlated and concordant with Roche VL, and the test performed with high specificity. Seroconversion specimens missed by Xpert VL had a Roche VL <100 copies/mL. FDA approval of the simple Xpert VL may allow laboratories that cannot bring on large, complex VL tests to conduct HIV monitoring.



573 CELLULAR HIV-1 NUCLEIC ACID DETECTION IN CASES WITH UNDETECTABLE PLASMA VIRAL LOAD

Linda Jagodzinski[1], Holly R. Hack[2], Ying Liu[2], Jennifer Malia[1], Mark M. Manak[2], Nittaya Phanuphak[3], Mark de Souza[3], Eugène Kroon[3], Donn Colby[3], Nitiya Chomchey[3], Merlin L. Robb[2], Nelson L. Michael[1], Jintanat Ananworanich[2], Sheila A. Peel[1]
[1]Walter Reed Army Institute of Research, Silver Spring, MD, USA, [2]US Military HIV Research Program, Silver Spring, MD, USA, [3]SEARCH, Bangkok, Thailand

Background: HIV-1 diagnosis based solely on HIV serological tests can result in misclassification of HIV-1 infection status of HIV vaccinated individuals, infants born to HIV infected mothers and individuals that start highly-active antiretroviral therapy (HAART) during early infection. Individuals at-risk for HIV infection on pre-exposure prophylaxis (PrEP) may also demonstrate reduced or absent serological response to infection. The objective of this study was to determine if a HIV total nucleic acid (TNA) test could be used to determine HIV-1 infection status.
Methods: The Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 test v2.0 (CAP/CTM), which detects RNA/DNA, was used to evaluate HIV TNA in peripheral blood mononuclear cells (PBMCs) in infection cases where plasma HIV-1 RNA was not detected. PBMCs from Thai individuals (N=21) who initiated HAART at Fiebig (F) stage I-VI of acute HIV infection (RV254/SEARCH010) were collected at 8 and 60 weeks post treatment and tested by CAP/CTM. In a separate US study, cell pellets from HIV-1 infected individuals on HAART (N=67) and from HIV-1 uninfected individuals (N=92) were also tested. All individuals demonstrated undetectable plasma HIV-1 RNA at the time of sample collection.
Results: Five of six individuals who initiated HAART in early acute infection (F I) were undetectable by HIV-1 TNA at 8 and 60 weeks; one individual demonstrated a low threshold value in 1 of 3 replicates. Individuals who initiated treatment at F II (N=6) were detectable by HIV-1 TNA at week 8, but at week 60 were either not detected or approaching the lower limit of detection by TNA. Of the 3 individuals treated at F III only one had detectable TNA at week 8 and none by week 60. Six individuals who started treatment at Fiebig IV - VI had detectable HIV-1 TNA, but the relative values reported decreased two to fifteen-fold from 8 weeks to 60 weeks post HAART initiation. All chronically infected individuals from the US study were HIV-1 TNA positive. As expected, HIV-1 TNA was not detected in uninfected individuals.
Conclusion: Our data suggests that the CAP/CTM test is more useful in detecting HIV infection than plasma viral load in individuals on HAART, although verification of HIV infection status post initiation of HAART in acute and primary infection may be difficult.

574 QUANTIFICATION OF UNDETECTABLE PLASMA HIV RNA (<20 COPIES/ML) WITH SINGLE-COPY ASSAY

Nicolas A. Margot[1], Dianna L. Koontz[2], Scott McCallister[1], John W. Mellors[2], **Christian Callebaut**[1]
[1]Gilead Sciences, Inc, Foster City, CA, USA, [2]University of Pittsburgh, Pittsburgh, PA, USA

Background: Plasma HIV RNA or viral load (VL) is measured in clinical practice and trials of antiretrovirals using FDA-cleared assays such as COBAS TaqMan HIV-1 Assay v2.0. The TaqMan assay provides quantification of viremia at or above 20 copies/mL, but lower values are reported as "<20" or "Target Not Detected" (TND). Current "kick & kill" HIV eradication strategies may require more sensitive assays to detect changes in low-level persistent viremia. Here, the novel integrase single-copy assay (iSCA) (Cillo JClinMicro 2013) was evaluated for measurement of low-level persistent viremia in a large number of clinical trial samples.
Methods: Plasma samples were from Week 24 visits of a Phase 2 study in previously treatment naïve HIV-1-infected patients treated with a single tablet regimen containing an integrase inhibitor. HIV-1 RNA levels were assessed at a central laboratory using HIV-1 TaqMan 2.0 Assay (Roche Diagnostics, Indianapolis, IN). The iSCA assay was performed in a blinded fashion on matched samples (University of Pittsburgh) and results from the 2 assays were compared.
Results: Paired TaqMan/iSCA data were obtained for 151 HIV-infected adults. All participants were on treatment and virologically suppressed (mean 110 days) at week 24. Most samples (117/151, 77%) had non-quantifiable TaqMan result, either <20 copies/mL (n=44) or TND (n=73). Quantification was achieved with iSCA for all 117 samples (mean VL 2.6 copies/mL for 73 samples with TND; mean VL 8.2 copies/mL for 44 samples with <20 copies/mL). Zero copy control samples included with each assay run were all negative for HIV RNA (<1 copy). For samples quantified with both assays (n=34), iSCA values were slightly lower than TaqMan (mean VL of 29.5 copies/mL compared to 61.4 copies/mL, respectively).
Conclusion: In this large sample collection from virologically suppressed HIV-infected adults, use of iSCA led to quantification of low-level viremia below the limit of detection of the TaqMan assay in 77% (117/151) of previously non-quantifiable plasma samples. This dataset emphasizes the value of the iSCA over classical HIV VL assays for measurement of low-level viremia and its potential for use in HIV cure studies to assess whether experimental interventions alter viremia.

575 REPLICATE APTIMA VL TESTING DETECTS RESIDUAL VIREMIA IN MOST ART-TREATED ADULTS

Sonia Bakkour[1], Sheila M. Keating[1], Xutao Deng[1], Mars Stone[1], Andrew Worlock[2], Steven G. Deeks[3], Peter Bacchetti[3], Melanie Dimapasoc[1], Joseph Lau[1], Leilani Montalvo[1], Scott Hauenstein[2], Douglas D. Richman[4], **Michael P. Busch**[1]
[1]Blood Systems Research Institute, San Francisco, CA, USA, [2]Hologic Corporation, Bedford, MA, USA, [3]University of California San Francisco, San Francisco, CA, USA, [4]University of California San Diego, La Jolla, CA, USA

Background: The ability to determine if a curative intervention reduces the reservoir or if a latency reversing agent is effective will depend on access to ultrasensitive, high-throughput measurements of residual viremia. Current viral quantification methods are limited by lack of sensitivity or the need for specialized, lengthy processing.
Methods: The Aptima HIV-1 Quant Assay provides standard viral load (VL) measurements on a 0.5mL sample, but it also provides a reactive/non-reactive digital readout that may be reasonably sensitive even when only a single copy is present in the 0.5 mL sample. Readouts on multiple replicates (reps) on the system's automated platform using the standard sample volume can provide ultrasensitive estimates of copies/mL (cp/mL) via Poisson analysis. An analytical panel comprised of 5 serial dilutions each of 4 HIV+ window period donation samples (2 clade B and 2 clade C) was blindly tested using the Aptima Assay in 45 reps on 25 mL per dilution, and 110 large volume samples from antiretroviral-suppressed RAVEN study participants with consistently negative standard VL assay results were subjected to rep testing.

Results: The true target concentrations for the 4 samples were estimated by applying a standard VL assay to pre-dilution aliquots of the source plasma samples (VL 20 to 339 cp/mL), and dilutions calculated to range from 9 to 0.2 cp/mL had VL estimates generated via the 45-rep Poisson analysis that ranged from no underestimation to underestimation of the target concentrations by up to 3-fold. On initial 9-rep testing of 110 samples from 59 ART-treated adults followed in the RAVEN cohort, 63 samples (57%) from 37 individuals (63%) had detectable VL. An additional 36 reps were performed on a subset of 19 samples, 7 of which were initially undetectable. Four of seven (57%) initially undetectable samples had positive results when tested with the additional reps. The Poisson-derived estimates in the 19 samples tested with 45 total reps ranged from 0 [95% confidence interval (CI) 0 – 0.18] to 2.197 [95% CI 1.52 – 3.21] cp/mL.
Conclusion: The Aptima HIV-1 Quant Assay provides a high throughput means to quantify VL to <1 cp/mL with large volume plasma specimens which allows detection and quantitation of VL in most ART-suppressed patients. Given the assay's performance characteristics, its lack of reliance on specialized specimen handling and the highly automated approach, this assay is well-suited to early- and late-phase clinical trials of HIV curative interventions.

576 EFFECTIVENESS OF BEST PRACTICE ALERT AND PROVIDER EDUCATION FOR HEP C SCREENING

Mamta K. Jain[1], Joanne Sanders[1], Lisa Quirk[1], Brian Adamson[1], Barbara J. Turner[2], Amit G. Singal[1]
[1]University of Texas Southwestern, Dallas, TX, USA, [2]University of Texas at San Antonio, San Antonio, TX, USA

Background: Hepatitis C is a curable disease and effective screening and treatment of hepatitis C virus (HCV) among baby boomers, born between 1945-1965, can significantly reduce the burden of liver complications in this population. We examined the effectiveness of a simple best-practice alert (BPA) within our electronic medical record coupled with provider education to increase HCV screening and linkage rates among baby boomers in a safety-net hospital system.
Methods: We implemented a BPA in June 2015 coupled with provider education at a large urban safety net health system. We compared baby boomers without prior HCV screening and an outpatient appointment between 6/1/13-5/31/15 to a group of unscreened baby boomers with an outpatient appointment between 6/1/15-8/26/17. Comparison of rates for HCV antibody (Ab), HCV RNA, and linkage-to-care (i.e. completing a liver clinic appointment after HCV diagnosis) were performed using generalized estimating equations controlling for gender, race/ethnicity, insurance, and clinic.
Results: Of 56,727 at-risk baby boomers seen prior to BPA implementation, 10.3% had HCV screening performed. HCV RNA confirmatory testing was performed in 54.2% of the 1117 HCV Ab-positive patients, and 43.1% (n=201) of patients with confirmed HCV infection (RNA positive) were linked to a liver clinic appointment. Among the 39,351 baby boomers seen after BPA implementation, the BPA was not acknowledged in most (52.7%) cases; providers ordered HCV Ab in 36.3%, and opted to not order HCV testing in 11%. HCV RNA confirmatory testing was performed in 74.7% of the 1205 HCV Ab-positive patients, and 45.7% (n=289) of patients with confirmed HCV infection (RNA positive) were linked to a liver clinic appointment. The intervention including BPA and provider education was associated with significantly increased odds of HCV antibody screening (AOR 5.42; 95%CI 5.22-5.62), confirmatory testing with HCV RNA (AOR 2.38; 95%CI 1.95-2.90); however, linkage to care rates were not significantly improved (AOR 1.61; 95%CI 0.88-1.54) (see Table).
Conclusion: Implementation of a simple BPA and provider education significantly increased hepatitis C screening; however, linkage to care rates are still not adequate at only 50%. Further interventions to improve linkage to care of patients with HCV infection are needed to eradicate hepatitis C.

Table	Screened by HCV Ab adjusted OR (95% CI), p value	Confirmed by HCV RNA Test Adjusted OR, adjusted OR (95% CI), p value	Linked to HCV Care, adjusted OR (95% CI) p value
Pre-BPA	Reference		
Post-BPA	5.42 (5.22-5.62), <.0001	2.34 (1.95-2.90), <.0001	1.16 (0.88-1.54), 0.30
Gender			
Female	Reference		
Male	0.98 (0.94-1.0), 0.18	0.89 (0.73-1.08), 0.23	0.85 (0.65-1.11), 0.23
Race/Ethnicity			
Hispanic	Reference		
Black	1.06 (1.01-1.10), .009	0.98 (0.72-1.32), 0.87	0.77 (0.5-1.18), 0.23
Other	1.0 (0.94-1.090), 0.78	0.74 (0.41-1.35), 0.33	0.52 (0.21-1.32), 0.17
White	0.97 (0.922-1.02), 0.29	1.24 (0.89-1.74), 0.21	0.96 (0.60-1.54), 0.96
Age	0.99 (0.99-0.99), <.0001	1.00 (0.98-1.03), 0.78	0.99 (0.96-1.02), 0.60
Insurance			
Uninsured	Reference		
Medicaid	1.11 (1.04-1.17), 0.0008	0.91 (0.72-1.16), 0.46	0.85 (0.61-1.20), 0.37
Medicare	1.02 (0.97-1.07), 0.40	1.03 (0.78-1.35), 0.86	1.04 (0.71-1.52), 0.86
Private	0.81 (0.74-0.88), <.0001	0.73 (0.41-1.30), 0.28	1.12 (0.46-2.93), 0.76
Other/unknown	0.58 (0.53-0.64), <.0001	0.86 (0.50-1.50), 0.59	0.79 (0.43-1.48), 0.46

577 CHANGES IN HEPATITIS C VIRUS (HCV) TESTING AWARENESS IN MASSACHUSETTS, 2015-2016

Monina Klevens, Monica Morrison, Liisa Randall, H D. Fukuda, Daniel Church, Shauna Onofrey, Kevin Cranston, Alfred DeMaria
Massachusetts Department of Public Health, Boston, MA, USA

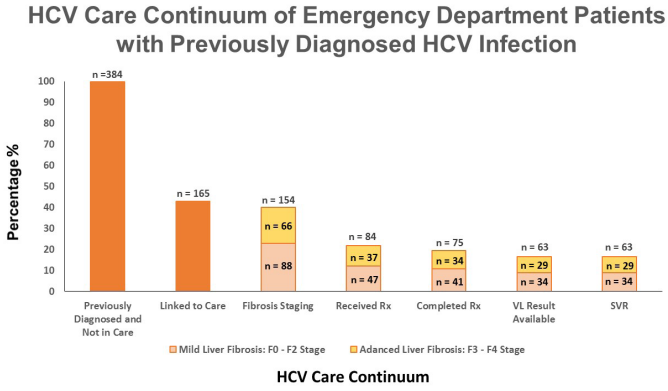
Background: Identification of infected persons who are unaware of their status is essential to eliminate HCV infection. In March 2015, the Massachusetts Department of Public Health (MDPH) implemented universal HIV and HCV antibody testing at funded integrated HIV, HCV, and sexually transmitted infection (STI) screening sites.
Methods: There were 189 sites contracted by MDPH to conduct HIV, HCV, and STI testing and linkage to care. Anti-HCV enzyme immunoassays were conducted at the Massachusetts State Public Health Laboratory on all serum specimens submitted for HIV and HCV testing. Persons with positive antibody test results are referred for supplemental testing to diagnose current HCV infection and assessed for treatment. We compared number of tests, history of testing and results from all anti-HCV tests conducted in 2015 and 2016 and tested differences using the Chi-square test.
Results: The number of HCV tests overall increased from 25747 in 2015 to 29490 in 2016, and the proportion of clients with no reported previous test decreased from 32.6% (8394/25747) to 27.1% (7982/29490; p<0.01). HCV seroprevalence increased from 12.4% (3194/25747) to 17.2% (5080/29490; p <0.01), as did the proportion of new positives among persons reporting a previous negative test, from 5.8% (646/11046) to 6.5% (963/14787; p<0.05). The proportion of newly positive persons among those reporting no previous test also increased from 4.7% (393/8394) to 6.7% (532/7982; p<0.05). The proportion of persons testing positive who were aware of their infection increased from 57.4% (1820/3173) to 65.4% (3316/5074; p<0.01).
Conclusion: Implementation of universal HCV antibody screening in public health integrated infectious disease screening and referral programs yielded an increase in seroprevalence, including new positives. HCV antibody positive persons were more frequently aware of their status in 2016 than 2015; still, about a third of infected remained reportedly unaware. To eliminate HCV infection, awareness of infection and linkage to care must increase.

578 LINKAGE TO CARE FOR PREVIOUSLY DIAGNOSED HCV-INFECTED EMERGENCY DEPARTMENT PATIENTS

Yu-Hsiang Hsieh, Anuj Patel, Danielle Signer, Erica Shelton, Jacob Cohen, Mustapha Saheed, David L. Thomas, Richard Rothman
Johns Hopkins University, Baltimore, MD, USA

Background: With up to 15% of HCV seroprevalence in urban emergency department (ED) patients, the burden of HCV infections in EDs remain high. Although highly effective, oral HCV treatment has been available since 2014, most of those previously diagnosed patients have not been treated. An ED-based linkage-to-care (LTC) program for those patients with chronic HCV infection was implemented in 2015 to improve treatment outcomes.
Methods: From March 2015 to May 2016, ED-based HCV LTC program staff identified patients with HCV RNA-positive from an electronic medical record system for HCV LTC services. Eligible patients were approached and were provided LTC services to on-site viral hepatitis clinic for HCV care if they were not already in care. On the same day, clinic staff met patients in the ED. Reminder phone calls were made regarding the first scheduled clinic appointment as well as phone calls for rescheduling that appointment if missed. Demographic and

clinical information including scheduled clinic visits, liver fibrosis staging by FibroScan or FibroSure, initiation and completion of treatment, RNA testing for sustained viral response (SVR) was abstracted via chart review.
Results: Overall , 446 ED patients with HCV infection were identified and 384 (86%) had chronic HCV infection and were not already in care. The majority were male (66%), African American (76%) and aged ≥ 50 years (66%). Of those 384 patients eligible for the LTC program, 165 (43%) were linked to care. Of 165 linked to care, 93% (n=154) had liver fibrosis staging information available and 66 (42.9%) patients had advanced (metavir stage F3 and F4) liver fibrosis. Among 154 with fibrosis staging, 84 (55%) initiated HCV treatment and 89% (n=75) completed the treatment regimen. Among those who completed HCV treatment, 63 (84%) had HCV RNA testing result available and all (100%) achieved SVR after treatment. LTC was positively associated with older age and being black race (p<0.05). There was no difference in recipient or completion of treatment, or SVR by advanced fibrosis.
Conclusion: A program to improve LTC substantially improved HCV cure rates even among patients attending EDs. However, further improvement in LTC and treatment rates are needed to achieve the ultimate success of the program and more work is needed to identify new methods to link additional patients through increasing patients' level of HCV



579 VERY LOW HEPATITIS C VIRAL LOADS IN ABSENCE OF THERAPY: IMPACT ON HCV ANTIGEN TESTING

Barbara Bertisch[1], Matteo Brezzi[1], Francesco Negro[2], Beat Muellhaupt[3], Patrizia Kuenzler-Heule[4], Patrick Schmid[4], Olivier Clerc[5], Alberto Moriggia[6], Darius Moradpour[7], **Olivia Keiser**[1]
[1]University of Geneva, Geneva, Switzerland, [2]University Hospitals of Geneva, Geneva, Switzerland, [3]University Hospital Zurich, Zurich, Switzerland, [4]St. Gallen Cantonal Hospital, St. Gallen, Switzerland, [5]Cantonal Hospital Neuchatel, Neuchatel, Switzerland, [6]Epatocentro Ticino Foundation, Lugano, Switzerland, [7]Lausanne University Hospital, Lausanne, Switzerland

Background: HCV antigen testing is a less expensive alternative to PCR but it has a low sensitivity for very low viral loads (VLVL ≤ 3,000 IU/ml). So far, data on VLVL came from treated persons and results are therefore not applicable to screening in a treatment-naïve population.
Methods: We assessed the prevalence and analyzed predictors of VLVL by logistic regression in treatment-naïve participants in the Swiss Hepatitis C Cohort Study (SCCS). We analyzed if the last viral load after the first documented VLVL continued to be low; and we compared prevalent as well as incident cirrhosis and mortality in persons with VLVL. For persons with VLVL and cirrhosis, we extracted information on immunosuppressive conditions from the patient charts.
Results: We included 2,460 persons (45.5% of 5,409 persons enrolled in the SCCS) with HCV viral loads measured in the absence of antiviral therapy. Overall, 5.3% of these ever had a VLVL. Age ≤ 40 years (aOR 1.90, 95% CI 1.26-2.85) was associated with VLVL, while gender, HCV genotype and intravenous drug use were not. In 21 of the 70 persons with viral load available after VLVL, the last viral load was still ≤ 3,000 IU or undetectable, including 8 persons with spontaneous HCV clearance during long-term follow-up. Among the 130 persons with VLVL, 24 had prevalent or incident cirrhosis. All of them had either excessive alcohol consumption, HIV coinfection, organ transplantation or other potential immunosuppressive conditions. The mortality rate was comparable in persons with and without VLVL.
Conclusion: In the SCCS, 5.3% of patients with chronic hepatitis C had a VLVL in the absence of antiviral therapy. Morbidity and mortality were comparable in patients with and without VLVL. Interestingly, and counterintuitively, many had conditions associated with immunosuppression. Missing patients at risk of disease progression may limit the applicability of HCV antigen testing.

580 EVALUATION OF DBS HCV RNA QUANTIFICATION AND GENOTYPING IN RESOURCE LIMITED SETTINGS

Jayaseelan Boobalan[1], Thongadi R. Dinesha[1], Sathasivam Sivamalar[1], Selvamurthi Gomathi[1], Rajendran Revathi[1], Aylur K. Srikrishnan[1], Amrose Pradeep[1], Shruti H. Mehta[2], Sunil S. Solomon[2], Pachamuthu Balakrishnan[1], **Shanmugam Saravanan**[1]
[1]YR Gaitonde Center for AIDS Research and Education, Chennai, India, [2]Johns Hopkins University, Baltimore, MD, USA

Background: High burden of HCV infection in people who inject drugs (PWID) in resource limited settings (RLS) like India coupled with low access to HCV services necessitates an urgent need for evaluating less invasive DBS based HCV virological assays for appropriately tailored therapy and successful treatment scale up programs in RLS.
Methods: Paired 36 plasma/DBS samples were collected from PWID. Two blood spots were excised into 1.7 mL of Abbott lysis buffer. RNA extracted from plasma and DBS according to the standard 0.5 mL HCV RNA Abbott extraction protocol (Abbott Molecular Inc, IL, USA). In addition, patient with >3 $\log_{10}$ IU/mL HCV RNA were further subjected to in-house one-step core/E1 RT-PCR followed by Sanger's sequencing. All the values were log transformed and analysed on GraphPad Prism 5.0, A p <0.005 was considered significant.
Results: There was a good correlation between standard Abbott plasma and DBS HCV assay (r = 0.97, p<0.001).Median PVL of standard plasma and DBS HCV RNA by Abbott Real-time PCR was 4.45(IQR 2.54-5.43) and 4.18 (IQR 2.24-5.74) log IU respectively. The mean difference between plasma and DBS HCV RNA assays were 0.250 and the upper and lower 95% Limit of Agreement -0.7321 to 1.23374. Out of 36 samples, 21 (58%) [Median = 5.74, (IQR=4.96-5.91)] of them were able to do HCV genotyping and majority of them were genotype 3b (42.8%) followed by 6xa (33%).
Conclusion: This study supports the use of DBS as an alternate to plasma for the reliable quantification of HCV RNA and genotyping. Therefore, the DBS specimens could be effectively used in resource-limited settings for therapeutic and research purposes.

581 CLUSTERING OF HEPATITIS C VIRUS INFECTION AMONG PEOPLE WHO INJECT DRUGS IN BALTIMORE

Oluwaseun Falade-Nwulia[1], Shruti H. Mehta[1], Mark Sulkowski[1], Carl A. Latkin[1], David L. Thomas[1], Zach Downing[1], Rachel Latanich[1], Gregory D. Kirk[1], Rebecca Rose[2], Stuart C. Ray[1], Oliver Laeyendecker[3]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]Bioinfoexperts, LLC, Thibodaux, LA, USA, [3]NIAID, Baltimore, MD, USA

Background: The availability of effective, safe, oral direct acting antivirals (DAAs) for hepatitis C virus (HCV) treatment has increased interest in treatment as prevention (TasP) for HCV infection among people who inject drugs (PWID). Identifying characteristics of individuals in high transmission networks would provide critical information for the development and implementation of effective, targeted HCV TasP strategies.
Methods: The AIDS linked to the IntraVenous Experience (ALIVE) cohort has followed current and former PWID in Baltimore since 1988. Sequencing of the HCV core/E1 region was performed on HCV viremic samples from the most recent study visit attended by ALIVE participants between August, 2005 and December, 2016 (n=600). Individuals with HCV genotype 1 infection (85%) were included in the analysis. Analyses of pairwise distances among participant HCV sequences was performed using the TN93 model. Clustering of HCV infection was defined as ≥ 2 participants with HCV sequences more similar than a previously-determined genetic distance threshold of 4%. Logistic regression was used to assess sociodemographic factors associated with being in an HCV cluster.
Results: Among 512 HCV genotype 1 viremic PWID, the median age of participants was 54 years, 68% male, 87% Black, and 38% HIV infected. Of the 425 genotype 1a samples evaluated, 31% were grouped in 2 large clusters (cluster 1: n=42 & cluster 2: n=66), a triad (n=3), or pairs (n=24). Among 87 PWID with HCV genotype 1b, 40% were in 2 clusters (cluster 1: n=14 & cluster 2: n=8), 3 triads (n=9), and 2 pairs (n=4). 342 (67%) of evaluated samples

were genetically unrelated. In unadjusted analyses, membership in a cluster, was associated with younger age (Odds ratio (OR) 1.4 [95% Confidence Interval (CI) 1.2-1.7] per 10 year age decrease), female sex (OR 1.5 [95% CI 1.0-2.2]), HIV infection (OR 1.8 [95% CI 1.2-2.6]), and living in East (versus West Baltimore, OR 2.2 [95% CI 1.4-3.6]). In adjusted analyses, younger age (OR 1.4 [95% CI 1.0-1.8-] per 10 year age decrease), HIV infection (OR 1.6 [95% CI 1.1-2.4] and living in East (versus West Baltimore, OR 1.97 [95% CI 1.2-3.2]) remained independently associated with being in a cluster of related hepatitis C infections.
Conclusion: In a cohort of PWID in Baltimore, 25% of participants were in large genetic clusters suggestive of HCV transmission networks. Targeted treatment of PWID in transmission networks should be explored as a means to enhance effectiveness of HCV TasP and elimination efforts.

582 UNRAVELLING HCV1A WHEREABOUTS IDENTIFIES A NEED FOR A PAN-EUROPEAN PREVENTION PROGRAM

Lize Cuypers[1], Bram Vrancken[1], Lavinia Fabeni[2], Velia C. Di Maio[3], Milosz Parczewski[4], Vladimir Chulanov[5], Perpetua Gomes[6], Anna Maria Geretti[7], Christoph Sarrazin[8], Cillian De Gascun[9], Saleta Sierra[10], Federico García[11], Anne-Mieke Vandamme[1], Francesca Ceccherini Silberstein[3]
[1]Katholieke University Leuven, Leuven, Belgium, [2]IRCCS Lazzaro Spallanzani, Rome, Italy, [3]University of Rome Tor Vergata, Rome, Italy, [4]Pomeranian Medical University, Szczecin, Poland, [5]Central Research Institute of Epidemiology, Moscow, Russian Federation, [6]Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal, [7]University of Liverpool, Liverpool, UK, [8]University Hospital Frankfurt, Frankfurt, Germany, [9]University College Dublin, Dublin, Ireland, [10]University of Cologne, Cologne, Germany, [11]Hospital Universitario San Cecilio, Granada, Spain

Background: Viral factors can impair the efficacy of direct-acting antiviral (DAA) based therapies for the hepatitis C virus (HCV). Naturally occurring and treatment-emerging resistance-associated variants (RAVs) in the NS3 and NS5A genes have been observed to interfere with the action of DAAs, especially in case of HCV1a. Therefore, investigating the origins of new infections is of public health relevance.
Methods: NS3 (n=2514) and NS5A (n=1957) sequences from HCV1a patients, including 1825 newly generated taxa from nine European countries (Belgium, Germany, Ireland, Italy, Poland, Portugal, Russia, Spain and the United Kingdom (UK)), were complemented with publicly available time and geo-referenced virus genetic data from around the world, among which sequences from four additional European countries (France, Netherlands, Sweden and Switzerland). A fast and scalable Bayesian phylogeographic approach was used to elucidate the population level transmission patterns through time and space using a model that allows for different migration rates depending on the direction of movement. To minimize the potentially biasing impact of the sampling process on the migration rate estimates, the latter were informed by both gene datasets simultaneously.
Results: Mapping migration pathways for both genes shows extensive movements both across continents, with an almost exclusive role for the United States (US) in seeding HCV1a into Europe (74.6%), as well as within Europe. Within the European continent there are no clear source-sink relations, and the migration network becomes increasingly complex and diffuse over time. Particularly Germany seems to function as a hub for the introduction of HCV1a lineages in Europe, seeding mainly to France, Italy, the UK and Spain. There were no specific patterns observed for known NS5A RAVs. In line with previous findings, the NS3 variant Q80K was highly abundant in one of the two clades in which HCV1a segregates.
Conclusion: In-depth phylogeography of the European HCV1a epidemic illustrates complex patterns of human migrations, without a clear differentiation of HCV1a patients at risk of acquiring RAVs. The existence of a pan-European migration network impairs the efficacy of national-based intervention programs. In turn, this indicates that a supra-national coordinated approach is needed to more quickly and more thoroughly avert the spread of HCV, including of strains that could restrict DAA treatment options.

583 NS5A RESISTANCE ASSOCIATES WITH ADVANCED LIVER FIBROSIS BUT NOT TRANSMISSION CLUSTERS

Milosz Parczewski[1], Ewa Janczewska[2], Justyna Kordek[1], Iwona Cielniak[3], Arkadiusz Pisula[2], Monika Bociąga-Jasik[4], Władysław Łojewski[5], Aleksandra Szymczak[6], Łukasz Socha[1], Magdalena Leszczyszyn-Pynka[1], Anna Urbańska[1], Ewa Siwak[3], Nadine Lübke[7]
[1]Pomeranian Medical University, Szczecin, Poland, [2]ID Clinic, Mysłowice, Poland, [3]Hospital for Infectious Diseases, Warsaw, Poland, [4]Jagiellonian University, Kraków, Poland, [5]Regional Hospital in Zielona Góra, Zielona Góra, Poland, [6]Wrocław Medical University, Wrocław, Poland, [7]Heinrich Heine University Hospital, Düsseldorf, Germany

Background: In the era of HCV treatment with directly acting antiviral (DAA) regimens presence of drug resistant variants (RAVs) negatively affecting treatment efficacy remains a concern. This study aimed to characterize pretreatment NS5A RAV frequency among Polish genotype 1 HCV-monoinfected and HIV/HCV-coinfected patients including transmission patterns and association with liver fibrosis.
Methods: NS5A sequences from 388 DAA-naive G1 infected individuals [54, 13.92% genotype 1a (G1a) and 334 (86.08%) 1b (G1b)] were obtained by population sequencing. Within this dataset 122 (31.44%) samples were obtained from HIV/HCV coinfected [including 55 (14.17%) HIV patients with the documented history of acute hepatitis C (AHC)] and 388 (68.55%) from HCV monoinfected cases. RAVs were called using the geno2pheno algorithm. A maximum likelihood methodology was used to identify the clustering, separately for G1a and G1b sequences, with clusters defined by posterior values >0.85 for both G1a and G1b. Liver fibrosis was assessed based on histopathology or ultrasound elastography (available for 190 cases, METAVIR scale). For statistics Chi2 test or two-sided Fisher's exact test were used, as appropriate.
Results: NS5A RAVs were found among 35/388 (9.02%) sequences, being similarly distributed between G1a (3/54, 5.56%) and G1b (32/334, 9.58%) (p=n.s). Variation in 31 and 93 NA5A codon positions was only found in G1b cases (14/334 (4.19%) for L31I/F/M and 18/334 (5.39%) for Y93H). Among HIV/HCV coinfected RAVs were present in 2/122 (5.71%) cases compared to the 33/233 (12.41%) HCV monoinfected individuals (p<0.001), being absent among AHC patients. Increased frequency of NS5A RAVs was found among cases with advanced fibrosis (6/40, 15.0% for F3-F4, vs. 7/150, 4.67% for F0-F2, p=0.02) and liver cirrhosis (6/28, 21,43% for F4 vs. 7/162, 4.32% for F0-F3, p<0.001). Higher prevalence of Y93H variant among cirrhotic patients was also noted (3/28, 10.71% vs. 3/162, 1.85%, p=0.04). No clustering of NS5A drug resistance variants was observed neither for G1a nor G1b sequences.
Conclusion: Selection of NS5A RAVs including Y93H associated with more advanced liver fibrosis and represents de novo selection of variants rather than transmission of drug resistant strains. This is reflected by lack of clustering for sequences containing RAVs and absence of this resistance among cases with AHC. Higher frequency of NS5A RAVs in cirrhotic patients may associate with lower virologic response rates to DAA treatment.

584 GENETIC CORROBORATION OF HCV TRANSMISSION AMONG YOUNG ADULT INJECTING PARTNERSHIPS

Damien C. Tully[1], Judith Hahn[2], David J. Bean[1], Jennifer Evans[2], Kimberly Page[3], Todd M. Allen[1]
[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]University of New Mexico, Albuquerque, NM, USA

Background: The current opioid epidemic across the US has fueled a dramatic surge in the rate of HCV infections among young persons who inject drugs (PWID). Central to designing and monitoring effective HCV prevention measures is the identification of partners who transmitted HCV. Viral genetic sequence data can then be used to infer the transmission network by reconstructing the path that links individuals who are infected with genetically similar viruses. Here, using a cohort of sero-discordant injecting partners we evaluated the degree of overlap between self-reported injecting partnerships and inferred genetic networks.
Methods: We conducted a prospective study of injecting partnerships, utilizing a large community-based epidemiologic study of HCV infection in young PWIDs in San Francisco ("UFO" study), in which index cases (chronic HCV positive) were invited to bring their current regular injecting partner(s) who were HCV RNA sero-discordant or had evidence of recent HCV infection. Partnerships in which new HCV infection occurred were subjected to Illumina deep sequencing of 2 distinct genomic regions (Core-NS2 and NS5B). Transmission clusters were identified using maximum-likelihood methods with stringent genetic distance and bootstrap support thresholds.
Results: Deep sequencing of 51 specimens from 25 partnerships in which new HCV infections occurred identified 15 phylogenetic clusters at a conservative genetic threshold of 0.01 substitutions/site. The majority of clusters, 71%

(11/15), found were from previously identified injecting partnerships while four additional genetic links were found with individuals outside of the partnership. Taken together, over half (56%) of new infections occurred outside the a priori injecting dyad as the virus sequence from the new infections were no more similar to the HCV sequence isolated from the corresponding index case than to a randomly chosen sequence.

Conclusion: Reconstruction of genetic transmission networks illustrate that only 44% of new HCV infections within the partnerships enrolled in the UFO cohort likely stemmed from direct transmission from their index partners. These results highlight the degree of difficulty in pinpointing the source of HCV transmission among PWID and demonstrate the importance and complementarity of partner naming and genetic surveillance for characterizing HCV transmission networks in an effort to guide public health interventions for disrupting transmission among communities.

585 HCV RNA AND ANTIGEN DETECTION FOR DIAGNOSIS OF ACUTE HEPATITIS C AMONG MSM ON PrEP

Julien Gras[1], Nadia Mahjoub[1], Isabelle Charreau[2], Laurent Cotte[3], Cécile Tremblay[4], Julie Chas[5], François Raffi[6], Eric Cua[7], Brigitte Guillon[2], Nicolas Guigue[1], Marie-Laure Chaix Baudier[1], Laurence Meyer[2], Jean-Michel Molina[1], Constance Delaugerre[1]

[1]Hôpital Saint-Louis, Paris, France, [2]INSERM, Le Kremlin-Bicetre, France, [3]CHU de Lyon, Lyon, France, [4]Université de Montréal, Montreal, QC, Canada, [5]Tenon Hospital, Paris, France, [6]CHU Hôtel-Dieu, Nantes, France, [7]CHU de Nice, Nice, France

Background: High incidence of HCV infection has been reported among high risk MSM. Current guidelines recommend that these individuals should be screened at least once a year with ALT and anti-HCV antibodies. Our aim was to assess the sensitivity of the different tests for early diagnosis of acute hepatitis C in high risk MSM.

Methods: In the ANRS IPERGAY PrEP trial among high risk MSM, a 3rd generation (3thG) antibody immunoassay (EIA ARCHITECT HCV Ab®, Abbott) was used for HCV diagnosis at screening and if ALT (performed every 2-months) ≥ 2.5 times the upper limit of normal. In patients with a positive EIA, we used stored sera to perform the following tests at the date of diagnosis and at previous visits (until HCV RNA was negative): antibodies (EIA 3thG ARCHITECT Anti-HCV, Abbott), rapid tests for detection of HCV antibodies (OraQuick® and Toyo®), plasma HCV RNA (AmpliPrep/COBAS® TaqMan® HCV Test, Roche and Xpert® HCV Viral Load, Cepheid), and the antigen immunoassay (EIA ARCHITECT HCV Ag®, Abbott). We evaluated the sensitivity of each test, including ALT, for the diagnosis of acute hepatitis C. HCV subtype was determined for each patient.

Results: From March 5, 2012 to June 30, 2016, among 428 enrolled participants , 14 were diagnosed with HCV infection including one co-infected with HIV, with a median follow-up of 2.1 years (IQR: 1.5-2.8). One case was diagnosed at enrollment and 13 during follow-up, leading to an HCV incidence of 1.40 per 100 person-years (95%CI: 0.74-2.39). Phylogenetic analysis identified HCV genotype 1 in 6 patients (43%), type 3 in 1 (7%) and type 4 in the remaining 7 (50%). Stored sera were available in all 14 cases at diagnosis. At previous visit, which occurred within a median of 2 months earlier (IQR: 1.5-2), stored sera were available for most patients for EIA 3thG, HCV RNA Roche and ALT (Table). On the visit before the first positive HCV-antibodies, among 12 patients who were tested with both HCV RNA (Roche) and ALT, 7 had an HCV RNA detectable and no increased ALT (p=0.008 McNemar's test).

Test	Visit of diagnosis		Previous visit	
	Number of positive tests /number of sera tested	Sensitivity (95% CI)	Number of positive tests /number of sera tested	Sensitivity (95% CI)
EIA 3thG	14/14	100% (77-100)	0/14	not tested
TROD OraQuick®	13/14	93% (66-99)	0/9	0% (0-34)
TROD Toyo®	11/14	79% (49-95)	0/9	0% (0-34)
HCV RNA Roche (cp/mL)	14/14 (median[IQR]: 1 539 693 [10 414-3 415 663])	100% (77-100)	11/13 (median[IQR]: 1 935 372 [71 036-10 900 000])	85% (55-98)
HCV RNA Cepheid UI/mL	13/13 (median[IQR]: 903 500 [115 643-4 600 000])	100% (75-100)	8/8 (median [IQR]: 1 545 000 [28 475-3 712 000])	100% (63-100)
HCV Ag UI/ml	13/13 (median[IQR]: 938 [12-5 274])	100% (75-100)	8/9 (median[IQR]: 13 475 [2 936-33 351])	89% (52-100)
Increased ALT IU/mL	13/13 (median[IQR]: 451 [103-597])	100% (75-100)	3/12 (median[IQR]: 291 [83-381])	25% (2-57)

Conclusion: The HCV antigen immunoassay and plasma HCV RNA test were positive within a median of 2 months before the detection of antibodies and ALT elevation, when patients were asymptomatic. These tests should be used in high risk MSM for early diagnosis of acute HCV infection and prevention of transmission.

586 ESTIMATING HIV, HCV AND HSV-2 INCIDENCE FROM EMERGENCY DEPARTMENT SEROSURVEYS

Oliver Laeyendecker[1], Simon E. Spencer[2], Louise Dyson[2], Yu-Hsiang Hsieh[3], Eshan U. Patel[3], Richard Rothman[3], Gabor Kelen[3], Thomas C. Quinn[1], T. Deirdre Hollingsworth[2]

[1]NIAID, Baltimore, MD, USA, [2]University of Warwick, Coventry, UK, [3]The Johns Hopkins University, Baltimore, MD, USA

Background: Historically, the Johns Hopkins Hospital Emergency Depart (JHH ED) has conducted serial identity-unlinked sero-surveys to monitor the HIV epidemic among the marginalized inner-city populations of Baltimore, Maryland. These surveys demonstrated a high burden of HSV-2, HIV and HCV, particularly among African Americans. We sought to determine temporal changes in incidence for these three viral infections in this population using age-based prevalence models.

Methods: A novel differential equation model was fitted to the survey rounds of 2003, 2007 and 2013 using Markov chain Monte Carlo methods. Those survey rounds contained 1,490, 2,298 and 2,972 black individuals aged 18 to 90. We jointly modelled incidence of infection and coinfection with HIV, HCV and HSV-2 within age/gender cohorts. This model was fitted to observed prevalence within a non-parametric Bayesian framework, allowing us to infer incidence rates that vary smoothly with time and age. Incidence (and 95% credible intervals) were estimated for all viral infections using ten five-year intervals from birth cohorts from ≤1947 to ≥1988.

Results: There was no change in HCV incidence in women between the ≤1947 cohort and the 1963-1967 cohort. HCV incidence decreased between women in the 1963-1967 cohort and the ≥1988 cohort from 1.7% (0.2, 3.4) to 0.6% (0.0, 1.6). HIV incidence in women similarly decreased from 1.3% (0.1, 2.8) in the 1973-1977 cohort to 0.6% (0.0-1.8) in the ≥1988 cohort. HSV-2 incidence was higher for women in younger birth cohorts increasing from 2.5% (0.4, 4.9) in the ≤1947 cohort to 3.4% (1.2, 5.7) in the ≥1988 cohort. For men, HCV incidence did not change between the ≤1947 cohort to 1958-1962 cohort. HCV incidence decreased in men from 1.7% (0.2, 3.4) in the 1958-1962 cohort to 0.68% (0.0, 1.9) in the ≥1988 cohort. Among men, HIV incidence was stable at 1.1% (0.6, 1.7) as was HSV-2 incidence (2.0%, 1.1-3.1). The greatest burden of multiple infections were seen in the birth cohorts from 1948 to 1972.

Conclusion: The incidence of HCV among black women and men attending the JHH ED has substantially decreased among younger age cohorts. Additionally, the incidence of HIV has also decreased among women but not among men. These changes reflect a decreasing burden of disease in younger cohorts, rather than a reduction in incidence across the whole population. HSV-2 incidence remains high for men and women showing a continued burden and risk for sexually transmitted infections.

587 ESTIMATING HIV AND HCV INCIDENCE AMONG PERSONS WHO INJECT DRUGS IN INDIA

Denali Boon[1], Sunil S. Solomon[2], Aylur K. Srikrishnan[3], Allison M. McFall[2], Pachamuthu Balakrishnan[3], Syed Iqbal[3], Gregory M. Lucas[2], Oliver Laeyendecker[1], Thomas C. Quinn[1], Shruti H. Mehta[2]

[1]NIAID, Baltimore, MD, USA, [2]The Johns Hopkins University, Baltimore, MD, USA, [3]YR Gaitonde Center for AIDS Research and Education, Chennai, India

Background: Estimating HIV and Hepatitis C virus (HCV) incidence from cross-sectional data is critically important to monitor epidemics, and plan and evaluate intervention programs. To date, incidence estimation has focused on HIV using multiassay algorithms (MAA), pooled RNA testing, or age based prevalence models. Leveraging estimated infection duration as a proxy for time-at-risk, a method proposed by Osmond et. al. (1994) for use in populations of young men who have sex with men, we estimate HIV and HCV incidence among persons who inject drugs (PWID) in India.
Methods: 14,450 PWID were recruited from 15 Indian cites using respondent driven sampling. Using Osmond's approach, annual HIV incidence was estimated as the ratio of the number of individuals seropositive divided by person-years (PY) at risk, which was time since injection initiation for those HIV- or HIV+ without a prior positive test. For HIV+ individuals with a prior positive test, PY at risk was estimated as the time between injection initiation and last test date. Modifications were made by reducing PY by predetermined fractions (1/2, 1/3, 1/4) among those who HIV+ without a prior positive test to account for the likelihood of seroconversion earlier in an individual's injection history. Estimated HIV incidence from the Osmond approach was compared to estimates from a validated MAA. We also used the Osmond approach to estimate HCV incidence.
Results: Annual HIV incidence using the Osmond approach was 2.4% (95% CI: 2.3-2.5) compared to 2.5% (CI: 2.0-2.9) using the MAA (Figure 1). Annual HIV incidence estimates increased to 2.6%, (CI: 2.5-2.7), 2.7% (CI: 2.6-2.8), and 2.7% (CI: 2.6-2.8), when truncating PY by 1/2, 1/3, and 1/4 respectively. Osmond annual HIV incidence by site ranged from 0.7% in Bhubaneshwar to 6.8% in Moreh. The Osmond approach tended to overestimate the MAA in sites where fewer PWID reported prior HIV testing. Osmond annual HCV incidence was 4.8% (CI: 4.7-4.9), and increased to 6.1%, (CI: 6.0-6.3), 6.7% (CI: 6.5-6.9), and 7.1% (CI: 6.9-7.2), when truncating the PY of HCV+ individuals without a prior positive HCV test by 1/2, 1/3, and 1/4, respectively. Osmond annual HCV incidence by site ranged from 0.4% in Gangtok to 9.7% in Kanpur.
Conclusion: These findings suggest HIV incidence among PWID can be estimated from cross-sectional data using a simpler and less laboratory intensive approach. HCV incidence was higher than HIV incidence, and was more variable because prior HCV testing in this population was low (8.7%).

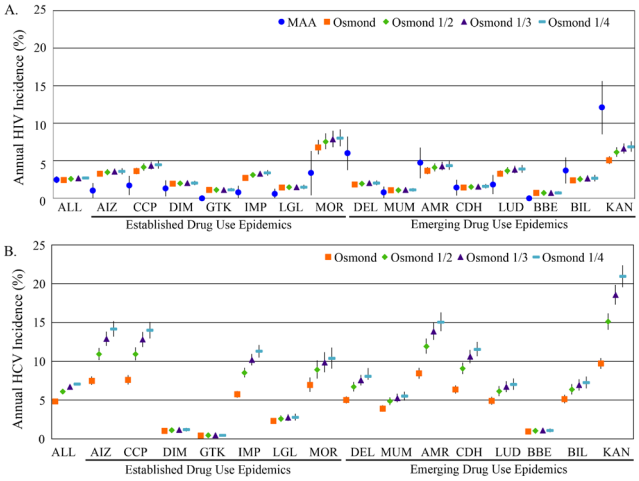


Figure 1. Estimated Incidence of HIV (panel A) and HCV (panel B) among 14,550 PWID from 15 cities in India. Annual incidence was calculated using a multiassay algorithm (for HIV only), Osmond's approach, or modified Osmond's approaches for all sites combined (ALL) and for each site individually. City abbreviations: AIZ – Aizawl, CCP – Churachandpur, DIM – Dimapur, GTK – Gangtok, IMP – Imphal, LGL – Lunglei, MOR – Moreh, DEL – New Delhi, MUM – Mumbai, AMR – Amritsar, CDH – Chandigarh, LUD – Ludhiana, BBE – Bhubaneshwar, BIL – Bilaspur, KAN – Kanpur.

588 HIV-1 ENHANCES SEXUAL TRANSMISSION OF HEPATITIS C VIRUS BY HUMAN LANGERHANS CELLS

Bernadien Nijmeijer, Ramin Sarrami Forooshani, Gaby Steba, Richard Molenkamp, Renee Schreurs, Matthijs Siegenbeek van Heukelom, Marc van der Valk, Carla Ribeiro, Teunis Geijtenbeek
Academic Medical Center, Amsterdam, Netherlands

Background: Sexual transmission of Hepatitis C virus (HCV), until recently, was thought to be rare. However, there has been a significant rise in the incidence of HCV infection among HIV-infected men-who-have-sex-with-men (MSM) and studies suggest that HCV can be sexually transmitted within this population. The mechanisms underlying this sexual transmission are unclear. Human Langerhans cells (LCs) have been shown to be involved in limiting dissemination upon sexual contact by degrading HIV-1 and preventing HIV-1 transmission. The activation state of LCs changes susceptibility to HIV-1, leading to LC infection and subsequent HIV-1 transmission. In this study we investigated the role of LCs in HCV infection and transmission. We hypothesized that HIV-1 replication in HIV-1-infected MSM leads to mucosal changes that allow HCV entry and subsequent dissemination to hepatocytes.
Methods: Therefore, we analyzed the immune cells within mucosal anal biopsies from HIV-1 infected MSM individuals as a potential entry route for HCV during sexual contact. We investigated the role of LCs in HCV infection and transmission using human primary isolated LCs and the ex vivo tissue transmission model.
Results: Notably, we detected Langerhans cells (LCs) within the mucosal anal tissue. Immature LCs were neither infected nor transmitted HCV to hepatocytes in vitro and ex vivo. As sexual transmission is mostly observed within HIV-1 infected individuals, we pre-exposed tissues with HIV-1 and, strikingly, HIV-1 pre-exposure significantly increased HCV transmission by LCs. HIV-1 replication is crucial for the increased HCV transmission as treating ex vivo tissue with HIV-1 replication inhibitors significantly decreased HIV-1-induced HCV transmission. Activation of LCs did not lead to infection by HCV but these activated LCs, in contrast to immature LCs from same donor, were efficient in transmitting HCV to hepatocytes.
Conclusion: Thus, our data strongly suggest that HIV-1 replication in mucosal tissues in HIV-1 infected MSM changes LC function, which causes HCV capture and subsequent transmission to hepatocytes. This novel transmission mechanism by LCs implicates also that the activation state of LCs is an important determinant for HCV susceptibility after sexual contact.

589 CHANGE IN HIV RISK BEHAVIOR IN PWID ON HCV TREATMENT WITH OR WITHOUT OAT AND PrEP

Sarah Kattakuzhy[1], Laura Nussdorf[2], Kristi Hill[2], Rachel Silk[1], Chloe Gross[1], Elizabeth Akoth[1], Poonam Mathur[1], Benjamin Emmanuel[1], Nadeera Sidique[3], Chloe S. Chaudhury[2], David Sternberg[4], Henry Masur[2], Shyam Kottilil[1], Elana S. Rosenthal[1]
[1]University of Maryland, Baltimore, MD, USA, [2]NIH, Bethesda, MD, USA, [3]Drexel College of Medicine, Philadelphia, PA, USA, [4]University of Maryland, College Park, College Park, MD, USA

Background: People who inject drugs (PWID) have a significantly increased risk for HIV infection. In this regard, HCV infection may foreshadow HIV acquisition in current epidemics. Studies of PWID have demonstrated a high desire to obtain HCV treatment, therefore, offering HCV treatment may provide an opportunity to engage PWID in services to prevent HIV transmission, such as buprenorphine and pre-exposure prophylaxis (PrEP). The ANCHOR study was developed to investigate a model of comprehensive care to treat HCV and reduce harm in PWID.
Methods: The ANCHOR study is an ongoing single center study evaluating treatment of HCV embedded in an urban harm reduction center. Enrolled patients have chronic HCV, opioid use disorder, and injected opioids within 3 months. Patients are treated with sofosbuvir/velpatasvir and offered uptake of buprenorphine and PrEP. The Darke HIV Risk Taking Behaviour Survey (HRBS) is administered at day 0, weeks 4, 12, 24, 48, 72, and 96. Paired t-test analysis was performed to evaluate for statistically significant changes in HIV risk behavior from day 0 to week 4.
Results: 55 HIV seronegative patients are enrolled and started on sofosbuvir/velpatasvir. Participants are predominantly male (76%), median 57 years, black race (96%). Week 4 data is available on 44 (80%) participants. Of those, 16 (29%) were on opioid agonist therapy (OAT) at screening and 22 (50%) started buprenorphine by week 4. No patients were on PrEP at baseline, and 11 (20%) started PrEP by week 4. There was an overall significant mean decrease in HRBS score in all patients (-2.3, P=0.0028) and among patients who started both PrEP and buprenorphine (-5.1, P=0.007). In patients who started buprenorphine alone, a significant decrease in HRBS drug risk sub-score was found (mean -2.4, p=0.03), however not in the overall score. There was no significant HRBS change based on baseline OAT status or PrEP uptake alone. At the time of CROI, results will be available for 100 patients.
Conclusion: Preliminary results at week 4 of the ANCHOR study support that initiation of HCV treatment is associated with decreased HIV risk taking behaviors in PWID with HCV. Collocating buprenorphine and PrEP with HCV therapy in PWID may provide an opportunity to further ameliorate the risk of HIV acquisition. However, long term outcome data are needed to assess if this effect is amplified over the course of treatment, and sustained beyond SVR.

590 HCV INCIDENCE IN HIV-INFECTED AND IN PrEP-USING MSM

Laurent Cotte[1], Eric Cua[2], Jacques Reynes[3], François Raffi[4], David Rey[5], Pierre Delobel[6], Amandine Gagneux-Brunon[7], Christine Jacomet[8], Romain Palich[9], Hélène Laroche[10], André Cabié[11], Bruno Hoen[12], Christian Chidiac[1], Pierre Pradat[1]
[1]Hospices Civils de Lyon, Lyon, France, [2]CHU de Nice, Nice, France, [3]CHU de Montpellier, Montpellier, France, [4]CHU de Nantes, Nantes, France, [5]Hôpitaux Universitaires de Strasbourg, Strasbourg, France, [6]CHU de Toulouse, Toulouse, France, [7]CHU de Saint Etienne, Saint Etienne, France, [8]CHU de Clermont-Ferrand, Clermont-Ferrand, France, [9]AP–HP, Paris, France, [10]Assistance Publique–Hopitaux Marseille, Marseille, France, [11]CHU Fort de France, Fort de France, Martinique, [12]CHU de Guadeloupe, Pointe à Pitre, France

Background: Despite a high level of engagement in care, priority access to DAAs and high HCV treatment uptake, acute HCV incidence still appears on the rise in HIV+ MSM in France. Acute HCV have been reported in HIV negative PrEP users, but there are currently no data regarding the incidence in this population. We assessed the incidence of acute HCV in PrEP users MSM and in HIV+ MSM enrolled in a large French cohort.
Methods: The DatAIDS cohort covers about 25% of French HIV+ patients in care. HIV+, HCV-negative MSM with serological follow-up in 2016 and HIV-negative, HCV-negative MSM PrEP users enrolled from January 2016 to May 2017 in 13 of the 15 cohort sites were analyzed to assess the incidence of a first acute HCV. The incidence of HCV reinfection was determined in patients having cured a previous one. Since PrEP recruitment was highly heterogeneous between sites, a sub-analysis was conducted based on the 5 sites with the highest number of PrEP patients.
Results: Among 13,825 HIV+ MSM followed in 2016, HCV serological status was available in 13,051 (94.4%). 666 patients were already HCV+ when entering the study (prevalence 5.1%) and serological follow-up was available in 2016 for 4,151 HCV-negative patients. Virological follow-up was available for 440 patients who had cured a previous infection. 59 acute HCV infections occurred in 2016 (42 first infections, 17 reinfections). Incidence of first HCV infection, reinfection and overall acute HCV was respectively 1.01, 3.77 and 1.28 / 100PY. 930 HIV-negative subjects were enrolled for PrEP. HCV serology was available in all patients and serological follow-up was available for 916 (972 PY). 17 patients were already HCV-infected when entering the study (prevalence 1.8%), of whom 14 were cured and 3 had an active HCV infection. 12 acute HCV infections occurred during follow-up (12 first infections, 2 reinfections). Incidence of first HCV infection and overall acute HCV was respectively 1.03 and 1.24/100PY. In a sub-analysis restricted to 5 sites contributing to 90% of PrEP patients and 44% of HIV+ MSM, the overall incidence of acute HCV infection was 1.38 and 1.52 / 100PY in HIV+ and HIV-negative MSM, respectively.
Conclusion: Incidence of a first HCV infection and of all acute HCV infections in HIV+ MSM and in HIV-negative MSM PrEP users was similar in France in 2016-2017. HIV+ and HIV-negative MSM PrEP users probably share similar at-risk practices for HCV and should be similarly targeted for preventive interventions.

591 HCV INCIDENCE IS STILL INCREASING IN FRENCH HIV-INFECTED MSM

Laurent Cotte[1], Thomas Huleux[2], François Raffi[3], Pierre Delobel[4], Jacques Reynes[5], Pascal Puglièse[6], David Rey[7], Firouze Bani-Sadr[8], Isabelle Poizot-Martin[9], André Cabié[10], Antoine Chéret[11], Claudine Duvivier[11], Marc-Antoine Valantin[11], Pierre Pradat[1]
[1]Hospices Civils de Lyon, Lyon, France, [2]Centre Hospitalier de Tourcoing, Tourcoing, France, [3]CHU de Nantes, Nantes, France, [4]CHU de Toulouse, Toulouse, France, [5]CHU de Montpellier, Montpellier, France, [6]CHU de Nice, Nice, France, [7]Hôpitaux Universitaires de Strasbourg, Strasbourg, France, [8]CHU de Reims, Reims, France, [9]Assistance Publique–Hopitaux Marseille, Marseille, France, [10]CHU Fort de France, Fort de France, Martinique, [11]AP–HP, Paris, France

Background: High HCV treatment uptake combined with very effective direct-acting antiviral (DAA)-based regimens recently resulted in a dramatic decline in active HCV infection in French HIV-infected patients in all risk groups except MSM. Recent data suggested that wide access to DAA in the Netherlands led to a 51% decline in acute HCV between 2014 and 2016. However, this decrease was observed for genotype 1 only, and not for genotype 4 (Rijnders et al, abstract # 137LB, CROI 2017). We assessed the yearly incidence of acute HCV infection in HIV-infected patients enrolled in a large French cohort from 2012 to 2016.
Methods: The DatAIDS cohort covers about 25% of HIV-infected patients in care in France. HCV negative patients with serological follow-up between 2012 and 2016 were enrolled and the incidence of first acute HCV infection was determined yearly. For patients who had cured a previous infection, the incidence of HCV reinfection was also determined yearly.
Results: Among 40,714 HIV-patients followed between 2012 and 2016, HCV status was available in 38,217 (94%). 5,559 patients (15%) were already HCV infected at the time of the study. HCV treatment uptake was 43% among patients with a detectable HCV-RNA in 2016. By the end of 2016, 82% of all patients had cured HCV, either spontaneously or following treatment. Among 21,518 HCV negative patients with serological follow-up between 2012 and 2016 (63,447 PY), 218 first HCV infections occurred. Similarly, among 3,392 patients who had cured a previous infection (10,595 PY), 74 reinfections occurred. The yearly HCV incidences for MSM and for patients with other HIV-risk factors are reported in the following table.
Conclusion: Despite a high HCV treatment uptake and cure rate, the incidence of acute HCV infection regularly increased in French MSM between 2012 and 2016. The incidence of reinfection fluctuated but remained constantly higher than the incidence of first infection, suggesting that a subgroup of patients pursued high-risk practices following a first infection. The incidence in patients with other HIV-risk factors including IVDUs also increased during the period but remained considerably lower than in MSM.

HCV infection incidence /100 patient-years	2012	2013	2014	2015	2016
First infection					
MSM	0.35	0.46	0.64	0.78	0.92
Other risk factor	0.04	0.06	0.17	0.16	0.08
Reinfection					
MSM	2.20	3.78	1.59	2.16	3.44
Other risk factor	0.14	0.26	0.06	0.33	0.56
All acute infections					
MSM	0.42	0.61	0.70	0.89	1.15
Other risk factors	0.05	0.10	0.15	0.21	0.23

592 LOW PREVALENCE OF HEPATITIS C VIRUS AMONG NYC MSM INITIATING PrEP AND PEP, 2016-2017

Tarek Mikati, Kelly Jamison, Christine M. Borges, Demetre C. Daskalakis
New York City Department of Health and Mental Hygiene, Long Island City, NY, USA

Background: There is some evidence that hepatitis C virus (HCV) may be sexually transmitted among HIV-positive men who have sex with men (MSM). There have been recent reports of elevated HCV prevalence among HIV-negative MSM initiating HIV pre-exposure prophylaxis (PrEP). The aim of this analysis was to determine HCV prevalence among HIV-negative MSM initiating HIV post-exposure prophylaxis (PEP) or PrEP at New York City (NYC) Sexual Health Clinics (SHC). The HCV prevalence among MSM attending sexual health clinics in the United States has not been recently reported.
Methods: NYC SHC began providing PEP and PrEP to patients at increased risk of HIV infection in September 2016. At the time of medication initiation, HCV serology (HCV Ab) with reflex HCV RNA PCR is obtained per New York State PrEP/PEP Guidelines. Using electronic medical record data from the PrEP/PEP initiation visit, we examined HCV testing, demographics, incident sexually transmitted infections, and reported sexual behavior and recent recreational drug use. Patients who tested positive for HCV antibody were matched against the NYC HCV surveillance registry to determine if they were newly diagnosed.
Results: From September 2016-August 2017, 1142 HIV-negative MSM initiated PEP (N=760) or PrEP (N=382) in NYCSHCs; HCV Ab testing was performed for 99.7% (1139/1142). Among patients tested for HCV Ab, median age was 28 years (IQR 25-33); 26% (290/1139) were black non-Hispanic and 30% (345/1139) were Hispanic. Patients reported a median of 3 sex partners in past three months (IQR 2- 6); 25% were diagnosed with chlamydia, gonorrhea, and / or early syphilis at the time of PrEP/PEP initiation. In the three months prior to the visit, 4% (45/1139) of patients reported methamphetamine, gamma-hydroxybutyrate (GHB), or injection drug use (IDU). Three patients (0.26%, 95% CI: 0.1-0.8 %) tested positive for HCV Ab; one reported IDU. The patient with an IDU history was a previously diagnosed chronically infected HCV case with

no prior treatment. A second patient had a new diagnosis of HCV which had spontaneously cleared. The third patient had been previously diagnosed with HCV, and successfully treated.

Conclusion: At NYCSHC's, HCV prevalence among HIV-negative MSM initiating PrEP and PEP is 0.26%. This prevalence is lower than the prevalence estimated in the general population of NYC and the U.S. The PrEP/PEP programs at sexual health clinics provide a good opportunity for monitoring trends in sexually transmitted HCV.

593 ASSESSING DIFFERENCES IN HISTORIC AND RECENT HIV/HCV COINFECTION IN PHILADELPHIA

Dana Higgins, Danica Kuncio, Kathleen Brady, Coleman Terrell
Philadelphia Department of Public Health, Philadelphia, PA, USA

Background: In Philadelphia, 17% of people living with HIV (PLWH) are coinfected with hepatitis C virus (HCV). Historically, the burden of coinfection in Philadelphia has been greatest among males, Non-Hispanic (NH) Blacks and Hispanics, people who inject drugs (PWID) and those >50 years old. More recently reports of coinfection in populations different from what was historically observed have been seen. The purpose of this analysis was to assess risk factors and compare historic HCV coinfection to recent HCV coinfection to understand if recent trends, including sexual acquisition of HCV, are occurring among PLWH in Philadelphia.

Methods: HIV and HCV surveillance information, including a subset of recently identified HCV seroconversion cases, was matched on first and last name, date of birth, and social security number. Patients with historic coinfection were defined as those living with HIV through December 31, 2016 with an HCV diagnosis date prior to January 1, 2012. Patients with recent coinfection were defined as those living with HIV as of December 31, 2016 with an HCV diagnosis after January 1, 2012. Chi-square analysis and multivariable logistic regression were used to assess demographic, clinical, and risk factor differences among the two groups.

Results: In 2016, 3,219 PWLH in Philadelphia were coinfected with HCV. From 2012 -2016, 58 confirmed HCV seroconversions occurred among PWLH. The majority of HCV seroconversions occurred in MSM (50%) and Heterosexuals (16%), respectively. Overall, compared to HIV monoinfections, a significantly greater proportion of HIV/HCV coinfected individuals were Hispanic, PWID, >50 years old, and diagnosed with HIV >10 years ago. When stratified by historic versus recent HCV coinfection, the odds of recent coinfection were increased among younger patients and those diagnosed with HIV <5 years ago. In comparison to PWID, the odds of recent HCV coinfection were also significantly increased among MSM and Heterosexuals.

Conclusion: This study highlights a shifting trend in coinfection in Philadelphia. Overall, the majority of coinfection occurs in those >50 years old and PWID. However, recent HCV coinfections highlight that younger MSM and Heterosexual PWLH may be at increased risk for sexual acquisition of HCV. As HIV providers strive to eradicate HCV in PWLH, prevention and treatment strategies, including updated HCV screening guidelines for emerging at-risk populations, need to be prioritized as well.

Table 1. Demographic and Risk Factor Distribution & Logistic Regression Results of Historic and Recent HIV/HCV Coinfection; Philadelphia, PA, 2016

	Historic Coinfection N (%)	Recent Coinfection N (%)	Unadjusted Logistic Regression OR (95% CI)	Adjusted Logistic Regression OR (95% CI)
Birth Sex				
Male	1,489 (69.0%)	806 (75.4%)	1.00 (REFERENCE)	1.00 (REFERENCE)
Female	663 (30.8%)	263 (24.6%)	0.747 (0.634 – 0.879)	**0.742 (0.609 – 0.906)**
Race/Ethnicity				
NH Black	1,221 (56.8%)	634 (59.3%)	1.00 (REFERENCE)	1.00 (REFERENCE)
NH White	422 (18.8%)	159 (14.9%)	**0.726 (0.591 – 0.892)**	**0.651 (0.518 - 0.820)**
Hispanic	431 (20.1%)	238 (22.3%)	1.063 (0.884 – 1.280)	0.976 (0.790 – 1.205
Multi-race/Other/Un	76 (3.5%)	38 (3.6%)	1.424 (0.940 – 2.157)	0.839 (0.535 – 1.317)
Current Age				
0-29	40 (1.9%)	79 (7.4%)	9.868 (6.174 – 15.733)	**7.608 (3.933 – 14.719)**
30-39	154 (7.1%)	172 (16.1%)	3.161 (2.492 – 4.009)	**2.771 (2.104 – 3.650)**
40-49	360 (16.7%)	254 (23.8%)	1.997 (1.691 – 1.656)	**2.025 (1.650 – 2.484)**
50+	1,596 (74.2%)	564 (52.8%)	1.00 (REFERENCE)	1.00 (REFERENCE)
HIV Diagnosis Date				
<1 Year	9 (0.4%)	39 (3.7%)	11.117 (5.352 – 23.091)	**5.428 (2.511 – 11.734)**
1 – 5 Years	99 (4.6%)	213 (19.9%)	5.519 (4.270 – 7.135)	**3.486 (2.635 – 4.613)**
6 – 10 Years	531 (24.7%)	228 (21.3%)	1.102 (0.918 – 1.321)	**0.744 (0.605 – 0.916)**
> 10 Years	1,511 (70.3%)	589 (55.1%)	1.00 (REFERENCE)	1.00 (REFERENCE)
HIV Transmission Risk				
PWID	1,266 (58.9%)	391 (36.6%)	1.00 (REFERENCE)	1.00 (REFERENCE)
MSM	239 (11.1%)	272 (25.4%)	**3.685 (2.994 – 4.535)**	**2.762 (2.189 – 3.483)**
Heterosexual	484 (22.5%)	325 (30.4%)	**2.174 (1.815 – 2.605)**	**1.938 (1.583 – 2.374)**
MSM/PWID	120 (5.6%)	58 (5.4%)	**1.565 (1.121 – 2.184)**	**1.449 (1.016 – 2.067)**
Other/No Risk Reported	41 (1.9%)	23 (2.2%)	**1.816 (1.077 – 3.064)**	1.290 (0.704 – 2.362)

594 ACTIVE-C: A COMMUNITY-BASED PROGRAM TO TEST AND CURE HEPATITIS C IN ALABAMA

Ricardo A. Franco, James W. Galbraith, Ashley Gilmore, Anthony Lee, Ashutosh Tamhane, Ronada Anderson, DeAnn Jones, Brendan McGuire, Ashwani K. Singal, E. Turner Overton, Omar Massoud, Michael Saag
University of Alabama at Birmingham, Birmingham, AL, USA

Background: Limited data exist about the effectiveness of community-based programs in achieving key goals of the National Viral Hepatitis Action Plan. We report results of ACTIVE-C (Alabama Coalition for Testing, Interventions and Engagement in Hepatitis C Care), a state-wide, community-based test and treat program focused on disease awareness, testing, patient navigation and hepatitis C treatment co-location in Primary Care.

Methods: The University of Alabama at Birmingham (UAB) Center for AIDS Research, the UAB Liver Center, the Alabama Department of Public Health (ADPH) and 12 community centers across 7 cities in Alabama engaged in formal partnerships. Clinics provided aggregate hepatitis C antibody screening data from 2013 through March 2017. Nine on-site coordinators assisted clinics with patient navigation, prior authorizations and de-identified, individual-level data collection of positive cases in the community. Primary care providers (PCPs) attended overview lectures and case-based discussions. We analyzed testing trends over time before and after launching ACTIVE-C. We compared patient characteristics and the care cascade of community sites with the UAB's tertiary center.

Results: Starting in July 2015, ACTIVE-C distributed 655 continued medical education credit-hours to 242 providers, and achieved state-wide reach within the first year. By June 2017, quarterly community hepatitis C antibody testing and diagnosis had a cumulative increase of 2.7 and 2.2 fold respectively and 70 PCPs had prescribed direct-acting antivirals (DAAs) in Primary Care setting. Comparative analysis of the proportion of patients moving downstream care cascade steps are shown in the table attached. PCPs in community clinics compared to specialists at UAB achieved similar SVR rates (table). Compared to specialists at UAB, PCPs treated with DAAs significantly higher proportions of persons who were uninsured (55% versus 3%, $p < 0.0001$), African Americans (47% versus 28%, $p < 0.0001$), living in urban counties (83% versus 64%, $p < 0.0001$) and in low income zip codes (69% versus 46%, $p < 0.0001$).

Conclusion: ACTIVE-C interventions were in alignment with key goals of the National Viral Hepatitis Action Plan, resulting in effective state-wide expansion of hepatitis C testing and treatment access to vulnerable groups within primary care clinics. We verified comparable results to what is observed in our academic medical center, confirming that treatment via community clinics is feasible and effective.

Table: Comparative Analysis of the Proportion of Patients Moving Downstream Hepatitis C Care Cascade Steps at Community Sites (Primary Care) and the UAB Health System (Tertiary Care) – 2013 through June 2017

Cascade steps	Community Sites N (%)	UAB System N (%)	Univariate analysis[a]	
			Crude OR (95% CI)	p-value
Screened	17,164	67,378	-	-
HCV AB +	2,043 (12)	7,464 (11)	1.07 (1.02 – 1.13)	0.01
HCV VL +	1,164 (57)	5,362 (72)	0.79 (0.73 – 0.85)	<0.001
Rx Uptake	339 (29)	1,558 (29)	1.00 (0.87 – 1.15)	0.97
SVR Data[b]	155	1,299	-	-
Cure[c]	148 (95)	1,283 (99)	0.97 (0.76 – 1.23)	0.78

Abbreviations: AB, antibody; CI, confidence interval; HCV, hepatitis C virus; OR, odds ratio; Rx, treatment with direct-acting antivirals; SVR, Sustained Virologic Response; UAB, University of Alabama at Birmingham; VL, viral load.
[a]Unconditional logistic regression.
[b]SVR Data: includes patients with SVR data available at the time of analysis.
[c]Cure: as per protocol analysis.

595 MASSACHUSETTS HEPATITIS C CARE CASCADE, 2007-2015

Quynh Vo, Shauna Onofrey, Daniel Church, Kevin Cranston, Alfred DeMaria, Monina Klevens
Massachusetts Department of Public Health, Boston, MA, USA

Background: Despite the high mortality and morbidity burden, the population impact of effective treatment for hepatitis C virus (HCV) infection has not been fully characterized due to under-ascertainment of screening and retention in care. We examined state-level reports of the number of HCV-infected persons who received key services along the continuum of HCV care.

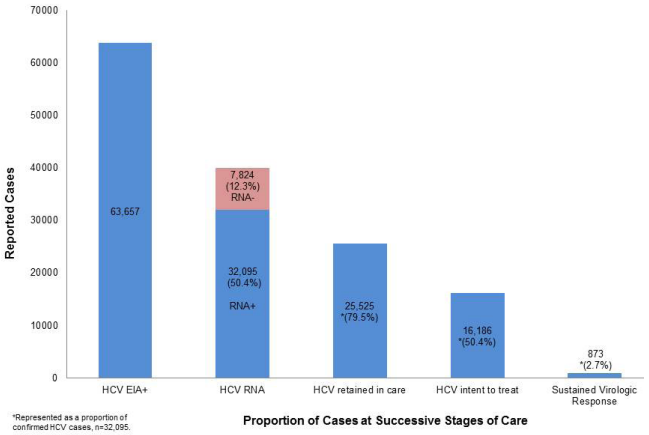
Methods: Data from 76,825 Massachusetts residents who were reported to the state HCV surveillance system and received an anti-HCV antibody test

(EIA) from 2007 to 2015 were included. Outcomes of all cases were categorized as confirmed HCV (RNA+), retained in care (≥ 2 RNA test or 1 genotype test post EIA+ test), initiated treatment (≥ 1 genotype test post RNA+ test), and sustained virologic response (RNA- test ≥ 12 weeks after a positive RNA test). The proportion of cases achieving each step in the cascade was calculated as a conditional proportion. Chi-square was used to test for differences in achieving each step in the cascade by gender, age, birth cohort, risk history, region of residence, and viral load. Wilcoxon Rank Sum was used to test for differences in time from an antibody test (EIA) to a confirmatory test (RNA).

Results: In Massachusetts, 63% (n=39,919/63,657) of reported EIA+ cases received an RNA test. Of cases identified with confirmed HCV infection (n=32,095), 80% were retained in care, 50% initiated treatment, and 3% could be documented through surveillance to have sustained virologic response (Figure 1). Differences in achieving each step in the care cascade were observed for all case characteristics. A higher proportion of cases with history of injection drug use (42%) and Boston area residence (31%) were retained in care (p<0.0001). Baby boomers reported a shorter median time to an RNA after an EIA (28 days) than young adults (65 days) (p<0.0001).

Conclusion: While only 50% of EIA+ cases reported to the Massachusetts surveillance system had a positive HCV RNA test reported, 80% of those that did so were retained in care and 50% had a genotype test reported. Documentation of sustained virologic response was extremely low (3%) and differences by case characteristics were observed across all stages of care. The higher retention in care among certain groups may reflect the success of targeted linkage to care efforts. Improved surveillance capture of negative HCV RNA test results will likely support detection of treatment response as antiviral treatment becomes more common.

Figure 1. Care Cascade, all HCV EIA+ patients, MA 2007-2015



596 THE HEPATITIS C CONTINUUM OF CARE AMONG HIV INFECTED INDIVIDUALS IN AUSTRIA

Michaela Rappold[1], Armin Rieger[2], Martin Gisinger[1], Mario Sarcletti[1], Brigitte Schmied[3], Maria Geit[4], Alexander Zoufaly[5], Bernhard Haas[6], Ninon Taylor[7], Manfred Kanatschnig[8], Laura Simula[1], Sara Krüger[1], Bruno Ledergerber[9], **Robert Zangerle**[1]

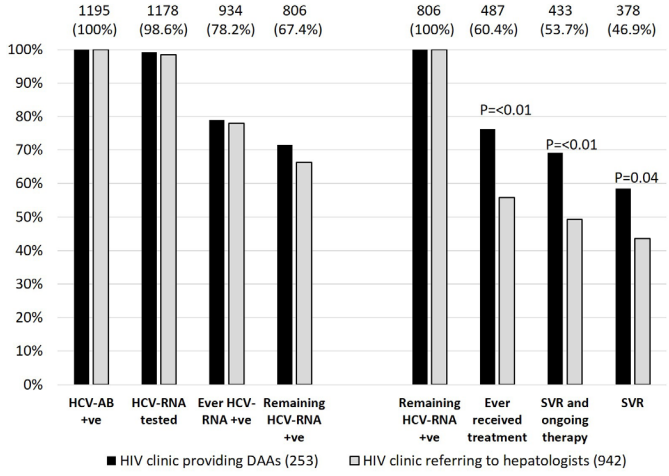
[1]Medical University of Innsbruck, Innsbruck, Austria, [2]Medical University of Vienna, Vienna, Austria, [3]Otto-Wagner Hospital, Vienna, Austria, [4]Kepler University Hospital Linz, Linz, Austria, [5]Kaiser Franz Josef Spital, Vienna, Austria, [6]General Hospital Graz South-West, Graz, Austria, [7]Paracelsus Medical University, Salzburg, Austria, [8]General Hospital Klagenfurt, Klagenfurt, Austria, [9]University Hospital Zurich, Zurich, Switzerland

Background: In Austria, prescription of direct antiviral agents (DAAs) is restricted almost exclusively to hepatologists. However, 3 of 8 HIV clinics are allowed to prescribe DAAs directly without referring their HIV/HCV coinfected patients. The aim of this study was to evaluate whether this restriction negatively impacts on the HCV continuum of care.

Methods: We analyzed data from patients of the Austrian HIV cohort study from January 2014 to August 2017. Stages of the continuum included anti-HCV positive, HCV-RNA tested, ever HCV-RNA positive, remaining HCV-RNA positive without therapy, treatment (latest, if measured more than once), the composite of ongoing therapy (including a 12 week follow-up period) and sustained virologic response (SVR), and SVR alone. SVR was measured 12 weeks after stopping treatment or later (reinfections were thus captured and taken as failing SVR). In addition, multivariable logistic regression models were performed to identify factors associated with DAA use.

Results: Among 5613 patients, HCV antibody test was not performed in 249 (4.4%) and 1195 (21.3%) had a postive antibody test, of whom 1178 (98.6%) were HCV-RNA tested and 934 (78.2%) were ever HCV-RNA positive (Figure). HCV genotype was known for 821 (87.9%), 520 (55.7%) showed genotype 1 and 218 (23.4%) genotype 3. Among the 806 individuals that remained HCV-RNA positive, 487 (60.4%) individuals initiated HCV treatment, 261 (53.6%) received DAAs without interferon and 226 (46.4%) interferon based regimens. The composite endpoint of ongoing therapy and SVR occurred in 433 (53.7%) patients and 378 (46.9%) achieved SVR. Significant differences between HIV clinics, according to providing DAAs directly or not were found for all treatment related stages of the continuum of care. The proportion of those starting treatment ranged from 76.2% in clinics providing DAAs without referral to 55.8% for clinics who have to refer patients to hepatologists. DAA use was strongly associated with clinics providing DAAs (OR 3.36; 2.16 – 5.24) to a lesser extent with younger age (OR 0.68; 0.46 – 1.01) compared to being 50 years of age or older, but was not associated with transmission category, sex, origin and HCV genotype.

Conclusion: Austria is "en route" to eliminate HCV from HIV/HCV coinfected individuals. To improve and hasten this process a "no matter who provides HCV therapy" strategy is warranted.



597 THE HCV DIAGNOSIS AND TREATMENT UPTAKE AMONG PATIENTS IN HIV CARE

Daniel Radwan[1], Oluwaseun Falade-Nwulia[1], Ryan Westergaard[2], W. C. Mathews[3], Edward R. Cachay[3], Judith Aberg[4], Richard D. Moore[1], Kelly Gebo[1]

[1]Johns Hopkins University, Baltimore, MD, USA, [2]University of Wisconsin, Madison, WI, USA, [3]University of California San Diego, San Diego, CA, USA, [4]Mt Sinai School of Medicine, New York, NY, USA

Background: Despite the high prevalence of HIV/HCV coinfection and the availability of safe, effective direct acting antiviral (DAA) drugs, the prevalence of HCV testing, treatment, and sustained virologic response (SVR) among people with HIV (PWH) is unknown. The objective of this study is to establish an HCV testing and treatment cascade among patients in HIV care.

Methods: We examined rates of HCV testing, HCV coinfection, DAA prescription, and SVR between 2013-15 among adult patients enrolled and followed at 12 sites in the HIV Research Network (HIVRN). Multivariate logistic regression, adjusting for care site, was performed to identify demographic and clinical characteristics associated with the outcomes.

Results: Among 28,821 PWH – with a median age of 47 (IQR 37-54), 68.2% non-white; 48.5% MSM, 11.2% IDU; 13.5% CD4<200, 76.5% on ART, 72.9% HIV-1 RNA <200; and 60.7% Medicaid and/or Medicare, 16.0% private insurance – 22,425 (77.8%) were tested for HCV while in HIV care. After adjustment for other factors, Black race, IDU (AOR 3.40 95% CI (2.99, 3.86)), CD4<200 (AOR 1.34, (1.21, 1.49)) and having HIV-1 RNA >200 (AOR 1.43, (1.31, 1.56)) were associated

with increased odds of HCV testing. Of those tested, 7,499 (33.4%) were HIV/HCV coinfected. Blacks and those with detectable VL were less likely to be co-infected. Of the coinfected patients at HCV treating sites; 10.2% were prescribed DAA. MSM (AOR 0.65 (0.43, 0.98)), Whites (AOR 0.50, (0.36, 0.70)) and Hispanics (AOR 0.49 (0.32, 0.73) and those with HIV-1 RNA >200 (AOR 0.35 (0.26, 0.58)) were significantly less likely to be prescribed DAA than blacks or those with undetectable VL. Of those prescribed DAA, 95.5% successfully achieved SVR.

Conclusion: While providers appear to be targeting PWH who are more likely to be HCV coinfected for testing, clinical guidelines indicate that all PWH be tested for HCV, and there is opportunity to increase HCV testing rates. Only 10% of HIV-HCV patients were prescribed DAA in the first two years of market availability, despite high rates of treatment success. Higher rates of HCV screening and treatment are needed among HIV/HCV co-infected patients.

Table 1. Multivariate Adjusted Odds Ratios of clinical and demographic characteristics of PWH tested for HCV, prescribed DAA therapy, and achieving SVR, controlling for age and site (bolded values indicate significance at P=0.05)

	Tested (N=28821)	HIV/HCV Coinfected (N=22425)	Prescribed DAA (N=4298)	Achieved SVR (N=178)
Male Sex	0.96 (0.88-1.05)	**1.23 (1.12-1.35)**	1.21 (0.90-1.62)	0.23 (0.02-3.43)
White, not Hispanic (vs. Black Race)	**0.89 (0.81-0.97)**	1.07 (0.98-1.17)	**0.50 (0.36-0.70)**	0.52 (0.04-6.72)
Hispanic	**0.84 (0.77-0.91)**	**1.32 (1.21-1.43)**	**0.49 (0.32-0.73)**	1.96 (0.07-55.77)
IDU HIV Risk Factor (vs. Hetero)	**3.40 (2.99-3.86)**	**8.48 (7.54-9.53)**	1.32 (0.96-1.83)	1.61 (0.68-37.87)
MSM HIV Risk Factor	**1.11 (1.02-1.21)**	1.07 (0.98-1.17)	**0.65 (0.43-0.98)**	5.26 (0.45-61.89)
ART (vs. no ART)	**1.32 (1.23-1.44)**	**1.49 (1.37-1.63)**	0.95 (0.68-1.32)	0.12 (0.01-1.78)
Detectable HIV Viral Load (vs. Undetectable)	**1.43 (1.31-1.56)**	**0.90 (0.82-0.97)**	**0.39 (0.26-0.58)**	0.13 (0.0-6.23)
CD4 Count <200 (vs. >500)	**1.34 (1.21-1.49)**	**1.29 (1.16-1.43)**	0.68 (0.44-1.04)	0.07 (0.0-1.23)
Private Insurance (vs. Public)	**0.75 (0.68-0.82)**	**0.60 (0.54-0.66)**	0.70 (0.48-1.01)	0.13 (0.0-6.27)
Uninsured/Ryan White	0.95 (0.87-1.03)	**0.61 (0.55-0.67)**	0.57 (0.28-1.14)	1
Intermediate (1.45-3.25) Fibrosis Score (vs. Low (<1.45))	-	-	**2.68 (2.06-3.48)**	0.14 (0.01-1.87)
Severe (>3.25)	-	-	**4.71 (3.30-6.72)**	0.21 (0.11-4.28)

598 HEPATITIS C CARE CASCADE IN JAIL: IMPLICATIONS FOR HARD-TO-REACH POPULATIONS

Caroline Abe[1], Esmaeil Porsa[2], **Ank E. Nijhawan**[1]
[1]University of Texas Southwestern, Dallas, TX, USA, [2]Parkland Health and Hospital Systems, Dallas, TX, USA

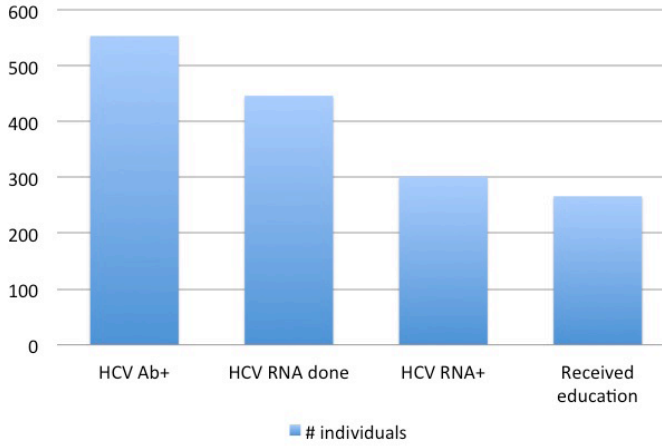
Background: Drug development for Hepatitis C virus (HCV) has lead to well-tolerated treatments for HCV with high rates of cure. However, identifying and treating HCV in hard-to-reach and vulnerable populations remains a challenge to the eradication of HCV. We determined the prevalence of HCV, factors associated with HCV infection and evaluated the HCV care cascade among jail inmates.

Methods: Opt-out HCV antibody (Ab) testing is offered at the time of routine blood draw for individuals incarcerated at the Dallas County Jail. Demographics and testing results were extracted from electronic medical records from April-August 2017; self-reported HCV risk factor and health insurance status were recorded by nursing staff. If the HCV Ab was positive, an HCV ribonucleic acid (RNA) test was completed. Patients with a positive HCV RNA were initiated in a linkage-to-care protocol that started with in-house disease education, prevention counseling, and information about linkage to HCV care including a hotline number routed to a navigation specialist. Post release, the navigation specialist would follow-up by phone to encourage linkage to HCV care. Data analyses were completed using SAS v. 9.3.

Results: Of 3174 unique individuals tested for HCV, 553 (17.4%) had a positive HCV antibody (Ab). 446/553 completed RNA testing, 301/446 (67%) tested positive for HCV RNA. Disease notification and education were provided to 266/301 (88.4%) (Figure 1). The 301 with confirmed HCV infection were 79% male, 48% non-Hispanic black, 37% non-Hispanic white, 15% Hispanic, with a median age of 50. Over half (51%) reported a history of injection drug use, 17% reported tattoos and 53% were sent to prison from jail. 186/240 (78%) had no insurance/charity care, 10% Medicaid, 5% Medicare, 5% Veterans affairs and <1% had private insurance. Among HCV+ individuals released to the community who were contacted by phone, 2/23 were scheduled with an HCV provider, 3 were planning an appointment, 2 did not desire HCV treatment, 17 were unable to be reached.

Conclusion: HCV is prevalent among jail inmates, and the most common risk factors for infection are injection drug use and tattoos. Proximal steps in the HCV care cascade, including antibody testing and RNA confirmation of infection, as well as education and risk reduction counseling were feasible in this setting. Half of HCV+ inmates were transferred to prison and the majority were uninsured, highlighting challenges to continuity of care and completion of HCV treatment in this population.

Figure 1. HCV Care Cascade from Screening to Education, Dallas County Jail, April-August 2017



599 OPERATIONALIZING ELIMINATION: CURING HEPATITIS C IN THE PATIENT-CENTERED MEDICAL HOME

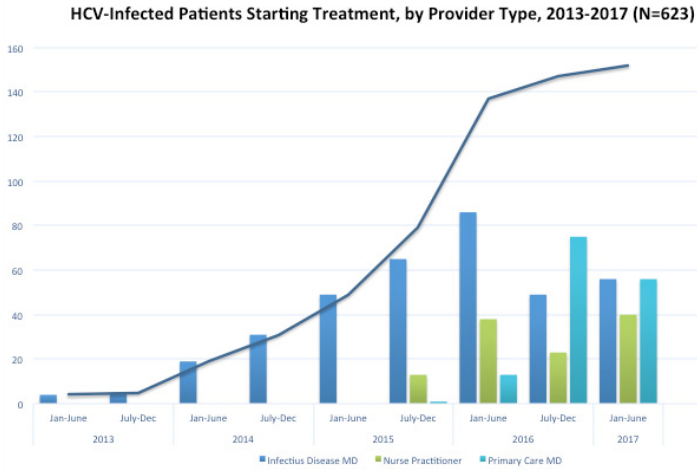
Sarah Rojas, Lisa Asmus, Christopher Cavanaugh, Maureen Khasira, Stephanie Constantino, Christian B. Ramers
Family Health Centers of San Diego, San Diego, CA, USA

Background: Given current methods to assess and treat HCV, the AASLD and IDSA have encouraged primary care providers (PCPs) to join in efforts to eradicate Hepatitis C (HCV). Recent studies demonstrate PCPs' efficacy in treating single HCV genotypes or non-cirrhotic patients, but can PCPs treat complex disease in diverse, vulnerable and medically complicated patients? If so, than FQHC's, with the PCMH model and accessible locales, can be important resources for eradicating HCV. The current study describes the experience of a single FQHC center in expanding HCV treatment.

Methods: In 2013, we developed an HCV treatment program within an urban FQHC in San Diego. With support from the CDC and a state-funded initiative, a single infectious disease doctor (ID MD) trained and supported several PCPs annually, starting in 2015. These PCPs practice in five surrounding clinics, and participate in weekly telehealth sessions, using the ECHO model. They are supported by an interdisciplinary team which performs rapid point-of-care testing, links HCV+ individuals to care, and guides patients through complex barriers to care, i.e. health insurance authorization, linkage to drug/alcohol or mental health services. Fibrosis assessment was non-invasive and patients were treated according to published guidelines.

Results: Between 1/1/13 and 9/20/17, 799 individuals tested positive for active HCV infection; 797 received further evaluation, 610 completed HCV treatment, 91 are currently on treatment. In 2013-4, a single ID MD treated 42 pts. Since 2015, he trained 5 NPs and 3 PMDs. In 2016, ID MD initiated 124 therapies, while PCPs initiated 155 (2.35x the initiations of ID MD alone; see Figure). 65% of evaluated patients were baby boomers; 43% white; 70% male. 97% had federal or state-sponsored insurance; 58% (N=459) had stage F3 or F4 fibrosis. 47 (6%) were HIV/HCV co-infected; 60% had Genotype 1A. Of those treated, 520 were >12 weeks post therapy; 393 had labs 12 weeks post-treatment. Cure rates (SVR12) were 71% (ITT analysis) and 94% (per protocol). Twelve patients had 14 treatment failures, 10 of which had cirrhosis; one patient was re-infected. Eleven of these initiated a second regimen: 6 initial failures achieved cure, while 4 are being treated.

Conclusion: PCPs trained and supported by an ID MD, along with an interdisciplinary staff, can double HCV treatment capacity and decentralize resources, reaching vulnerable populations without sacrificing cure rates.



600 INCREASING INCIDENCE OF DENIAL OF DAA THERAPY FOR CHRONIC HCV BY INSURANCE TYPE

Charitha Gowda[1], Stephen Lott[2], Matthew Grigorian[3], Dena M. Carbonari[4], M. Elle Saine[4], Stacey Trooskin[5], Jason A. Roy[4], **Jay Kostman**[5], Paul N. Urick[3], Vincent Lo Re[4]

[1]The Ohio State University, Columbus, OH, USA, [2]University of Michigan, Ann Arbor, MI, USA, [3]EnvoyHealth, Flint, MI, USA, [4]University of Pennsylvania, Philadelphia, PA, USA, [5]Philadelphia FIGHT, Philadephia, PA, USA

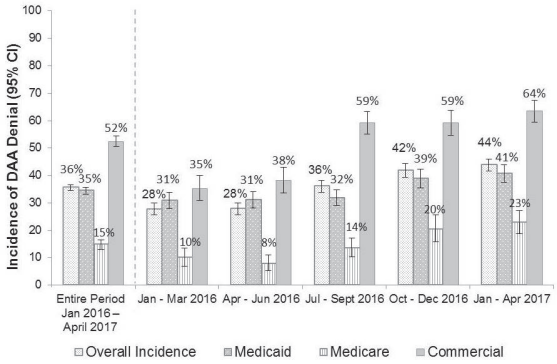
Background: The high costs of direct-acting antiviral (DAA) regimens to treat chronic hepatitis C virus (HCV) infection have led public and private insurers to restrict access to these medications. Studies conducted after their release showed that denial of DAA regimens by insurers was common, but these analyses were not nationally representative and evaluated access during initial availability. Given the advent of new DAAs, perceived relaxation of treatment restrictions, and public health focus on HCV elimination, we evaluated changes in the incidence of insurer denial of DAA therapy over time and by type of insurance within a national specialty pharmacy.

Methods: We conducted a prospective cohort study among patients who had a DAA prescription submitted between January 1, 2016 and April 30, 2017 to Diplomat Pharmacy, Inc., which provides HCV pharmacy services to patients across the United States. The main outcome was absolute denial of DAA prescription, defined as lack of approval of any DAA fill by the insurer. The status of all prescriptions with insurers was ascertained through August 31, 2017. Insurers' requests for alternative DAA regimens due to formulary restrictions were not recorded as absolute denials. We calculated the incidence of absolute denial of DAA prescription, overall and by type of insurance (Medicaid, Medicare, or commercial), for the 16-month study period and for each quarter.

Results: Among 9,025 patients from 45 states who were prescribed a DAA regimen (4,702 covered by Medicaid; 1,821 by Medicare; 2,502 by commercial insurance), 3,200 (35.5%; 95% CI, 34.5-36.5%) received an absolute denial of their treatment. Absolute denial was more common among patients covered by commercial insurance (52.4%) than by Medicaid (34.5%; p<0.001) or Medicare (14.7%; p<0.001). The incidence of absolute denial increased across each quarter of the 16-month study period, overall (27.7% in the first quarter to 43.8% in the last quarter; test for trend, p<0.001) and for each type of insurance (test for trend, p<0.001 for each type; see Figure).

Conclusion: Despite the availability of new DAA regimens and changes in restrictions to these therapies, absolute denials of DAA regimens by insurers have remained high and increased over time, regardless of type of insurance. The influence of liver fibrosis stage, substance use, and type of prescriber on DAA denials requires further investigation. To achieve the goal of HCV elimination, access to antiviral treatment must be improved.

Figure 1. Incidence of absolute denial of DAA prescription from Jan 2016 to April 2017, overall and by type of insurance.



601 HEPATITIS C TREATMENT UPTAKE AMONG INSURED HIV/HCV-COINFECTED PATIENTS

Jennifer O. Lam[1], Leo Hurley[1], Scott Chamberland[1], Jamila Champsi[1], Laura C. Gittleman[1], Daniel G. Korn[1], Jennifer B. Lai[1], Charles P. Quesenberry[1], Joanna Ready[1], Varun Saxena[1], Suk Seo[1], David J. Witt[1], Michael J. Silverberg[1], Julia L. Marcus[2]

[1]Kaiser Permanente, Oakland, CA, USA, [2]Harvard University, Boston, MA, USA

Background: Patients coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are prioritized for HCV treatment because of their elevated risk of liver disease. However, the high cost of direct-acting antivirals (DAAs) for the treatment of HCV infection may contribute to disparities in access and initiation.

Methods: Using a retrospective cohort design, we measured factors associated with DAA initiation among HIV/HCV-coinfected patients at Kaiser Permanente Northern California (KPNC) from October 2014 (when DAAs became widely used in KPNC) through December 2016. Potential predictors of DAA initiation were demographic characteristics, including age, sex, race/ethnicity, census-based neighborhood deprivation index (NDI; proxy for socioeconomic status); behavioral factors, including HIV risk, alcohol use, smoking, and drug abuse diagnosis; economic factors, including insurance type and individual out-of-pocket maximum healthcare costs; and clinical factors, including HCV genotype, advanced fibrosis (based on most recent Fibroscan if available, otherwise FIB-4), prior HCV treatment, hepatitis B virus (HBV) infection, baseline CD4 count, and baseline HIV RNA level. Adjusted rate ratios (aRRs) were obtained from multivariable Poisson regression models.

Results: Among 555 HIV/HCV-coinfected patients, 232 (41.8%) initiated DAAs (90% on ledipasvir/sofosbuvir). There were no significant differences in DAA initiation by race/ethnicity, NDI, maximum out-of-pocket healthcare costs, HIV risk, alcohol use, smoking, HBV infection, or HIV RNA levels. Factors associated with initiation of DAAs included male sex (aRR 1.86, 95% confidence interval [CI]: 1.01-3.33), ages 60-69 years (compared with <50 years, aRR 1.60, 95% CI: 1.07-2.38), advanced fibrosis (aRR 1.68, 95% CI: 1.14-2.50), HCV genotype 1 (aRR 2.45, 95% CI: 1.65-3.64), and no prior HCV treatment (aRR 2.10, 95% CI: 1.47-3.02). Factors associated with reduced DAA initiation included CD4 <200 cells/μL (compared with ≥500 cells/μL, aRR 0.35, 95% CI: 0.16-0.79), Medicare enrollment (compared with commercial insurance, aRR 0.63, 95% CI: 0.41-0.95), and drug abuse diagnosis (aRR 0.66, 95% CI: 0.47-0.92).

Conclusion: We found little evidence of racial/ethnic or socioeconomic disparities in initiation of DAAs among HIV/HCV-coinfected patients during the initial years of DAA availability within KPNC. Efforts are needed to increase DAA uptake among women, younger patients, Medicare enrollees, and those with drug abuse diagnoses.

602 TREATMENT OF CHRONIC HEPATITIS C GT1,2,4 IN AFRICA: FINAL RESULTS OF ANRS TAC TRIAL

Karine Lacombe[1], Raoul Moh[2], Corine Chazallon[3], Babacar Sylla[4], Maud Lemoine[5], Charles Kouanfack[6], Eric Tchoumi Leuwat[6], Magloire Biwole Sida[6], Fatoumata Fadiga[2], Michèle Tagni-Sartre[6], Viviane Marie Pierre Cisse[1], Lawson-Ananissoh Laté Mawuli[2], Pierre-Marie Girard[1], Alain Attia[2]
[1]INSERM, Paris, France, [2]PAC-CI Program, Abidjan, Côte d'Ivoire, [3]INSERM, Bordeaux, France, [4]IMEA, Paris, France, [5]Imperial College London, London, UK, [6]IRD, Montpellier, France

Background: With the advent of highly effective oral therapy for hepatitis C virus (HCV) infection and the recent World Health Organization commitment, HCV elimination has become a realistic goal. However, in sub-Saharan Africa the HCV epidemic remains a neglected issue and access to care and treatment is almost inexistent. The TAC ANRS 12311 trial is an international multicenter open label trial aimed to assess the feasibility, efficacy and safety of interferon-free therapy in HCV-infected patients in the sub-Saharan African setting.
Methods: Adult patients with treatment-naïve chronic hepatitis C were recruited in Senegal, Côte d'Ivoire and Cameroon. Patients without decompensated cirrhosis received either a 12 week-combination of sofosbuvir plus weight-based ribavirin (SOF+RBV) if infected with genotype (GT) 2 or sofosbuvir/ ledipasvir (SOF+LDV) if infected with GT1 or 4. This trial included 120 participants in total (40 in each GT group). The primary endpoint was the sustained virological response (threshold of detectability 12 or 25 IU/mL), observed 12 weeks after the end of treatment (SVR12).
Results: Of the 120 participants (male 54%, median age 58 years [IQR 49 –63], median plasma HCV-RNA 6.0 log IU/MI [IQR 5.5 –6.6]), 36 were HIV-coinfected (median CD4: 624/mm^3, IQR 442 - 844), all with plasma HIV-RNA<200 copies/MI. 14 (12%) patients had APRI score > 2 (F4) at baseline. All but one patient completed the 12-week treatment course, and the remaining one discontinued treatment for personal reason (travel abroad) but reached SVR12. No patient died or was lost to follow-up. 8 (7%) patients had an adverse event of grade 3 or 4 During treatment, 3 patients had a decrease in haemoglobin level between 70 and 94 g/L, one of whom with a consequent reduction of RBV dosage. 37 cases of arterial hypertension were documented, 35 being pre-existing conditions and the 2 others unrelated to HCV drugs. HCV-RNA was measured at week 24 (documenting SVR12) in 119 patients, of whom 107 (90%) had undetectable viral load including 36 (90%) in GT-1, 36 (90%) in GT-2, and 35 (90%) in GT-4. 3 out of the 12 failing patients had an APRI score>2 (F4) at baseline.
Conclusion: HCV treatment with SOF+RBV in GT-2 or SOF+LDV in GT-1 or GT-4 infected patients is feasible, safe and effective in sub-Saharan Africa including in HIV co-infected patients. With the growing access to HCV drugs at generic price worldwide, it is time to prompt scaling up of HCV treatment in Africa.

603 DAA IMPLEMENTATION RATE IN HIV/HCV PATIENTS IN SPAIN: 2 YEARS OF UNRESTRICTED ACCESS

Antonio Rivero-Juárez[1], Francisco Téllez[2], Manuel Castaño[3], Dolores Merino[4], Nuria Espinosa[5], Jesus Santos[3], Juan Macías[6], Maria Paniagua-Garcia[7], Angel Zapata-Lopez[8], Antonio Collado[9], Amparo Gomez-Vidal[10], Javier Perez Stachowski[11], Leopoldo Muñoz-Medina[12], Elisa Fernandez-Fuertes[13], Antonio Rivero[1]
[1]Hospital Universitario Reina Sofia, Cordoba, Spain, [2]Hospital Universitario de Puerto Real, Cadiz, Spain, [3]Hospital Regional Universitario de Málaga, Málaga, Spain, [4]Hospital Juan Ramón Jiménez, Huelva, Spain, [5]Hospital Universitario Virgen del Rocio, Sevilla, Spain, [6]Hospital Universitario de Valme, Seville, Spain, [7]Hospital Universitario Virgen Macarena, Sevilla, Spain, [8]Hospital Universitario Jerez de la Frontera, Jerez de la Frontera, Spain, [9]Hospital Universitario Torrecardenas, Alemria, Spain, [10]Complejo Hospitalario de Jaén, Jaén, Spain, [11]Hospital Costa del Sol, Marbella, Spain, [12]Complejo Hospitalario Universitario de Granada, Granada, Spain, [13]Hospital de Poniente, El Ejido, Spain

Background: In April 2015, the Spanish National Health System developed a strategic plan for unrestricted access to HCV direct-acting antiviral (DAAs) drug therapy. We evaluate the implementation of this strategy in HIV/HCV coinfected patients.
Methods: The HERACLES cohort is a multicenter, prospective observational cohort initiated in April 2015, which includes HIV-infected patients with chronic HCV coinfection in follow-up at 19 reference centers for the care of HIV-infected patients in Andalusia (southern Spain). Subjects were included in the cohort if they presented active chronic HCV coinfection and were not receiving HCV treatment. The treatment rate in our cohort was evaluated for 24 months after implementation of the Spanish HCV strategic plan. Multivariate analysis was performed to identify factors associated with a low DAA therapy implementation rate.
Results: Of 15,556 HIV patients tested, 3,075 (19.7%) were chronically infected with HCV and were enrolled in the study. Of these patients, 68 (2.2%) were lost to follow-up after study inclusion. So, the target population consisted of 3007 patients. Of these, 86.7% were people who inject drugs (PWIDs), 58% were HCV G1, 16.4% HCV G3, 23.8% cirrhotic, and 30.8% were treatment-experienced patients. 1957 (65.1%) patients started DAA therapy. Rate of treatment according to liver fibrosis was: 90.1% in liver cirrhosis patients (647 of 718), 85.7% in F3 (662 of 772), 68.01% in F2 (319 of 469), 37.8% in F0-F1 (329 of 870). Of the 1483 patients with sustained virological response (SVR) who could be evaluated, 94.8% achieved it. During the study period, 158 (5.1%) patients died before receiving HCV therapy. At the end of study period, 892 patients with chronic HCV infection were pending to be treated. Thus, the prevalence of HCV RNA-positive in the whole HIV population at the end of the study period was 5.7%. In multivariate analysis, independent factors associated with a lower rate of treatment implementation were liver fibrosis stage of F0-F1 (OR = 0.073; 95% CI: 0.053-0.1) and use of opioid substitution therapy (OR = 0.594; 95% CI: 0.492-0.8).
Conclusion: In the study period, a high number of HIV/HCV coinfected patients from our cohort received DAA therapy. In this difficult to treat cohort, with a high proportion of PWIDs and cirrhotic patients, the real-world SVR rate was 95%. Consequently, both these facts meant a significant reduction in HCV RNA-positive prevalence among HIV infected subjects.

604 MULTICENTER REGISTRY IN HIV/HCV CO-INFECTED PATIENTS INITIATING LEDIPASVIR/SOFOSBUVIR

Kristen M. Marks[1], Nwora L. Okeke[2], Lawrence Park[3], Cody A. Chastain[4], Kimberly Workowski[5], Chris Woods[2], Kenneth E. Sherman[6], Gregory K. Robbins[7], Stefan Mauss[8], Jürgen K. Rockstroh[9], Susanna Naggie[3]
[1]Weill Cornell Medicine, New York, NY, USA, [2]Duke University, Durham, NC, USA, [3]Duke Clinical Research Institute, Durham, NC, USA, [4]Vanderbilt University, Nashville, TN, USA, [5]Emory University, Atlanta, GA, USA, [6]University of Cincinnati, Cincinnati, OH, USA, [7]Massachusetts General Hospital, Boston, MA, USA, [8]Heinrich Heine University Hospital, Düsseldorf, Germany, [9]Bonn University Hospital, Bonn, Germany

Background: HCV treatment for HIV/HCV co-infected patients in the direct acting antiviral (DAA)-era is the same as for HCV-infected patients without HIV, but there is a need for attention to drug-interactions between antiretrovirals (ARVs) and DAAs. Switches in ARVs to limit drug interactions are common prior to initiating DAA, although there is limited data to guide this practice and the risk of loss of HIV control is unknown.
Methods: This is the planned interim analysis of a multicenter (N=9), observational clinical registry. The study population includes patients with HIV/HCV co-infection treated with ledipasvir/sofosbuvir. Cases (ARV switch prior to HCV therapy) and controls (no ARV switch prior to HCV therapy) are enrolled in a 1:1 ratio with a planned enrollment of 300 patients. The primary endpoint is HIV treatment failure defined by a combined endpoint of HIV virologic failure (confirmed HIV RNA >50 copies/mL >1 week apart), discontinuation of ARV regimen, lost to follow-up, progression to AIDS, or death. Secondary endpoints include nephrotoxicity and sustained virologic response (SVR12), defined as an undetectable HCV RNA 12 weeks after DAA therapy. Planned analyses include Fischer's exact for differences in proportions.
Results: To date 171 patients have enrolled and 146 had data entry completed and available for the analysis. The cohort is predominantly male (80%), with a mean age of 55.7 years, and 47% black race. The table summarizes the primary and secondary outcomes. Overall, 8 patients met the primary outcome. Nephrotoxicity events (change from baseline creatinine of ≥0.4 mg/dL, decrease in clearance of creatinine <50 mL/min or incident >1+ proteinuria) occurred in 30% of patients on tenofovir disoproxil fumarate (TDF)-containing regimens and 35% of patients on regimens without TDF. There was no difference in nephrotoxicity between cases and controls. Eleven patients were on boosted-ARV regimens containing TDF, one met nephrotoxicity criteria. The overall SVR for the 123 patients with follow-up during the SVR12 study windows was 100%.

Conclusion: In this interim analysis of a real world cohort of HIV/HCV co-infected patients receiving ledipasvir/sofosbuvir, switches in ARVs were not associated with HIV treatment failure. While nephrotoxicity events did occur, these were not more common in controls and were not associated with TDF-containing regimens. HCV treatment success was independent of ARV switch and was achieved by all participants with complete follow-up to date.

Characteristic	Overall (N=146)	ARV Switch (N=56)	No ARV Switch (N=90)	p-value
HIV treatment failure, n(%)	8 (5.5%)	3 (5%)	5 (5.6%)	1.00
HIV viral failure, n(%)	1 (0.7%)	0	1 (1%)	1.00
ARV switch, n(%)	6 (4%)	3 (5%)	3 (3%)	0.67
Development of AIDS, n(%)	1 (0.7%)	0	1 (1%)	1.00
Death, n(%)	0	0	0	--
Nephrotoxicity, n(%)	47 (32%)	14 (25%)	33 (37%)	0.15
Incident Proteinuria >1+, n(%)	24 (16%)	7 (12.5%)	17 (19%)	0.36
Creatinine ≥0.4 mg/dL, n(%)	12 (8%)	6 (11%)	6 (6.7%)	0.54
Creatinine clearance <50 mL/min, n(%)	19 (13%)	5 (9%)	14 (15.6%)	0.32
On TDF-containing regimen, n(%)	82 (56%)	29 (52%)	53 (59%)	0.38

605 UNREPORTED ALCOHOL USE WAS COMMON BUT DID NOT IMPACT HCV CURE IN HIV-INFECTED PWID

Risha Irvin, Geetanjali Chander, Kathleen Ward, Oluwaseun Falade-Nwulia, Juhi Moon, Catherine Sutcliffe, Sherilyn Brinkley, Taryn Haselhuhn, Stephanie Katz, Kayla Herne, Lilian Arteaga, David L. Thomas, Shruti H. Mehta, Mark Sulkowski
Johns Hopkins University, Baltimore, MD, USA

Background: With interferon, alcohol could impair immunological responses and reduce the effectiveness of hepatitis C virus (HCV) treatment. Therefore, alcohol cessation was often required. However, HCV guidelines from the AASLD/IDSA now prioritize treatment for all persons including those with heavy alcohol use with direct-acting antivirals. We investigated the prevalence of heavy alcohol use and the impact on the HCV care continuum in HIV/HCV coinfected persons who inject drugs (PWID).

Methods: In the CHAMPS study, 144 HIV/HCV coinfected PWID were randomized to contingent cash incentives and peer-mentors to evaluate the impact on HCV treatment uptake and cure as compared to usual clinical care. At baseline, alcohol use was ascertained using the 10-item AUDIT and Phosphatidylethanol (PEth), an alcohol biomarker. Log binomial regression was used to evaluate associations between alcohol use with treatment initiation and cure.

Results: The median age was 55, 61% were male, 92% were Black, 91% reported a history of injection drug use, 97% were on antiretroviral therapy, all had HCV genotype 1 infection, and 12% had cirrhosis. By AUDIT, 38 (26%) reported hazardous drinking while 71 (49%) had a negative PEth, 17 (12%) had a PEth < 50 ng/ml, and 47 (33%) had a PEth ≥ 50 ng/ml which denotes heavy alcohol use. Of the 47 individuals with a PEth ≥ 50 ng/ml, 23 (49%) reported drinking never, monthly or less, or 2-4 times per month by AUDIT. LDV/SOF was initiated in 110 of 144 participants and, of those who initiated LDV/SOF, cure was achieved in 91%. Neither PEth ≥ 50 ng/ml (Relative Risk [RR] 1.12, 95% CI 0.60-2.09) nor hazardous drinking by AUDIT in women (RR 0.77, 95% CI 0.22-2.66) or men (RR 1.60, 95% CI 0.79-3.26) were significantly associated with failure to initiate HCV treatment. Similarly, neither PEth ≥ 50 ng/ml (RR 1.08, 95% CI 0.64-1.83) nor hazardous drinking in women (RR 0.54, 95% CI 0.17-1.74) or men (RR 1.59, 95% CI 0.89-2.83) were significantly associated with failure to achieve cure.

Conclusion: Alcohol use was common and frequently not detected by self-report which is concerning as alcohol use can lead to increased fibrosis and may impact liver disease progression post HCV cure. It was encouraging that heavy alcohol use, even when measured objectively, was not associated with failure to initiate HCV treatment or to achieve cure. This validates guidelines which prioritize treatment for persons who use alcohol including those with alcohol use disorders.

606 HIGH EFFICACY OF 8 WEEKS OF LEDIPASVIR/SOFOSBUVIR IN AFRICAN AMERICANS WITH HCV

Whitney Nichols, Alexander Geboy, Cathy Gurgol, Chinyere Ukaegbu, Nicole Brown, **Dawn Fishbein**
MedStar Health Research Institute, Hyattsville, MD, USA

Background: Current AASLD/IDSA guidelines recommend that black/African American (b/AA) genotype 1 hepatitis c virus (HCV) infected patients receive 12 weeks of ledipasvir/sofosbuvir (LDV/SOF) therapy, even if they otherwise meet criteria for 8 weeks. Recent studies have been conflicting regarding the efficacy in this group. This study aims to evaluate the efficacy of 8 weeks of LDV/SOF in a b/AA cohort.

Methods: A retrospective, convenience sample study was conducted of b/AA patients seen in a Washington, DC clinic from 11/2014 – 4/2017, who were eligible for 8 weeks of treatment. Patients who met criteria for 8 weeks of treatment but received 12 weeks were also evaluated. HCV RNA was collected at treatment week 4, end of treatment (EOT), and at sustained virologic response (SVR) (both 12 and 24 weeks). Data on adherence to medication and provider follow up, as well as acid-reducing (AR) medications, were collected.

Results: Of patients in this clinical treatment cohort, 10% (n=59/596) met the criteria for this study: (1) Thirty five 8-week patients, mean age was 64 +6 years, 77% (n=27) were female, 54% (n=19) had a fibrosis score >F2, 74% were genotype 1a, and the median RNA value was 761,300 IU/ml (14,700 - 3,955,810); 21% (n=7) took AR medications, 9% (n=3) were non-adherent to HCV medication (9 – 35 missed doses), and 18% (n=19/105) of treatment appointments were missed. Of the twenty four 12-week patients, mean age was 64 +4 years, 67% (n=16) were male, 83% (n=20) had a fibrosis score >F2, 79% were genotype 1a, and the median RNA was 2,598,480 IU/ml (241,380 - 5,817,461); 20% (n=4) were on AR medications, 10% (n=2) were non-adherent to medication (9 missed), and 15% (n=11/72) of treatment appointments were missed. All patients in both groups achieved SVR. There were no statistically significant differences in these variables and between groups regarding age, genotype, medication and appointment adherence and AR medication use. However, in the 8-week group, there were more females (p<0.01), earlier liver fibrosis (p<0.02), and lower baseline RNA (p<0.01).

Conclusion: The data show that b/AA patients in a real-world clinical setting achieved SVR when completing 8 weeks of HCV treatment. Larger studies should evaluate the utility of using 8 weeks of treatment in b/AA patients as shorter treatment duration would be less costly and allow for more patients to be treated.

607 HIV PREDICTS FAILURE OF LDV/SOF IN HCV G1 TREATMENT-NAÏVE NON-CIRRHOTIC PATIENTS

Juan Berenguer[1], José L. Calleja[2], Marisa Montes[3], Ángela Gil-Martín[4], Ana Moreno[5], Rafael Bañares[1], Teresa Aldámiz-Echevarría[1], Agustín Albillos[5], María J. Téllez[6], Antonio Olveira[3], Lourdes Domínguez-Domínguez[7], Javier García-Samaniego[3], Inma Jarrín[8], María J. Calvo[4], Juan González-García[3]
[1]General University Hospital Gregorio Marañón, Madrid, Spain, [2]Puerta de Hierro Research Institute and University Hospital, Madrid, Spain, [3]La Paz University Hospital, Madrid, Spain, [4]Servicio Madrileño de Salud, Madrid, Spain, [5]Hospital Ramon y Cajal, Madrid, Spain, [6]Hospital Universitario Clínico San Carlos, Madrid, Spain, [7]Hospital Universitario 12 de Octubre, Madrid, Spain, [8]Institute de Salud Carlos III, Majadahonda, Spain

Background: The efficacy of licensed DAA regimens is assumed to be the same for HCV-monoinfected patients (MoP) and HIV/HCV-coinfected patients (CoP). However, the high SVR rates of DAA regimens and the relatively small number of patients included in registration trials have made it difficult to identify predictors of treatment failure, including the presence of HIV. We compared treatment outcomes for LDV/SOF against HCV G1 in treatment-naïve MoP and CoP without cirrhosis.

Methods: Created in November 2014, RUA-VHC is a prospective registry of individuals receiving DAAs for HCV in hospitals from the Madrid Regional Health Service. For this study, we selected previously untreated non-cirrhotic patients with HCV G1 (the most prevalent genotype) who had received LDV/SOF (the most commonly used DAA regimen) without ribavirin for 8 or 12 wk. We assessed SVR at 12 wk after completion of treatment.

Results: Up to September 2017, 17,269 patients (3,549 CoP) were registered in RUA-VHC. A total of 1,407 patients (1,102 MoP/305 CoP) met inclusion criteria. Significant differences between MoP and CoP were observed at baseline for age, gender, and G1 subtype distribution (Table). Among CoP, 43% were CDC-C, 59% nadir CD4+ < 200/mm^3, median baseline CD4+ 612/mm^3, 99% on ART, and 94% undetectable HIV-RNA. SVR rates for LDV/SOF at 8 wk did not differ significantly between MoP and CoP (96.6% vs 94.0%; P=.25) (Table). However, the SVR rate for LDV/SOF at 12 wk was significantly higher for MoP than CoP (97.2% vs 91.9%; P<.001) (Table). A multivariable logistic regression model

including age, sex, liver stiffness, G1 subtype, HCV-RNA, HIV, and treatment duration showed the factors associated with treatment failure to be male sex (adjusted odds ratio [aOR] 2.37; 95%CI 1.24-4.52; P=.01) and HIV infection (aOR 2.16; 95% CI 1.76-4.87; P=.01). Similar findings were observed when we restricted the analysis to patients with HCV-RNA < 6 million IU/mL.

Conclusion: The results of this large prospective real-world study analyzing treatment outcomes for LDV/SOF against HCV G1 in treatment-naïve noncirrhotic patients suggest that HIV infection is a predictor of treatment failure in patients with chronic hepatitis C. Some characteristics of CoP, such as low nadir CD4+ count and prior clinical AIDS, which are indicative of immunosuppression, may explain these results and require further analysis.

Table. Characteristics at treatment outcomes for LDV/SOF against HCV G1 in treatment naïve patients without cirrhosis

	8 WEEKS				12 WEEKS			
	Total N=498	Monoinfected N=415	Coinfected N=83	*P*	Total N=909	Monoinfected N=687	Coinfected N=222	*P*
Age *	56 (49-66)	58 (49-68)	50 (46-54)	<.001	56 (50-67)	60 (52-70)	51 (47-54)	<.001
Male sex #	259 (52.0)	193 (46.5)	66 (79.5)	<.001	515 (56.7)	348 (50.7)	167 (75.2)	<.001
Genotype #				<.001				<.001
1a	160 (32.1)	95 (22.9)	65 (78.3)		408 (44.9)	235 (34.2)	173 (77.9)	
1b	323 (64.9)	312 (75.2)	11 (13.2)		468 (51.5)	432 (62.9)	36 (16.2)	
1 non-subtyped	15 (3.0)	8 (1.9)	7 (8.4)		33 (3.6)	20 (2.9)	13 (5.9)	
HCV RNA Log IU/mL *	5.9 (5.4-6.4)	5.9 (5.4-6.3)	6.1 (5.6-6.5)	.03	6.4 (6.0-6.8)	6.4 (5.9-6.8)	6.5 (6.0-6.8)	.05
Liver stiffness kPa *	8.6 (7.9-9.4)	8.6 (7.9-9.3)	8.6 (7.8-10.0)	.61	9.1 (8.1-10.4)	9.2 (8.1-10.5)	9.0 (8.1-10.3)	.31
SVR ITT #	479 (96.2)	401 (96.6)	78 (94.0)	.25	872 (95.9)	668 (97.2)	204 (91.9)	<.001
SVR ITT (95% CI)	94.1-97.7	94.4-98.1	86.5-98.0		94.4-97.1	95.7-98.3	87.5-95.1	
Relapse #	15 (3.0)	10 (2.4)	5 (6.0)		14 (1.5)	7 (1.0)	7 (3.1)	
Breakthrough #	0	0	0		0	0	0	
DC due to AEs #	1 (0.2)	1 (0.2)	0		5 (0.5)	2 (0.3)	3 (1.3)	
DC other reasons #	3 (0.6)	3 (0.7)	0		16 (1.8)	10 (1.5)	6 (2.7)	
Death #	0	0	0		2 (0.2)	0	2 (0.9)	
SVR m-ITT #	479 (96.8)	401 (97.3)	78 (94.0)	.11	872 (97.6)	668 (98.7)	204 (94.4)	<.001
SVR m-ITT #	94.8-98.1	95.3-98.7	86.5-98.0		96.4-98.5	97.5-99.4	90.5-97.1	

* median (IQR); # n (%). m-ITT= non-virological failures for reasons other than DC to AEs or death were not considered in the analysis

608 PREDICTIVE FACTORS OF INTERFERON-FREE THERAPY FAILURE IN HIV/HCV COINFECTION

Lourdes Domínguez-Domínguez[1], Maria Lagarde[1], Otilia Bisbal[1], Mariano Matarranz[1], Carlos Lumbreras[1], Asunción Hernando[2], Rafael Rubio[1], Federico Pulido[1]

[1]Hospital Universitario 12 de Octubre, Madrid, Spain, [2]Universidad Europea de Madrid, Madrid, Spain

Background: Many cohorts show effectiveness of all-oral direct acting antivirals (DAA) for HCV therapy > 90%. Few studies focus on predictive factors of failure in HIV coinfected patients.

Methods: HIV/HCV patients included in the cohort "VIH-DOC" were eligible if treated with DAA between 9th January 2015 and 31st August 2016. Sustained virological response (SVR) was analyzed 24 weeks after the end of therapy in the intention to treat population. SVR proportions were compared by the Fisher exact test in different subgroups depending on age, gender, transmission mechanism, associated diseases (mellitus diabetes, alcohol consumption, HBV coinfection, cirrhosis -defined by either liver stiffness ≥14.6kPa or clinical evidence-, estimated glomerular filtration rate impairment, and symptomatic or asymptomatic cryoglobulinemia), and factors related to the HCV (basal viral load, genotype, IL28B polymorphism CC vs. non-CC, previous interferon based therapy and DAA estimated adherence) and to the HIV (basal viral load and basal CD4+ cells count). Binary logistic regression was used for multivariate analysis which included clinically relevant variables (cirrhosis, response to previous interferon therapy and IL28B polymorphism) and factors with a Fisher exact test p value <0.15.

Results: DAA were prescribed to 423 patients. Mean age was 50.1 years old. Men were 74.4% of patiens. Main transmission mechanism was drug injection (84.9%). Men who had sex with men (MSM) accounted for 4.5% of cases. SVR was confirmed in 393 (92.9%, 95%CI:90.0-95.2). No difference was shown when comparing SVR in cirrhosis vs. non-cirrhosis (Dif% 1.9 [95%CI:(-3.1) - 8.3], p=0.540); nor in subgroups defined by gender, age and other associated diseases. Patients with DAA adherence <95% had lower SVR (Dif% 10.3 [95%CI:3.5-19.6], p=0.003); as well as those with basal CD4+ count <200/µL (Dif% 14.7 [95%CI:4.1-31.0], p=0.006). After logistic regression, both DAA adherence and basal CD4+ count remained with a role on SVR (OR 3.9 [95%CI:1.8-8.8, p=0.001] and 5.2 [95%CI:1.9-13.9, p=0.001], respectively). Moreover, MSM had 4.2 [95%CI:1.1-16.1, p=0.039] times less probability of SVR achievement. Model's Nagelkerke R square was 0.13.

Conclusion: DAA adherence < 95% and basal CD4+ count < 200/µL predict lower SVR. On the other hand, data sugest MSM transmission is also a risk factor for failure, but it could be due to higher rate of HCV reinfection. Larger number of MSM patients would be needed to confirm this latter finding.

609 PREDICTORS OF LACK OF HEPATITIS C ERADICATION USING DIRECT-ACTING ANTIVIRALS

Edward R. Cachay[1], Alvaro Mena[2], Laura Benitez[3], Ivana Maida[4], Carmen de Mendoza Fernández[3], Angeles Castro[2], Elena Dore[4], Craig Ballard[1], Vincent Soriano[5], W. C. Mathews[1]

[1]University of California San Diego, San Diego, CA, USA, [2]University Hospital of La Coruña, La Coruña, Spain, [3]Puerta de Hierro Research Institute and University Hospital, Madrid, Spain, [4]University of Sassari, Sassari, Italy, [5]La Paz University Hospital, Madrid, Spain

Background: The high efficacy of direct-acting antivirals (DAA) makes eradication of hepatitis C (HCV) an achievable goal for nearly all in need. Identification of factors involved in the lack of sustained viral response (SVR) following DAA treatment among patients living with HIV (PLWH) is paramount for global HCV eradication efforts.

Methods: Retrospective cohort analysis of PLWH treated for HCV in standard of care in 3 countries from January 2014 to January 2017. Bivariate analyses followed by logistic regression were used to identify factors associated with lack of SVR. Potential predictors included demographics; HIV regimen, CD4, and viral load; HCV-genotype(GT), prior treatment history, and DAA used; fibrosis stage, cirrhosis, and prior liver decompensation; Charlson comorbidity index; active alcohol, any illicit drug use, intravenous drug use (IDU), unstable housing and active psychiatric illness.

Results: A total of 450 PLWH were treated with different DAA regimens. Median age 52 years, CD4+ 457/mm^3, undetectable HIV viral load 86%. Most patients were male (76.4%), white (67%), heterosexual with IDU history (67.6%) and HCV treatment naïve (70.6%). The HCV GT distribution was GT1a (47.1%), GT1b (20.9%), GT4 (13.4%), GT3 (11%), GT1 untypeable (4.9%) and GT2 (2.7%). One-third of patients (n=151) were cirrhotics of whom 25% (n=38) had prior liver decompensation. The prevalence of current alcohol, drug use, unstable housing and active psychiatric illness at DAA initiation was 31.8% (n=141), 30.9% (n= 139, [26 were IDU]), 5.8% (n=26) and 24.2% (n=109), respectively. Overall 415 patients (92.2%) achieved SVR (GT1: 91.5%, GT2: 91.7%, GT3: 94%, GT4: 95%), including 91.4% of cirrhotics and 86.8% of those with prior liver decompensation. Of the 35 failures, 23 were HCV relapses, 9 were lost to follow-up, 2 discontinued DAA due to side effects, and 1 stopped DAA due to a severe comorbidity. In bivariate analysis(Table), active psychiatric illness (p<.0001) and illicit drug use (p=0.006) were associated with lack of SVR. In logistic regression analysis of effects of both drug use and psychiatric illness, only active psychiatric illness was associated with lack of SVR [OR: 2.7, CI; 1.2-5.8, P=0.01]. There was no interaction between drug use and active psychiatric illness.

Conclusion: In this multinational DAA cohort of PLWH, active psychiatric illness was independently associated with lack of SVR to DAA. The role of drug adherence and/or drug interactions should be further explored in this population.

Selected bivariate comparisons of negative predictors of sustained viral response using direct-acting antivirals in HIV-infected patients

Covariates	SVR-12: NO n= 35 (7.8%)	SVR-12: YES n = 415 (92.2%)	Total n = 450 (100%)	P-value
DAA[1] regimen-simplified, n (%)				
Sofosbuvir plus ribavirin (RBV),	1 (6.3)	15 (93.8)	16 (100.0)	0.186
Sofosbuvir plus ledipasvir ± RBV,	18 (7.1)	236 (92.9)	254 (100.0)	
Sofosbuvir plus simeprevir ± RBV,	8 (17.0)	39 (83.0)	47 (100.0)	
Sofosbuvir plus daclatasvir ± RBV,	3 (9.1)	30 (90.9)	33 (100.0)	
PrOD[2] ± RBV,	2 (3.4)	56 (96.6)	58 (100.0)	
Sofosbuvir plus velpatasvir ± RBV,	3 (13.6)	19 (86.4)	22 (100.0)	
Ombitasvir/paritaprevir/ritonavir+RBV,	0 (0.0)	17 (100.0)	17 (100.0)	
Grazoprevir plus elbasvir	0 (0.0)	2 (100.0)	2 (100.0)	
HIV risk factor, n (%)				
Men who have sex with men (MSM),	3 (7.1	39 (92.9)	42 (100.0)	0.544
Heterosexual,	6 (15.8)	32 (84.2)	38 (100.0)	
Hemophilia,	1 (10.0)	9 (90.0)	10 (100.0)	
MSM + Intravenous Drug Use (IDU)	2 (9.1)	20 (90.9)	22 (100.0)	
Heterosexual +IDU,	21 (6.9)	283 (93.1)	304 (100.0)	
Other,	2 (5.9)	32 (94.1)	34 (100.0)	
Current alcohol, baseline, n (%)				
No,	21 (6.9)	285 (93.1)	306 (100.0)	0.281
Yes,	14 (9.8)	129 (90.2)	143 (100.0)	
Current illegal drugs, baseline, n (%)				
No,	17 (5.5)	294 (94.5)	311 (100.0)	0.006
Yes,	18 (12.9)	121 (87.1)	139 (100.0)	
Current intravenous drug use, baseline, n (%)				
No,	31 (7.3)	393 (92.7)	424 (100.0)	0.136
Yes,	4 (15.4)	22 (84.6)	26 (100.0)	
Unstable housing, n (%)				
No,	32 (7.5)	392 (92.5)	424 (100.0)	0.461
Yes,	3 (11.5)	23 (88.5)	26 (100.0)	
Active major depression/psychiatric illness n (%)				
No,	18 (5.3)	323 (94.7)	341 (100.0)	< 0.0001
Yes,	17 (15.6)	92 (84.4)	109 (100.0)	
HCV genotype (grouped), n (%)				
1/1a/1b,	28 (8.5)	300 (91.5)	328 (100.0)	0.769
2/2b,	1 (8.3)	11 (91.7)	12 (100.0)	
3/3a/3b,	3 (6.0)	47 (94.0)	50 (100.0)	
4,	3 (5.0)	57 (95.0)	60 (100.0)	
HCV treatment naive, n (%)				
No,	12 (9.1)	120 (90.9)	132 (100.0)	0.509
Yes,	23 (7.3)	294 (92.7)	317 (100.0)	
Cirrhosis, n (%)				
No,	22 (7.4)	275 (92.6)	297 (100.0)	0.654
Yes,	13 (8.6)	138 (91.4)	151 (100.0)	
Child-Pugh score group, n (%)				
A5/A6,	8 (6.5)	116 (93.5)	124 (100.0)	0.208
B7/B8/B9,	4 (15.4)	22 (84.6)	26 (100.0)	
C10/C11,	1 (20.0)	4 (80.0)	5 (100.0)	
Cohort, n (%)				
UCSD-USA	15 (10.1)	134 (89.9)	149 (100.0)	0.350
La Coruña-Spain	9 (5.8)	145 (94.2)	154 (100.0)	
Puerta de Hierro-Spain	10 (8.9)	102 (91.1)	112 (100.0)	
Sassari - Italy	1 (2.9)	34 (97.1)	35 (100.0)	
Proportion of detectable HIV viral load, n (%)	4 (6.2)	61 (93.8)	65 (100.0)	0.597
Age (years), median (IQR) [3].	50 (45; 55)	52 (46; 56)	52 (46; 55)	0.682
Log_{10} HCV viral load, median (IQR).	5.85 (5.25; 6.63)	5.98 (5.29; 6.50)	5.97 (5.29; 6.50)	0.761
Charlson Comorbidity Score, median (IQR).	6 (2; 9)	6 (2; 8)	6 (2; 8)	0.737
MELD score, median (IQR).	9 (8;13)	10 (7; 10)	8 (7; 10)	0.158
CD4 prior to DAA initiation, median (IQR).	417 (256; 682)	461 (287; 712)	457(287; 707)	0.713

SVR-12 = sustained viral response after 12 weeks of hepatitis c treatment discontinuation.
1. DAA = Direct-acting antivirals; 2. PrOD = Paritaprevir/ritonavir-ombitasvir and dasabuvir; 3. IQR = Interquartile range.

610 DAA TREATMENT RESPONSE AMONG HIV/HCV-COINFECTED PATIENTS IN THE CNICS COHORT

H. Nina Kim[1], Robin M. Nance[1], Benigno Rodriguez[2], Kenneth H. Mayer[3], Richard D. Moore[4], Edward R. Cachay[5], W. C. Mathews[5], Elvin Geng[6], Joseph J. Eron[7], Ricardo A. Franco[8], Michael Saag[8], Mari Kitahata[1]

[1]University of Washington, Seattle, WA, USA, [2]Case Western Reserve University, Cleveland, OH, USA, [3]Fenway Health, Boston, MA, USA, [4]Johns Hopkins University, Baltimore, MD, USA, [5]University of California San Diego, San Diego, CA, USA, [6]University of California San Francisco, San Francisco, CA, USA, [7]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [8]University of Alabama at Birmingham, Birmingham, AL, USA

Background: Patients with HIV and chronic hepatitis C (HCV) coinfection have had high sustained virologic response (SVR) rates to direct-acting antiviral (DAA) therapy in clinical trials, and are no longer considered a treatment-refractory population. Yet these trials were nearly all open-label studies with strict eligibility criteria. We provide real-world SVR rates to DAA therapy in a large, diverse population of HIV/HCV patients across seven sites in the CNICS network.

Methods: We identified patients who started an interferon-free DAA combination (regimens outlined below) any time after respective FDA approval date through March 2017 and had post-treatment HCV viral level (VL) measured. SVR4 was defined as an undetectable HCV RNA ≥4 weeks post-treatment and SVR12, ≥12 weeks post-treatment. We calculated SVR4 rates and 95% confidence intervals (CI) using a modified intent-to-treat analysis (mITT), SVR12 rates by mITT and SVR12 per-protocol (excluding individuals with early treatment cessation). We evaluated SVR4 across key subgroups: age ≥50, female, black, genotype, ledipasvir-sofosbuvir (LDV-SOF), cirrhosis (FIB-4 >3.25), treatment experience (prior peginterferon/ribavirin), antiretroviral therapy (ART) status, HCV and HIV VL, and CD4 counts (measured pre-treatment) and <8-week duration.

Results: Among 373 HIV/HCV patients who underwent DAA therapy, 80% were men, 32% white, 59% black, with median age of 56. Median CD4 cell count was 549 cells/mm^3 and 90% were on ART. DAA regimens included: LDV-SOF (84.2%), simeprevir/sofosbuvir (8.6%), sofosbuvir/daclatasvir (3.2%), paritaprevir-ritonavir-ombitasvir/dasabuvir (2.1%), elbasvir-grazoprevir (1.1%) and sofosbuvir-velpatasvir (0.8%). Of these, 22 (6%) were also on ribavirin and 76 (20%) were treatment-experienced. The overall SVR4 rate was 97.6% (95% CI 95.5, 98.9). SVR12 by mITT was 98.2% (95% CI 96.1,99.3); SVR12 by per-protocol was similar. SVR4 rate remained high across key subgroups including blacks and those with high baseline HCV VL, FIB-4 >3.25 or prior HCV treatment. However, there was a trend toward lower SVR rates with treatment duration <8 weeks (90%, 95% CI 55.5, 99.9) and pre-treatment HIV VL >40 copies/ml (92.6%, 95% CI 75.7, 99.1). Among the 9 patients who did not achieve SVR, 1 had on-treatment breakthrough and 8 had virologic relapse.

Conclusion: SVR rates among HIV/HCV patients in routine clinical care appear to be comparable to that reported in clinical trials and high across subgroups traditionally considered difficult-to-treat.

Group	N	N with SVR*	SVR* rate	95% CI
Overall	373	364	97.6	95.5, 98.9
SVR12 or later by mITT	330	324	98.2	96.1, 99.3
SVR12 or later by per-protocol	322	317	98.4	96.4, 99.5
Age ≥50 years	293	286	97.6	95.1, 99.0
Female	74	72	97.3	90.6, 99.7
Black race	221	215	97.3	94.2, 99.0
Genotype 1a	239 of 340	233	97.5	94.6, 99.1
Genotype 1b	89 of 340	86	96.6	90.4, 99.3
Genotype 2	1 of 340	1	100	2.5, 100.0
Genotype 3	7 of 340	7	100	59.0, 100.0
Genotype 4	4 of 340	4	100	39.8, 100.0
Ledipasvir/Sofosbuvir overall	314	306	97.5	95.0, 98.9
Ledipasvir/Sofosbuvir 12 weeks	279	271	97.1	94.4, 98.8
Ledipasvir/Sofosbuvir 24 weeks	35	35	100	90.0, 100.0
Treatment-experienced	76	75	98.7	92.9, 100.0
Early treatment cessation (<8 weeks)	10 of 331	9	90.0	55.5, 99.7
FIB-4 index >3.25	81 of 320	80	98.8	93.3, 100.0
HCV RNA level ≥6,000,000 IU/mL	82 of 370	79	96.3	89.7, 99.2
CD4 count <200 cells/mm^3	19	18	94.7	74.0, 99.9
HIV RNA level >40 copies/mL	27 of 372	25	92.6	75.7, 99.1
On ART pre-treatment	336	329	97.9	95.8, 99.2

N, number; SVR, sustained virologic response. *SVR4 rates by mITT unless otherwise noted; CI, confidence interval; ITT, intent-to-treat analysis; ART, antiretroviral therapy. All labs indicate baseline (pre-treatment) values.

611 REDUCTIONS IN HEALTHCARE SERVICE USAGE FOLLOWING DIRECT ACTING ANTIVIRAL THERAPY

Sahar Saeed[1], Erica E. Moodie[1], Mark Hull[2], Sharon Walmsley[3], Curtis Cooper[4], Alexander Wong[5], Michael John Gill[6], Valerie Martel-Laferriere[7], Erin C. Strumpf[1], Marina Klein[8]

[1]McGill University, Montreal, QC, Canada, [2]St. Paul's Hospital, Vancouver, BC, Canada, [3]Toronto General Hospital, Toronto, ON, Canada, [4]Ottawa General Research Institute, Ottawa, ON, Canada, [5]Regina Qu'Appelle Health Region, Regina, SK, Canada, [6]Southern Alberta Clinic, Calgary, AB, Canada, [7]Centre de Research du Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada, [8]McGill University Health Centre, Glen site, Montreal, QC, Canada

Background: High costs of direct acting antivirals (DAAs) have limited treatment access worldwide. Empirical evidence on the cost benefits of DAAs in real world populations would support wider treatment access. We investigated the impact of all oral-DAA therapy on healthcare services utilization (HCSU) among HIV-Hepatitis C (HCV) coinfected individuals in Canada.

Methods: The Canadian Co-Infection Cohort Study prospectively follows 1785 HIV-HCV co-infected participants from 18 centres. Data on sociodemographic, clinical, HCSU and prescriptions are collected biannually through self-administered questionnaires. We used a segmented multivariate negative binomial mixed model to evaluate the impact of DAAs on annual HCSU rates. HCSU was defined as out-patient visits (including number of visits to walk-in, general/HIV practitioners and specialist) and in-patient visits (emergency room and hospitalization). Out-patient visits, pre-treatment were truncated 6-months prior to initiation to account for changes in HCSU in preparation of initiating DAAs. Follow-up time post-DAA treatment included visits following ascertainment of treatment response (>12 weeks post-DAA treatment). Multivariate models included time updated CD4 cell count, HIV viral load, injection drug use and fixed confounders; age, sex, fibrosis and psychiatric diagnoses.

Results: Between 2014-2016, 318 participants initiated oral DAAs, 200 completed at least 1 visit before and after DAA treatment (total of 1868 visits) with a mean of 3.2 years (SD 2.6) pre- and 0.7 years (SD 0.5) post-DAA follow up time. 70% of DAA regimens consisted of ledipasvir/sofosbuvir. Median age at DAA initiation was 52 (IQR 48, 56), 76% were male, 90% had HIV viral load

<50 copies/mL, median CD4 count was 505 cells/mL (IQR 297, 710) and 27% had evidence of liver fibrosis. Sustained virologic response rates were 95%. Table 1 summarizes changes in HCSU rates pre- and post- DAA treatment. Out- and in-patient visits increased 17% and 6% respectively before DAA initiation. Post-DAA treatment, there was a 41% reduction in annual out-patient visits compared to pre-treatment rates (Incidence Rate Ratio (IRR) 0.59, 95% CI 0.31, 1.12) and a 21% reduction in annual in-patient visits (0.79, 0.58, 1.07).
Conclusion: We found evidence of reductions in both in- and out- patient visits post DAA therapy in a real-world HIV-HCV coinfected population.

Table 1. Changes in health care service usage before, during and after all-oral DAA treatment

		Incidence Rate Ratio (IRR) Unadjusted	Incidence Rate Ratio (IRR) Adjusted
Out-Patient Visits	Pre-treatment Rate (Secular trend before DAA initiation, per year)	1.21 (1.13, 1.29)	1.17 (1.09, 1.26)
	Change in intercept (immediate effect)	1.19 (0.58, 2.41)	0.98 (0.45, 2.12)
	Post-DAA Rate (Compared to pre-treatment rate, per year)	0.71 (0.32, 1.07)	0.59 (0.31, 1.12)
In-Patient Visits	Pre-treatment Rate (Secular trend before DAA initiation, per year)	1.08 (1.05, 1.11)	1.06 (1.03, 1.10)
	Change in intercept (immediate effect)	0.97 (0.70, 1.36)	1.02 (0.71, 1.48)
	Post-DAA Rate (Compared to pre-treatment rate, per year)	0.86 (0.66, 1.14)	0.79 (0.58, 1.07)

612 HIGH INCIDENCE OF HCV REINFECTION IN MSM IN THE DAA ERA

Patrick Ingiliz[1], Malte Wehmeyer[2], Stefan Christensen[3], Thomas Lutz[4], Knud Schewe[5], Axel Baumgarten[1], Dietrich Hueppe[6], Karl-Georg Simon[7], Jürgen K. Rockstroh[8], **Christoph Boesecke**[8], Stefan Mauss[9]
[1]Center for Infectiology, Berlin, Germany, [2]University Hospital Hamburg–Eppendorf, Hamburg, Germany, [3]CIM Infectious Diseases, Münster, Germany, [4]Infektiologikum, Frankfurt, Germany, [5]DAGNÄ eV, Berlin, Germany, [6]Gastroenterology Practice, Herne, Germany, [7]Gastroenterology Practice, Leverkusen, Germany, [8]Bonn University Hospital, Bonn, Germany, [9]Center for HIV and Hepatogastroenterology, Düsseldorf, Germany

Background: Reinfection with the hepatitis C virus (HCV) has been described in patients with ongoing risk behaviour. Among men who have sex with men (MSM), users of intravenous (IDU) and non-intravenous drugs (mainly methamphetamine) for sexual enhancement (Chemsex) have been identified as a main risk group for HCV acquisition. The frequency of HCV reinfections after treatment with direct-acting antivirals (DAA) is not known. Here, we analysed the reinfection incidence rate in HCV mono-infected and HIV/HCV co-infected MSM or patients with IDU from the German hepatitis C cohort (GECCO).
Methods: Until September 2017, 2364 DAA treatment courses of HIV/HCV co-infected and HCV mono-infected patients from 9 hepatitis centers have been included in the GECCO database since February 2014. All patients who completed HCV antiviral therapy were included in our current analysis. A reinfection was diagnosed in patients with a detectable HCV viral load who previously achieved a sustained virological response 12 weeks after the end of treatment, or with evidence for a genotype switch.
Results: In total, 32/1960 patients (0.02%) had an HCV reinfection. The follow-up time for the entire cohort was 1141 person-years (median follow-up time 26 weeks per patient; range 4-205 weeks), indicating an HCV reinfection incidence of 2.8 per 100 person-years. All patients with an HCV reinfection were male, the mean age was 48 years (standard deviation 8.6 years), 3 (9.4%) suffered from liver cirrhosis, 26/32 (81.25%) had an HCV/HIV co-infection, 25 patients (78.1%) were MSM and 7 patients reported IDU (21.9%). Importantly, 8/25 (32%) MSM were occasional IDU. The median time from end of anti-HCV treatment to the diagnosis of the HCV reinfection was 53 weeks (range 2-115). A genotype switch occurred in 14/32 patients (44%). The reinfection rate in patients with IDU was 1.0% (7/710) during 390 person-years. Thus, the incidence of an HCV reinfection in patients with IDU was 1.8 per 100 person years. The reinfection rate in patients with MSM was 11.2% (25/223) during 175 person-years, indicating an incidence for an HCV reinfection of 14.3 per 100 person-years.
Conclusion: The overall incidence of an HCV reinfection in our large multicenter cohort remained low. However, patients with ongoing risk behaviour displayed an increased incidence for an HCV reinfection, in particular men who have sex with men.

613 PREVALENCE OF ACTIVE HEPATITIS B AMONG NEW YORK CITY MSM, PrEP AND PEP, 2016-2017

Tarek Mikati, Kelly Jamison, Christine M. Borges, Demetre C. Daskalakis
New York City Department of Health and Mental Hygiene, Long Island City, NY, USA

Background: The CDC recommended regimen for HIV pre-exposure prophylaxis (PrEP) and post exposure prophylaxis (PEP) contain tenofovir DF (TDF)/ emtricitabine (FTC). Providing this medication to those infected with Hepatitis B virus (HBV) could theoretically lead to hepatitis flares and liver injury with TDF/FTC discontinuation. The prevalence of chronic active HBV infection in the United States (U.S.) is 1.1 % among foreign born and 0.14% among U.S. born. The aim of this analysis is to determine the prevalence of active HBV infection among men who have sex with men (MSM) initiating PrEP or PEP at New York City (NYC) sexual health clinics (SHC).
Methods: Hepatitis B serologies are obtained from all patients who initiate PrEP and PEP at NYC SHC. Using electronic medical record data, we examined HBV serologies, demographics, and reported sexual behavior. Patients who tested positive for hepatitis B core antibody (anti-HBc) and hepatitis B surface antigen (HBsAg) were classified as actively infected while those who tested positive for Hepatitis B surface Antibody (anti-Hbs) and anti-HBc were considered naturally immune. Patients who tested positive only for anti-HBs were classified as vaccine induced immunity. All patients who tested positive for HBsAg were matched with NYC HBV surveillance registry to determine if they were newly diagnosed.
Results: From September 2016 to August 2017, 1142 HIV negative MSM initiated PEP and PrEP that contained TFD/FTC. HBV serologies were obtained from 1139 (99.7%). Their median age was 28 years (IQR 25-33); 30% were Hispanic, 29% were White non- Hispanic (NH) 26% were Black NH, and 6% were Asian NH. More than one third were foreign born (37%; n=424). Prevalence of HBV vaccine induced immunity was 57% (657/1139) and HBV natural immunity was 5.6% (64/1139). Six patients (0.53%, 95% CI: 0.24- 1.2 %) were actively infected with HBV. Foreign-born patients were more likely to be infected with HBV than US-born (1.2%vs. 0.14%; p<0.03). Five were considered newly diagnosed per the NYC HBV registry. All six patients were offered active referrals to HBV providers; five patients accepted.
Conclusion: Despite the high rate of HBV vaccine induced immunity of 57% among this MSM cohort, the prevalence of HBV active infection among US -born and foreign-born MSM initiating PEP and PrEP is similar to the national estimates Establishing access to HBV care through active referral systems to HBV providers is important, especially in clinics that provide PEP/PrEP to foreign-born MSM.

614 PREVALENCE AND PREDICTORS OF HEP B INFECTION AND HEP B/HIV CO-INFECTION, ZAMBIA 2016

Karampreet Sachathep[1], Kumbutso Dzekedzeke[1], Lloyd Mulenga[2], Nchimunya Nkombo[3], Webster Kasongo[4], Andrea Low[1], Suzue Saito[1], Stanley Kamocha[5], Kathy Hageman[5], Gina Mulundu[6], Eyasu Teshale[7]
[1]ICAP at Columbia University, New York, NY, USA, [2]Government of Zambia Ministry of Health, Lusaka, Zambia, [3]Central Statistical Office, Lusaka, Zambia, [4]Tropical Diseases Research Centre, Ndola, Zambia, [5]CDC Zambia, Lusaka, Zambia, [6]University Teaching Hospital, Lusaka, Zambia, [7]CDC, Atlanta, GA, USA

Background: : Estimating the prevalence of hepatitis B virus (HBV) infection and HBV/HIV coinfection is important given successful scale up of Antiretroviral Therapy (ART) in Zambia and concerns about HBV treatment resistance of current treatment regimens recommended in Zambia.
Methods: We used data from the 2016 Zambia Population-based HIV Impact Assessment (ZAMPHIA), a national household survey that includes rapid hepatitis B surface antigen (HBsAg) and HIV rapid tests in the home. Current HBV infection was defined by HBsAg+ results. We estimated the prevalence of HBV and HBV/HIV coinfection and conducted multivariate logistic regression to determine associated predictors using weighted data.
Results: ZAMPHIA recruited 26,888 individuals aged 0-59 years. The national HBV prevalence was 5.6% (95% CI=5.2-6.0%,) for adults and 1.3% (Table 1) for children, which translates to an estimated 410,377 adults and 93,753 children (Table 1), nationally. Amongst those HBV+, 13.6% were found to be coinfected

with HIV (Table 1). Provincial HBV prevalence was highest in Luapula (5.1%) with the highest rates of HIV infection amongst those HBV+ in Lusaka and Western (Table 1). HBV positivity was most common amongst men, those 25-34 years of age and lowest amongst the 0-14 age group (Table 1). HBV positivity was higher among HIV positive persons (aORHIV+ vs.HIV-]=1.49, 95% CI=1.24-1.79); male sex (aORMale vs.Female=1.69, 95% CI=1.47-1.93); highest among persons residing in Luapula (aORLuapula vs.Eastern=2.19, 95% CI=1.51-3.17) and among persons aged 25-34 years (aOR25-34y vs.15-24y=1.39, 95% CI=1.16-1.66). Persons aged 35-44 years were most likely to be coinfected with HIV (aOR34-44yvs.15-24y4= 6.61, 95% CI=3.75-11.64) as well as those residing in Western province (aORWestern vs.Eastern= 2.32, 95% CI=1.08-4.96).

Conclusion: These findings highlight, for the first time in Zambia, high levels of chronic HBV infection, and a need for hepatitis B vaccination programs, screening and treatment programs, and for careful attention to national HIV and HIV/HBV treatment and pre-exposure prophylaxis guidelines.

Table 1: Estimated prevalence of individuals 0-59 years of age with 95% confidence intervals of current hepatitis B virus infection and HIV prevalence amongst those HBV+ by sex, age, residence and province of residence in Zambia, 2016

	Description of Estimate	% HBV positive N= 26,988		% HIV positive amongst HBV+ N=1,139	
		%	95% CI	%	95% CI
	Overall	3.6	3.3-3.8	13.6	11.5-15.7
Sex	Female	2.8	2.5-3.0	16.19	13.0-19.4
	Male	4.4	3.9-4.8	11.93	9.2-14.7
Age	0-14 years	1.3	1.1-1.6	5.08	2.5-7.7
	15-24 years	4.9	4.3-5.5	5.2	2.7-7.8
	25-34 years	6.7	5.9-7.6	13.7	9.6-17.9
	35-44 years	6.1	5.3-6.9	27.2	20.9-33.6
	45-59 years	5	4.1-5.8	31	21.9-40.2
Residence	Urban	3.6	3.2-4.0	17.7	14.0-21.3
	Rural	3.5	3.2-3.9	10.7	8.3-13.1
Province	Central	2.5	1.7-3.4	15.1	4.5-25.8
	Copperbelt	3.7	3.2-4.4	10.7	6.0-15.3
	Eastern	2.4	1.7-3.2	14.2	5.9-22.4
	Luapula	5.1	3.9-6.3	11.5	5.6-17.3
	Lusaka	2.9	2.5-3.5	17.2	11.9-22.5
	Muchinga	2.8	2.1-3.6	11.7	1.4-21.9
	Northern	4.4	3.2-5.6	12.3	4.9-19.6
	North-Western	4	3.1-4.9	7.5	2.3-12.7
	Southern	4.5	3.6-5.4	15.3	9.4-21.0
	Western	4.1	3.5-4.8	19.1	12.6-25.7

615 NEAR FULL LENGTH GENOMES OF CHRONIC AND OCCULT HBV FROM HIV PATIENTS IN BOTSWANA

Motswedi Anderson[1], Wonderful T. Choga[1], Sikhulile Moyo[1], Bonolo B. Phinius[1], Tshepiso Mbangiwa[1], Lynnette Bhebhe[2], Theresa K. Sebunya[3], Richard G. Marlink[4], Max Essex[4], Rosemary Musonda[1], Jason T. Blackard[5], Simani Gaseitsiwe[6]

[1]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [2]National University of Science and Technology, Bulawayo, Zimbabwe, [3]University of Botswana, Gaborone, Botswana, [4]Harvard University, Cambridge, MA, USA, [5]University of Cincinnati, Cincinnati, OH, USA, [6]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana

Background: The World Health Organization plans to eradicate viral hepatitis by 2030; therefore, there is a need to study and understand the HBV virus further. It is important to evaluate occult HBV infections (OBI; HBsAg negative but HBV DNA positive) given that it is frequently undiagnosed and rarely treated. Few full-length OBI genomes are available, due to its low viremia. We aimed to molecularly characterize nearly full length HBV genomes from HIV co-infected individuals with chronic or occult HBV in Botswana.

Methods: This was a cross-sectional study of 109 individuals from previous HIV studies conducted at Botswana Harvard Partnership from 2009 to 2012. Full-length (3.2kb) and nearly full-length genomes (~3kb) were amplified by nested PCR. Sequences from OBI participants were compared to GenBank references and participants with chronic HBV (CHB) to identify occult-associated mutations. Signature amino acids (aa) and immune selection pressures were determined using the viral epidemiology signature pattern analysis (VESPA) and DataMonkey, respectively.

Results: HBV genomes from 50 (45.9%) individuals were successfully genotyped; 25 were CHB and 25 were OBI. 27 were whole genomes (18 CHB and 9 OBI), while 23 were near complete (~3kb) (7 CHB and 16 OBI). Among OBI participants, genotype A1 was identified in 12 (48%), D3 in 12 (48%), and E in 1 (4 %). Equivalent genotype proportions were observed in CHB participants. There were 43 OBI associated mutations of which 39 were novel mutations. In total, there were 83 codons under negative immune selection pressure and 2 under positive selection. Of the negatively selected codons in the CHB participants, 4 were in positions with OBI associated mutations. There were significantly more negatively selected codons in the CHB than in the OBI (p value = 0.031) sequences. There were 16 signature aa that distinguished occult from chronic HBV sequences. No drug resistance mutations were detected in this study.

Conclusion: Whole genome sequences representing occult and chronic HBV were compared for the first time in Botswana. Multiple occult-associated mutations, including several novel OBI associated mutations, were identified. There were more negatively selected codons in the CHB sequences. Future studies on large sample sizes and the functional analysis of the OBI associated mutations are warranted to understand the virologic and host genetic factors that influence HBV replication and the development of occult HBV infection.

616 IN SILICO ANALYSIS OF OCCULT HBV ASSOCIATED MUTATIONS IN BOTSWANA

Motswedi Anderson[1], Wonderful T. Choga[1], Sikhulile Moyo[1], Tshepiso Mbangiwa[1], Bonolo B. Phinius[1], Theresa K. Sebunya[1], Joseph Makhema[1], Richard G. Marlink[2], Max Essex[2], Rosemary Musonda[1], Jason T. Blackard[1], Simani Gaseitsiwe[3]

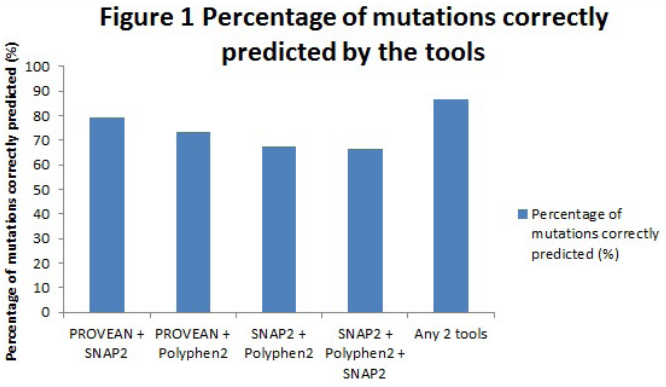
[1]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [2]Harvard University, Cambridge, MA, USA, [3]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana

Background: Occult hepatitis B infections (OBI; HBsAg negative but HBV DNA positive) represent a significant reservoir of undiagnosed and untreated HBV infection; there is a need to identify viral mutations that lead to this. Several studies of OBI have identified many occult-associated mutations than can be characterized functionally due to time-consuming and expensive nature of such studies. Fast, reliable, and cheap in silico approaches, which can predict the effect of amino acids (aa) variants on HBV protein function have been developed. This predicts the best candidates for functional analysis by distinguishing variants with a likely deleterious effect on protein function from those that likely do not have any impact. We sought to determine the functional impact of OBI-associated mutations identified in Botswana using several in silico approaches.

Methods: Three computational tools; PolyPhen2, SNAP2 and PROVEAN were utilized to predict the effects of OBI mutations in protein function. Reliability of these tools was determined by testing their ability to correctly classify 68 previously characterised occult-associated mutations as deleterious from previous studies. Studies that included HBV genotype information for the viral background including in the functional analysis were included for confirmation of tool reliability. The mutation was considered deleterious to protein function if detected by at least 2 tools. Using the same algorithm, we determined the impact of 43 OBI associated mutations we recently identified by comparing whole genome sequences of chronic HBV infected against those of OBI individuals in Botswana.

Results: PolyPhen2 and PAN2 predicted 52 (76.5%) and 55 (80.9%) of previously characterised mutations as deleterious, respectively. PROVEAN detected 65 (95.6%). A total of 59 (86.8%) of the previously characterized mutations were correctly predicted as deleterious by at least two tools (Figure1). In this study, 26 of the 43 OBI associated mutations from Botswana identified were predicted to have an impact on protein function, most of which were in the surface and core regions.

Conclusion: The majority of occult-associated mutations from Botswana were predicted as having an impact on protein function. To our knowledge, this is the first study to use an in silico approach to determine the impact of OBI associated mutations, thereby identifying potential candidates for functional analysis studies.



617 HIGHER RATES OF HBSAG CLEARANCE WITH TDF-CONTAINING THERAPY IN HBV/HIV COINFECTION

Pierre Gantner[1], Laurent Cotte[2], Clotilde Allavena[3], Firouze Bani-Sadr[4], Thomas Huleux[5], Claudine Duvivier[6], Marc-Antoine Valantin[7], Christine Jacomet[8], Veronique Joly[9], Antoine Chéret[10], Pascal Puglièse[11], Pierre Delobel[12], André Cabié[13], David Rey[1]

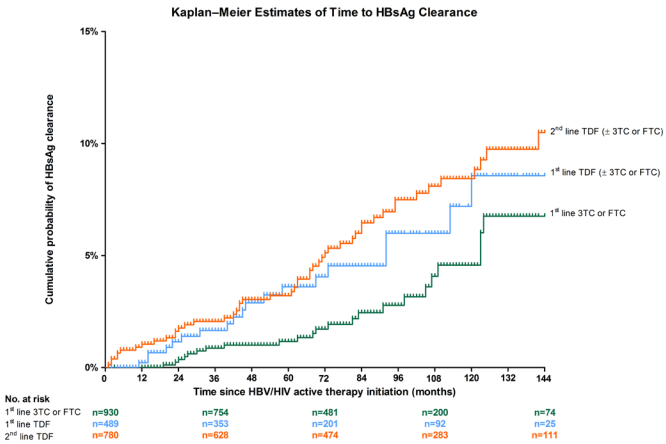
[1]Hôpitaux Universitaires de Strasbourg, Strasbourg, France, [2]Hospices Civils de Lyon, Lyon, France, [3]CHU de Nantes, Nantes, France, [4]CHU de Reims, Reims, France, [5]Centre Hospitalier de Tourcoing, Tourcoing, France, [6]Necker Hospital, Paris, France, [7]Pitié-Salpêtrière Hospital, Paris, France, [8]CHU de Clermont-Ferrand, Clermont-Ferrand, France, [9]Bichat–Claude Bernard Hospital, Paris, France, [10]Hôpital Bicêtre, Le Kremlin-Bicetre, France, [11]Nice University Hospital, Nice, France, [12]Toulouse University Hospital, Toulouse, France, [13]CHU Fort de France, Fort de France, Martinique

Background: HIV-infected individuals are at high risk of developing chronic hepatitis B (HBV) after acute infection, while functional cure of this chronic infection (Hepatitis B surface antigen [HBsAg] clearance, eventually followed by acquisition of anti-hepatitis B surface antigen [Anti-HBs]) is a rare event. Related factors to HBV cure in this setting are not fully characterized, and there are no data on quantitative HBsAg follow-up.

Methods: HIV-infected individuals with chronic HBV infection starting combined antiretroviral-anti-HBV treatment were retrospectively included from the French National Dat'AIDS cohort (NCT02898987). HCV co-infected subjects were excluded. Primary outcomes were confirmed HBsAg loss and Anti-HBs seroconversion. Bayesian analysis was used to study the risk factors for HBsAg clearance.

Results: A total of 1419 subjects were allocated to three HBV therapy schedule: 3TC/FTC only (group 1, n=150), TDF with or without 3TC/FTC (group 2, n=489) and 3TC/FTC as first line followed by adding/switching to TDF as second line (group 3, n=780). Subjects were primarily male (76%), had a median age of 36 years at baseline, and 6% of them were co-infected with hepatitis D virus. Patients were followed-up for a median of 89 months (IQR, 56-118). Median HBV-DNA decreased from 3.64 to 2.06 log IU/mL, from baseline to the end of follow-up, respectively. Overall, 97 individuals cleared HBsAg (0.7/100 patient-years), of whom, 67 seroconverted for Anti-HBs (0.5/100 patient-years). HBsAg clearance occurred in 25, 19 and 53 individuals in group 1, 2 and 3 at a median time of 73, 45 and 137 months, respectively. A high CD4 nadir, a short delay between HBV diagnosis and treatment, a longer time on HBV therapy, an African origin and TDF-based therapy were independent predictors of HBsAg clearance (Probability of odds ratio [OR]>1, >95%). Bayesian analysis suggested a 99% probability that TDF-based regimen as first line (OR, 3.03) or second line (OR, 2.95) increased rates of HBsAg clearance at 72 months when compared to 3TC/FTC alone as first line (Figure). Longitudinal follow-up of quantitative HBsAg on treatment showed a slow but significant decrease in HBsAg serum levels (-1 IU/mL per year).

Conclusion: HBsAg clearance rates were low while on HBV therapy; higher CD4 nadir, prompt initiation of HBV therapy, mainly with TDF-based regimen, improved HBsAg clearance and Anti-HBs seroconversion. Quantitative HBsAg significantly decreased, therefore could be a prognostic factor of HBV clearance.



618 HIGH HBV AND HIV SUPPRESSION WITH TREATMENT OF HIV/HBV COINFECTION IN B/F/TAF STUDIES

Jürgen K. Rockstroh[1], Paul E. Sax[2], Eric Daar[3], Sharon Walmsley[4], Kimberly Workowski[5], Chloe Orkin[6], Jose R. Arribas[7], Edwin DeJesus[8], David Wohl[9], Jean-Michel Molina[10], David Piontkowsky[11], Xuelian Wei[11], Hal Martin[11], Andrew Cheng[11], Erin Quirk[11]

[1]Bonn University Hospital, Bonn, Germany, [2]Brigham and Women's Hospital, Boston, MA, USA, [3]Harbor–UCLA Medical Center, Torrance, CA, USA, [4]Toronto General Hospital, Toronto, ON, Canada, [5]Emory University, Atlanta, GA, USA, [6]Royal London Hospital, London, UK, [7]La Paz University Hospital, Madrid, Spain, [8]Orlando Immunology Center, Orlando, FL, USA, [9]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [10]Hôpital Saint-Louis, Paris, France, [11]Gilead Sciences, Inc, Foster City, CA, USA

Background: HBV is a common coinfection in HIV patients. We report HBV and HIV outcomes in ART-naïve and experienced HIV/HBV-coinfected subjects enrolled in 4 studies of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF).

Methods: HBV serologies were collected at baseline (BL) and week (W) 48 in 4 B/F/TAF studies: Studies 1489 (B/F/TAF vs abacavir/lamivudine/ dolutegravir [DTG, ABC/3TC/DTG] as initial therapy), 1490 (B/F/TAF vs F/TAF+DTG as initial therapy), 1878 (switch from PI + 2 NRTIs to B/F/TAF vs stay on BL regimen [SBR]), and 1844 (maintain ABC/3TC/DTG vs switch to B/F/TAF). Studies 1490 and 1878 permitted HBV-infected patients to enroll; HBV coinfection was excluded from Studies 1489 and 1844 due to ABC/3TC in control arms. HBV seropositive patients had HBV DNA at baseline and W48. Proportion with W48 HBV DNA <29 IU/mL using missing=excluded data imputation was pre-specified for studies 1490 and 1878. HBV serology and DNA results were analyzed to identify incident HBV infections in all 4 studies through W48.

Results: In Study 1490, 14 naïve coinfected subjects (n=12 HBV surface antigen [HBsAg] positive and n=2 HBsAg-/core antibody+ and HBV DNA detectable) were randomized to B/F/TAF (n=8) or DTG+F/TAF (n=6). 1 HBsAg positive subject (DTG+F/TAF group) discontinued study at Day 68. At W48, 11/13 (85%) had HBV DNA <29 IU/mL. 2/11 had HBsAg loss. In Study 1878, 14 treatment experienced coinfected subjects were randomized to stay on BL regimen (SBR, n=6) or switch to B/F/TAF (n=8). 2/14 had HBV DNA >29 IU/mL at BL: 1 (SBR) who discontinued at Day 1 and had no post BL HBV DNA, and 1 (B/F/TAF) who at W48 had HBV DNA ≥29 IU/mL. 12/12 with suppressed HBV DNA at BL maintained HBV DNA <29 IU/mL at W48; none had HBsAg conversion. W48 HIV-1 RNA was <50 copies/mL in 25/28 of those with HIV/HBV coinfection at BL in these two studies (89%). In these two trials plus Studies 1489 and 1844, no patient receiving B/F/TAF, F/TAF or F/TDF acquired HBV. One naïve subject randomized to ABC/3TC/DTG acquired HBV infection by W48.

Conclusion: High rates of HBV suppression were achieved at W48 in naïve HIV/HBV coinfected patients treated with F/TAF regimens. HBV suppression was maintained in experienced patients switching to B/F/TAF. At W48, HIV suppression among HBV coinfected patients was high and comparable to those with HIV mono-infection. Further studies of B/F/TAF and other regimens containing F/TAF for HBV treatment and prevention in HIV-infected patients are warranted.

619 PROGRESSIVE HBSAG LOSS IN HIV-HBV COINFECTED INDIVIDUALS ON TDF-INCLUSIVE cART

Jennifer Audsley[1], Anchalee Avihingsanon[2], Margaret Littlejohn[1], Scott Bowden[1], Gail Matthews[3], Christopher K. Fairley[4], Sharon R. Lewin[1], Joseph Sasadeusz[1]

[1]Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia, [2]HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [3]Kirby Institute, Sydney, NSW, Australia, [4]Alfred Hospital, Melbourne, VIC, Australia

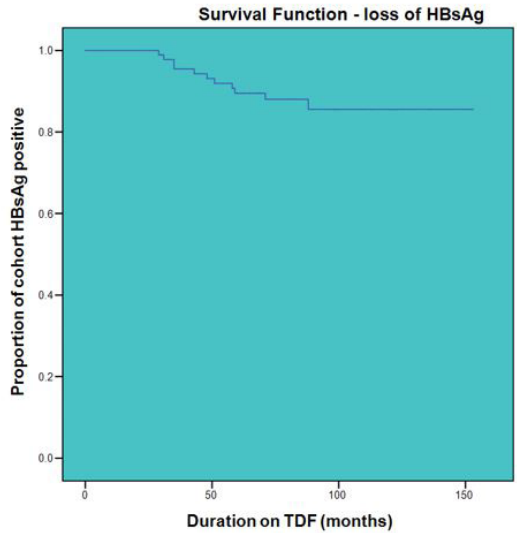
Background: Tenofovir disoproxil fumarate (TDF) is effective in suppressing HIV and HBV replication in HIV-HBV co-infection, although HBV DNA can persist in some individuals on TDF-containing combination antiretroviral therapy (ART). HBV resistance to TDF has not been reported to date. We initiated this study to assess long-term HBV suppression and the frequency of HBsAg seroconversion on TDF

Methods: We enrolled 92 HIV-HBV co-infected participants on or about to commence TDF-containing ART from Australia (n=41) and Thailand (n=52) in a prospective longitudinal study, with access to pre-TDF samples and data for those who commenced TDF prior to study entry. Participants were followed every 6 months for 2 years and then annually to 5 years, with clinical and laboratory assessments including HBV DNA, HBs and HBe serology, CD4 count and HIV RNA. This study compares follow-up at 2 years (Yr2) and 5 years (Yr5)

Results: Data were available for 92.4% (n=85) and 78.3 % (n=72) of the cohort at Yr2 and Yr5, respectively. The median [IQR] duration on TDF was 6.8 years (5.9-10.0) at Yr 5. 91.8% had undetectable HBV DNA (<20 IU/ML) at Yr 2 and this increased to 98.5% by Yr5. The one individual with detectable HBV DNA at Yr5 had a viral load too low (31 IU/ml) for sequencing, detectable HIV RNA (33,957 copies/ml), reported adherence to ART but had no mutations associated with HIV-related ARV resistance. By Yr 2 and 5, 7 and 11 participants respectively had lost HBsAg – 12.0% of the cohort by Yr5. Acquisition of HBsAb was also observed in two of these participants at Yr2, and a further two participants by Yr5. Two further participants gained sAb but did not lose sAg. Median (range) duration on TDF to HBsAg loss was 48 months (29-88) (survival curve - Figure 1). HBe serology changes at Yr5 were observed in 9 participants, including HBeAg loss/seroconversion (n=2), gain of HBeAg (n=4) and loss or gain of HBeAb (n=3). There were 3 deaths in the cohort, 2 from liver disease (hepatoma and end-stage liver disease) and 1 suicide. ALT, AST, ALP, GGT and LDH were all significantly lower at Yr 5 compared Yr 2 (Wilcoxon signed rank test)

Conclusion: Detectable HBV DNA after 5 years of follow-up was rare in HIV-HBV co-infected participants on TDF-containing ART. HBV serological changes continued over time and liver biochemistry improved, however liver-related deaths were still observed. Further follow up will be needed to determine if improvement continues with very long-term duration on TDF.

Figure 1 – Kaplan-Meier survival curve, time to HBsAg loss.



620 DETERMINANTS OF LIVER COMPLICATIONS AMONG HIV/HEPATITIS B-COINFECTED PATIENTS

Vincent Lo Re[1], Craig W. Newcomb[1], Dena M. Carbonari[1], Jason A. Roy[1], Mari Kitahata[2], Joseph Lim[3], Michael J. Silverberg[4], Angel Mayor[5], Michael A. Horberg[6], Edward R. Cachay[7], Mark Hull[8], Richard D. Moore[9], Marina Klein[10], H. Nina Kim[2]

[1]University of Pennsylvania, Philadelphia, PA, USA, [2]University of Washington, Seattle, WA, USA, [3]Yale University, New Haven, CT, USA, [4]Kaiser Permanente Northern California, Oakland, CA, USA, [5]Universidad Central del Caribe, Bayamon, Puerto Rico, [6]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [7]University of California San Diego, San Diego, CA, USA, [8]University of British Columbia, Vancouver, BC, Canada, [9]Johns Hopkins University, Baltimore, MD, USA, [10]McGill University, Montreal, QC, Canada

Background: Chronic hepatitis B (HBV) remains a leading cause of end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC) among HIV/HBV patients. Yet, the factors contributing to these liver complications in this group have not been thoroughly examined.

Methods: We evaluated the determinants of liver complications in HIV and HBV (positive HBV surface antigen, e antigen, or HBV DNA) coinfected patients in 9 US and Canadian clinical cohorts of the North American AIDS Cohort Collaboration on Research and Design that validated ESLD (ascites, spontaneous bacterial peritonitis, variceal bleed, hepatic encephalopathy) and HCC diagnoses from 1996-2010. Our outcome was a composite of first occurrence of ESLD or HCC diagnosis. Multivariable Cox regression was used to examine hazard ratios (HRs) and 95% confidence intervals of hypothesized factors associated with ESLD/HCC, including age ≥40 years, male sex, non-black/non-Hispanic race, diabetes, HIV RNA and CD4 count (as time-updated variables), history of at-risk alcohol use, hepatitis C coinfection, and baseline liver fibrosis by FIB-4. We also performed Cox regression to determine if increasing consecutive time with suppressed HIV RNA (≤500 copies/mL) on antiretroviral therapy (ART) was associated with lower rates of ESLD/HCC.

Results: Among 3,123 HIV/HBV patients (85% male; 38% non-black/non-Hispanic; 83% prescribed ART; 53% prescribed tenofovir-based ART) followed for 11,343 person-years, 185 incident ESLD/HCC events occurred (incidence rate=16.3 [14.0-18.8] events/1,000 person-years). Non-black/non-Hispanic race (HR=1.91 [1.34-2.73]), higher baseline FIB-4 (>3.25: HR=2.63 [1.72-4.03]; 1.45-3.25: HR=1.46 [1.01-2.10]), and lower CD4 count (<200 cells/μL: HR=4.09 [2.49-6.71]; 201-499 cells/μL: HR=1.96 [1.22-3.17]) were associated with increased rates of ESLD/HCC. HRs were similar when the cohort was restricted to the 1,643 patients on tenofovir-based ART. Increasing consecutive time with suppressed HIV RNA on ART was associated with a lower risk of ESLD/HCC (<6 months: HR=0.87 [0.54-1.40]; 6-12 months: HR=0.66 [0.36-1.22]; >12 months: HR=0.53 [0.35-0.81]; test for trend p=0.002).

Conclusion: Non-black/non-Hispanic race, higher baseline FIB-4, and lower time-updated CD4 count were risk factors for ESLD/HCC among HIV/HBV patients. Patients with >12 months of viral suppression were significantly less likely to develop ESLD/HCC. Clinicians should ensure that HIV/HBV patients maintain HIV suppression on ART to reduce their risk of liver complications.

621 HIGH PREVALENCE OF ADVANCED LIVER DISEASE AMONG AN HIV/HBV REAL-WORLD COHORT

Mamta K. Jain[1], Mandana Khalili[2], Raymond T. Chung[3], Kranthi Vysyaraju[1], David Wong[4], Mauricio Lisker-Melman[5], Mark Sulkowski[6], Marc Ghany[7], Richard K. Sterling[8]

[1]University of Texas Southwestern, Dallas, TX, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Toronto General Hospital, Toronto, ON, Canada, [5]Washington University in St Louis, St Louis, MO, USA, [6]Johns Hopkins Hospital, Baltimore, MD, USA, [7]NIH, Bethesda, MD, USA, [8]Virginia Commonwealth University, Richmond, VA, USA

Background: The HIV/HBV Cohort is a prospective ancillary study of the Hepatitis B Research Network (HBRN) whose goal is to define the clinical, virological, serological and histological characteristics of a cohort of HBV/HIV patients in North America on combination antiretroviral therapy (cART). We report on the HIV/HBV prescreened participants who did not enroll in the study.

Methods: We enrolled HIV/HBV patients from 8 centers across North America, obtained liver biopsies, and examined clinical, virological and serological characteristics. Those who were prescreened but did not enroll in the study were examined as a representation of a "real world cohort". Reasons for not participating in the ancillary study were obtained. A retrospective descriptive

analysis of a subgroup of non-enrollers was performed for clinical and serological characteristics and factors associated with hepatitis B e antigen (HBeAg)-positivity was assessed by logistic regression.

Results: Of the 353 subjects prescreened, 139 enrolled in the cohort and biopsies were obtained in 119. Enrolled patients were predominately male (92%), black (50%), HBeAg+ (62%) and had a mean age 49 (28-70) years. On biopsy 24% had evidence of Ishak 3-6 fibrosis. Clinically, some had detectable HBV DNA (20%) and HIV RNA (25%). Mean CD4 was 558 cells/μL (38-1520), ALT 36 IU (8-223) and AST 35 IU (13-202). Of all patients prescreened, 211 did not enroll in the study. The reasons for non-enrollment into the cohort study included: refusing liver biopsy (31%), hepatic decompensation (4%), hepatocellular cancer (2%), failure to consent (63%). Data was collected on 127 HBsAg+ non-enrollers who were predominately male (84%), black (36%), and on cART (99%). Half were HBeAg+ (51/103), 22% (21/87) had evidence of cirrhosis of which 24% (5/21) had hepatic decompensation and 1 had liver cancer without cirrhosis, 36% had detectable HIV RNA. Mean CD4 was 478 cells/μL (3-1428), ALT 38 IU (8-284), and AST 42 IU (15-229). HBeAg+ was not associated with gender, race, or liver function tests or cirrhosis but was significantly associated with HBV DNA detectability and age (see Table).

Conclusion: One fourth of HIV/HBV patients in this real world cohort had evidence of advanced liver disease. Of those in which HBeAg status was available, half were HBeAg+, which was independently associated with detectable HBV DNA and age. Focused efforts to reduce HIV and HBV viral load in younger HIV/HBV infected patients is needed to improve HBV outcomes in this group.

Table	Overall (n=127); n (%)	HBeAg positive (n=51); n (%)	Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)
HBV DNA detectable				
no	75 (61)	21 (41)	Reference	
Yes	48 (39)	30 (59)	6.8 (2.74-16.9)**	5.79 (2.21-15.1)**
HIV undetectable				
No	46 (36)	25 (49)	Reference	
Yes	81 (64)	26 (51)	0.35 (0.15-0.79)*	0.74 (0.28-1.99)
Age Mean	48.7 (22-67)	46.1 (22-67)	0.95 (0.91-0.99)*	0.95 (.91-1.0)*

*<.05 **<.001

622 HEPATITIS DELTA INFECTION IN PATIENTS WITH HIV/HBV COINFECTION

Giovanni B. Gaeta[1], Milensu Shanyinde[2], Giuseppina Brancaccio[1], Massimo Puoti[3], Antonella D'Arminio Monforte[4], Andrea De Luca[5], Alessandra Vergori[6], Stefano Rusconi[4], Antonio Mazzarelli[6], Antonella Castagna[7], Andrea Antinori[6], Alessandro Cozzi-Lepri[2]

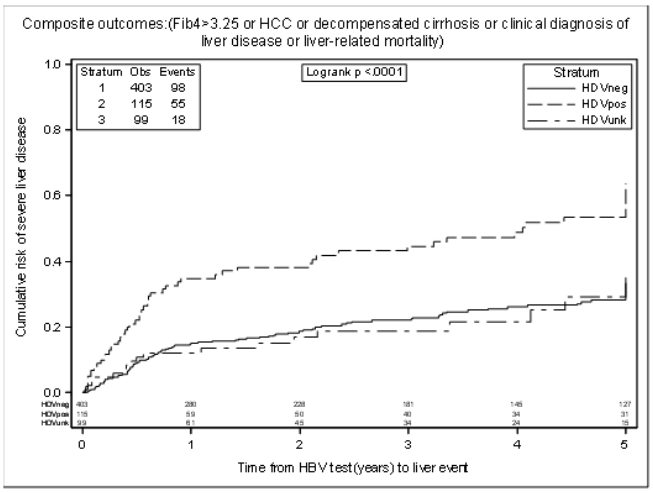
[1]University of Campania Luigi Vanvitelli, Naples, Italy, [2]University College London, London, UK, [3]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy, [4]University of Milan, Milan, Italy, [5]Siena University Hospital, Siena, Italy, [6]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, [7]San Raffaele Vita-Salute University, Milan, Italy

Background: Hepatitis Delta virus (HDV) co-infects about 20 million HBsAg+ individuals worldwide. HIV infected persons with HBV coinfection are at risk for HDV. We explored the prevalence of HDV infection and its clinical impact in the ICONA cohort.

Methods: Anti-HDV status was assessed among HBsAg+patients enrolled in1997-2015.We performed a cross-sectional analysis to compare baseline (the date of first HBV test) characteristics of HBV+/HDV+ vs. HBV+/HDV-patients. The proportion of patients HDV+ amongst patients who were HBV+ per year of enrolment was also calculated. Composite clinical outcome (CCO) was defined as the occurrence of any of the following events: Fib4 score >3.25; clinical diagnosis of cirrhosis; decompensation;hepato-carcinoma (HCC) or death. Kaplan Meier method was used to plot the time to develop the CCO,stratified by anti-HDV status. Univariable and multivariable Cox regression models adjusted for age, gender, nationality, region, education, CD4 count, HIV-RNA viral load, smoking status,alcohol consumption , mode of HIV transmission and HCV infection status, were fitted and relative hazards (RH) shown.

Results: Among 13,558 HIV positive patients enrolled as of September 2015, 10,988 were HBsAg-negative, 1,953 were nottested for HBsAg and 617 patients were HBsAg-positive; of these, 115 (18.6%) wereanti-HDVpositive, 403 (65.3%) anti-HDV negative and 99 (16.0%) not tested for HDV. Proportions of anti-HDV positive cases tended to decrease from the year 1997 to 2011 (from 28% to 4%) then appear to increase to 8% in the period 2012-2015. Overall, 171 patients (28%) developed the CCO over time of whom 55/115 (48%) HDV positive, 98/403 (24%) HDV negative and 18/99 (18%) HDV unknown (p<.001, Figure).In unadjusted Cox regression analysis, RH was 2.34 95%CI:1.68-3.26; the association was attenuated after controlling for HCV coinfection (RH=1.46; 95%CI:0.98, 2.17). Other factors independently associated with higher risk of CCO were: male gender, older age, lower CD4 count, alcohol use and smoking. In the subset of people who received anti-HBV therapy, 43/79 (54%) HDV+ patients and 84/320 (26%) HDV-neg patients developed CCO (OR=3.36; 95%CI:1.95-5.78).

Conclusion: Presence of anti-HDV antibodies in HIV-coinfected individuals is a marker of faster progression to severe liver disease and death even in participants who received anti-HBV therapy.



623 GAIN OF POSITIVE CHARGES IN HBSAG C-TERMINUS CORRELATES WITH HBV-INDUCED LIVER CANCER

Romina Salpini[1], Luca Carioti[1], Marianna Aragri[1], Domenico Di Carlo[1], Luna Colagrossi[1], Giuseppina Cappiello[2], Pascale Trimoulet[3], Herve J. Fleury[3], Simona Francioso[1], Loredana Sarmati[1], Massimo Andreoni[1], Mario Angelico[1], Francesca Ceccherini Silberstein[1], Carlo F. Perno[1], Valentina Svicher[1]

[1]University of Rome Tor Vergata, Rome, Italy, [2]Sandro Pertini Hospital, Rome, Italy, [3]Pellegrin Hospital, Bordeaux, France

Background: Gain of positively charged amino acids (aa) can alter the folding of a transmembrane protein domain. HBsAg C-terminus is a hydrophobic transmembrane domain, composed by alpha-helices, crucial for HBsAg secretion. HBsAg misfolding in endoplasmic reticulum (ER) membrane can impair HBsAg secretion and in turn favor HBV-induced hepatocellular carcinoma (HCC). The role of mutations associated with gain of charged aa in HBsAg C-terminus on HBV-induced HCC onset is unknown.

Methods: We analyze 807 HBV chronically infected patients from routine clinical practice: 28 with HCC (78.6% D; 21.4% A), and 779 patients without HCC (79.8% D; 20.2% A). Mutations associated with gain of charged aa in HBsAg C-terminus (aa189-226) are evaluated. Multivariable logistic regression model is used to assess association of mutations with HCC. The stability of a domain in a membrane is predicted by estimating hydrophobicity profiles of HBsAg C-terminus (Black,1991). I-Tasser is used to assess three-dimensional HBsAg structures (aa:1-226) and their stability (ΔΔG[wt-mutated]<0 indicating decreased stability in presence of mutation based on Quan,2016).

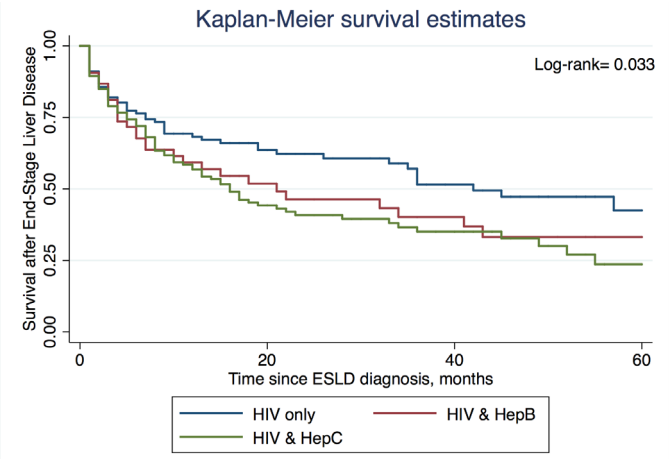
Results: The acquisition of ≥1 positively charged aa at HBsAg C-terminus positions 204, 207, and 210 strongly correlates with HCC (71.4% with HCC vs 30.2% without HCC, P<0.001). Multivariable analysis confirms this association stratifying for patients'demographics, HBV genotype, serum HBV-DNA and anti-HBV drugs use (OR[95%CI]:6.3[2.6-15.3], P<0.001). The acquisition of positively charged aa results from S204R, S207R and S210R mutations, found in 14.3%, 28.6% and 28.6% of HCC-patients, respectively. S204R, S207R and S210R decrease the hydrophobicity index of HBsAg C-terminus respect to wt (S204R:16.0, S207R:16.0, S210R:16.2 vs wt:16.4), and ΔΔG values (ΔΔG[S204R-wt]=-0.27; ΔΔG[S207R-wt]=-0.11; ΔΔG[S210R-wt]=-0.14). Furthermore, a shortening of membrane-spanning alpha-helix motif is observed in presence of S204R, S207R and S210R (predicted alpha-helix length: aa209-224 for S204R,

S207R and S210R vs 205-225 for wt). Overall, this suggests an impaired HBsAg C-terminus stability in presence of these mutations.
Conclusion: Gain of positively charged aa at specific HBsAg C-terminus positions tightly correlates with HCC, by affecting the folding of this domain in ER membrane. These mutations might affect HBsAg secretion and contribute to HBV-related carcinogenesis. Their detection may help identifying patients at higher HCC-risk that may deserves more intense liver evaluation.

624 SURVIVAL AFTER END-STAGE LIVER DISEASE IN ADULTS WITH HIV: DATA FROM THE NA-ACCORD

Eve-Marie A. Benson[1], Marina Klein[2], Mari Kitahata[3], Richard D. Moore[1], Vincent Lo Re[4], Michael A. Horberg[5], Angel Mayor[6], Michael J. Silverberg[7], H. Nina Kim[3], Joseph J. Eron[8], Edward R. Cachay[9], Mark Hull[10], Stephen J. Gange[1], Keri N. Althoff[1]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]McGill University, Montreal, QC, Canada, [3]University of Washington, Seattle, WA, USA, [4]University of Pennsylvania, Philadelphia, PA, USA, [5]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [6]Universidad Central del Caribe, Bayamon, Puerto Rico, [7]Kaiser Permanente Northern California, Oakland, CA, USA, [8]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [9]University of California San Diego, San Diego, CA, USA, [10]University of British Columbia, Vancouver, BC, Canada

Background: Liver disease is a leading cause of death among persons with HIV. Our objective was to investigate whether survival after end-stage liver disease (ESLD) differs among adults with HIV according to the presence of HBV and HCV coinfection.
Methods: Adults from 12 cohorts contributing data to the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) from 1 Jan 2000 to 31 Dec 2009 with validated ESLD diagnosis were included. Participants were followed from ESLD diagnosis until death, loss to follow up (defined as 1.5 years after last CD4 or HIV RNA measurement), or administratively censored at 5 years after diagnosis or 31 Dec 2009, whichever came first. Coinfection with HBV (positive HBV surface or e antigen or detectable HBV DNA) or HCV (positive HCV antibody test, detectable HCV RNA,or quantifiable HCV genotype), demographic characteristics, HIV transmission risk, CD4 count, detectable (>400 copies/mL) HIV RNA, platelet count, antiretroviral therapy (ART), alcohol use and smoking at ESLD diagnosis, and calendar time (in two year intervals) were accounted for in multivariate pooled logistic regression models to estimate the hazard odds ratios (aHOR) of death. Kaplan Meier survival estimates were plotted overall and stratified by HBV and HCV coinfection. Triply infected adults were excluded from these analyses (n=27).
Results: A total of 298 adults with validated ESLD diagnoses contributed 5921 person-months and 159 deaths (median time to death = 23 [17, 36] months); 35% were infected with HIV only, 16% had HBV coinfection, and 49% had HCV coinfection. Among participants, 84% were male and 49% were white. 45% were not on ART at ESLD diagnosis, 19% were on ART but had detectable HIV RNA, and 35% were on ART and had suppressed HIV RNA. In multivariate models, coinfection with HBV (aHOR=1.17 [0.70, 1.94]) and HCV (aHOR=1.45 [0.95, 2.22]) were associated with a higher risk of death compared with HIV monoinfection, as was smoking (aHOR=2.77 [1.39, 5.49]). After restricting to participants with HIV RNA ≤400 copies/mL at ESLD diagnosis and adjusting for confounders, the risk of death associated with HBV increased (aHOR=1.50 [0.62, 3.64]) but was unchanged with HCV (aHOR=1.45 [0.68, 3.14]).
Conclusion: Although not statistically significant, the magnitude of the estimates of the risk of death suggest a trend towards a decreased survival among those with HBV or HCV coinfection at the time of ESLD diagnosis, even among those with controlled HIV RNA.



625 HAV EPIDEMICS AMONG MSM : HIGH PREVALENCE OF HIV INFECTED PATIENTS

Veronique Lemee[1], Anne-Marie Roque-Afonso[2], Elodie Alessandri-Gradt[1], Lina Mouna[2], Laure Izquierdo[2], Odile Goria[1], Hélène Montialoux[1], Valerie Delbos[1], **Thomas Mourez**[1], Jeremie Leporrier[1], Jean-Christophe Plantier[1], Ghassan Riachi[1]
[1]Rouen University Hospital, Rouen, France, [2]AP–HP, Paris, France

Background: Transmission of HAV is mainly via fecal-oral route, including direct person-to-person contact. The population of men who have sex with men (MSM) whose sexual practices favors the fecal-oral transmission of the virus, is highly at risk of HAV infection. Since the summer of 2016, many European countries observed a growing number of hepatitis A infections among MSM. In December 2016, the European Center for Disease Control and Prevention (ECDC) reported the circulation of two strains of HAV genotype IA which resulted in the emergence of several epidemic foci in various European countries including the United Kingdom, Germany and the Netherlands. At the same date, we observed the first cases in Normandy, France, where the epidemic started in the country.
Methods: Risk factors, behavioral and biological data (including viral co-infections) collected for each HAV+ patient hospitalised in the Rouen University Hospital were analysed. A phylogenetic analysis of the amplified HAV positive strains was operated by the French National Reference Center for HAV, and compared to the current European data.
Results: From december 2016 to september 2017, 41 patients (Sex ratio M/F=40/1) with confirmed HAV were described in the Seine-Maritime county. Among them 35 were admitted in our hospital. A majority of the patients (n=22; 62%) described themself as MSM. All of them were infected with a genotype IA HAV strain VRD 521 2016, which is one of the epidemic strain that circulates in Europe since 2016 in the MSM community. Nine of these infected MSM (29%) were also infected with HIV and treated by HAART.
Conclusion: Sexual transmission is becoming a major route of transmission of hepatitis A in countries where the infrastructures reduce the risk of fecal contamination through the environment. Sexual behaviours must be included systematically when questionning about the origin of HAV epidemics. Regarding the high number of HIV+ among patients hospitalized with HAV infection, systematic screening for HBV, HCV and HIV should be proposed. Vaccination and control of the seropositivity against HAV should be systematically proposed among HIV MSM.

626 ACUTE HEPATITIS A AMONG HIV-INFECTED THAI MSM IS LINKED TO MSM IN EUROPE AND TAIWAN

Donn Colby[1], Nawarat Posuwan[2], Carlo Sacdalan[1], Jintana Intasan[1], Eugène Kroon[1], Tanyaporn Wansom[3], Nittaya Phanuphak[1], Jintanat Ananworanich[4], Merlin L. Robb[5], Praphan Phanunphak[1], Yong Poovorawan[2]
[1]Thai Red Cross AIDS Research Center, Bangkok, Thailand, [2]Chulalongkorn University, Bangkok, Thailand, [3]Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, [4]US Military HIV Research Program, Bethesda, MD, USA, [5]US Military HIV Research Program, Silver Spring, MD, USA

Background: In 2016-17 outbreaks of acute Hepatitis A virus (HAV) infection were reported among men who have sex with men (MSM) in Taiwan, the

Netherlands, Germany, and the United Kingdom. Phylogenetic analysis linked the outbreaks in Asia and Europe with transmission presumably through oral-anal sexual contact. No outbreak of HAV had been reported in the Bangkok metropolitan area since 2002.

Methods: The RV254/SEARCH010 cohort has recruited participants with acute HIV infection (AHI) since 2009. A total of 478 individuals enrolled through June 2017. No cases of acute HAV (anti-HAV IgM+ with symptoms of acute hepatitis) were identified until 2017. HAV phylogenetic analysis used a 378 bp sequence of vp1 compared to reference sequences from GenBank. The phylogenetic tree was produced in MEGA V6.0.

Results: Five cases of acute HAV were identified in the cohort in March-May 2017. All were symptomatic, with abdominal pain (n=5), fatigue (5), jaundice (3), fever (3), and nausea/vomiting (2) most frequently reported. All were male, median age 37 years (range 20-43). None had recent travel outside of Thailand. All reported male sexual partners within the preceding 3 months. Median (range) laboratory abnormalities included peak ALT 760 (572-2611) IU/L, total bilirubin 5.7 (3.4-7.8) mg/dl, and direct bilirubin 5.4 (2.5-5.9) mg/dl. Four cases were on antiretroviral therapy a median 19.5 (range 7-53) months; all with HIV RNA <20 copies/ml and median (range) CD4 804 (602-1008) cells/mm^3. The fifth case was diagnosed with acute HAV simultaneously with AHI and had HIV RNA 7.2 $\log_{10}$ copies/ml and CD4 132 cells/mm^3. HAV was sequenced from 3 cases; phylogenetic analysis showed 100% concurrence between the Bangkok MSM cases with HAV in recent Taiwan and Netherlands outbreaks (Figure 1). An additional female case in Bangkok not in the cohort and not known to have HIV (ChulaCU22-HAV17) was diagnosed in June 2017 with 99.7% similarity to the MSM cases on the 378 bp sequence and 99.9% similarity to the first identified MSM case on a longer 1110 bp sequence.

Conclusion: This is the first outbreak of acute HAV reported among HIV-infected MSM in SE Asia, and the first HAV outbreak locally transmitted in Bangkok since 2002. Phylogenetics shows that the Bangkok HAV cases are linked to outbreaks among MSM in Europe and Taiwan, most likely imported to Thailand by one or more MSM and transmitted locally via sexual networks.

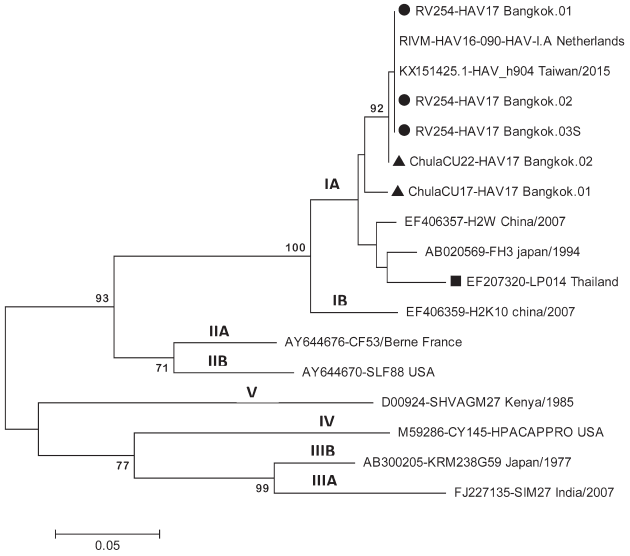


Figure 1: Phylogenetic analysis of selected hepatitis A isolates. ● = MSM case Bangkok 2017; ▲ = non-MSM case Bangkok 2017; ■ = Thailand case from outbreak prior to 2015

627 SEROPREVALENCE AND RISK FACTORS OF HEPATITIS E AMONG PLHIV IN SOUTH WESTERN FRANCE

Marc Vareil[1], Florence Abravanel[2], Heidi Wille[1], Anne-Christine Jaouen[1], David Leyssene[1], Jacques Izopet[2]

[1]Centre Hospitalier de la Côte Basque, Bayonne, France, [2]Toulouse University Hospital, Toulouse, France

Background: Hepatitis E virus is a common fecal-oral transmitted virus highly prevalent in southern France. Study's objective is to investigate the prevalence and infection's route of HEV in people infected by HIV (PLHIV) and the interaction with HBV and HCV.

Methods: Design: Cross sectional study in a single center in southern France. **Patients:** Patients attending at the ID department at "Centre Hospitalier de la Côte Basque" were included after writing consent from July 2016 to January 2017. Patient were tested for anti HEV IgG /IgM (Wantai Elisa) by the FRC for Hepatitis E. HBV, HCV and Syphilis were also tested with regular follow-up. HEV RNA assay was performed for anti-HEV IgM positive patients. Self-administered questionnaires were realized the same day to investigate routes of contamination. **Definition of cases:** Patients positive for HEV IgG, HCV IgG, HBc IgG and syphilis (TPHA/VDRL tests) were considered as exposed for these infections. **Statistical analysis:** Factors associated with HEV status were determined by multivariate analysis. **Clinical Trial number:** NCT02847507

Results: 307 patients were included. Patients were 52 years old,72% were men, 99,8% were on antiretroviral, median CD4 count was 744 c./mm^3, and 92% of patients were undetectable for HIV. Prevalence for HEV, HCV, HBc and TPHA were 21, 19, 37 and 24% respectively, 11.7% were positive for HEV and another hepatitis virus. In univariate analysis, diet, countries, and sexual orientation weren't associated with HEV. HEV+ patients were older, had significantly: higher transaminases, lower CD4, CD8 counts but same CD4/CD8 ratio. Seafood once week and pigs' meat bought at the farm were associated with HEV while CD4<200 c./mm^3 was negatively associated with HEV. In multivariate analysis, patient with markers of syphilis, were more likely to be HEV+, OR=2.84 and 3.8 for TPHA and VDRL ($p < 0.05$). Eight of the 52 HCV+, were positive for HEV but fibroscore® wasn't different (0.41 Vs 0.31, p=0.20, F2).

Conclusion: Prevalence of HEV is high in PLHIV, and often associated with exposure to other hepatitis. HEV is associated with lower CD4 count but not with CD4/CD8 ratio and fibrosis score in HIV/HCV patients. Usual routs of transmission were not found in our settings, but past history of syphilis was associated with HEV status, suggesting possible similar ways of transmission.

Table 1: Risf factor of HEV, partial dotas.

	univariate analysis			Multivariate analysis Model 1 (VDRL)			Multivariate analysis Model 2 (TPHA)		
Variables	**OR**	**IC 95**	***p***	**OR VDRL**	**IC 95**	***p***	**OR TPHA**	**IC 95**	***p***
Age < 50	1,94	0,98-3,85	*0,058*	0.87	1,01-3,46	***0,04***			
Drugs	**2,21**	0,75-6,5	*0,15*						
Rural	0,56	0,2-1,5	*0,25*	0.41	0,18-0,93	***0,03***			
MSM	0,99	0,88-1,11	*0,9*						
Seafood>1w	**2,12**	0,96-4,67	*0,06*						
At the farm	2	0,99-4,04	***0,05***	2,05	1,07-3,93	***0,03***			
CD4 > 800	0,55	0,28-1,06	*0,08*	0,53	0,29-0,98	***0,04***			
Nad 200	0,47	0,22-0,98	***0,04***	0,5	0,25-0,1	***0,05***			
Viral Load	0,24	0,03-2,17	*0,2*						
HAV	1,09	0,51-2,3	*0,83*						
TPHA	**2,1**	0,82-5,32	*0,12*				**2,84**	1,57-5,14	***<0,05***
VDRL	**3,18**	1,02-9,88	***0,05***	**3,79**	1,66-8,66	***0,002***			

628 HEPATITIS C VIRUS AND HUMAN PEGIVIRUS 2 SURVEILLANCE IN A LARGE CAMEROONIAN COHORT

Mary Rodgers[1], Vera Holzmayer[1], Ana Vallari[1], Ana Olivo[1], Kenn Forberg[1], Jill Fuhrman[1], Kelly Coller[1], Bih Awazi[2], Jules Bertrand Kenmegne Sidje[2], Matthew Frankel[1], Michael Berg[1], Dora Mbanya[2], Nicaise Ndembi[3], Gavin Cloherty[1]

[1]Abbott Labs, Abbott Park, IL, USA, [2]University of Yaoundé, Yaounde, Cameroon, [3]Institute of Human Virology Nigeria, Abuja, Nigeria

Background: Hepatitis C virus (HCV) is a major global health burden that threatens more than 100 million people with chronic infections and human pegivirus 2 (HPgV-2) is a recently discovered flavivirus largely restricted to HCV patients. Estimates of the global burden of HCV and HPgV-2 rely on surveillance of diverse populations; however, limited data are available on the prevalence of these viruses in sub-Saharan Africa. To characterize the relative prevalence of HCV and HPgV-2 in South Cameroon, well characterized archived samples were screened for HCV RNA, and positive specimens were then screened for HPgV-2 antibodies and RNA.

Methods: Plasma specimens were received from N=12,462 consenting subjects participating in surveillance studies in South Cameroon collected from 2012 – 2016. Within this cohort, N=7737 HIV negative and N=4725 HIV positive specimens were screened for HCV RNA using the Abbott RealTime HCV viral load test. HCV RNA positive specimens with remaining volume were also screened

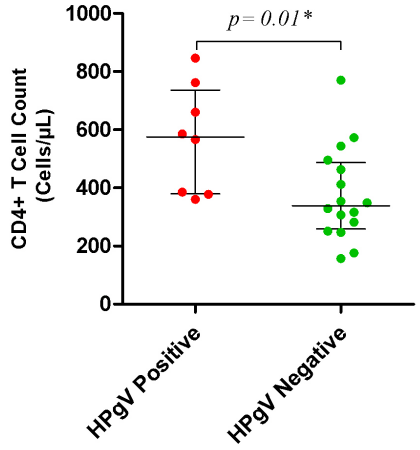
for HPgV-2 antibodies on the ARCHITECT instrument, followed by molecular characterization. All viral sequences were classified by phylogenetic analysis.
Results: Overall, HCV RNA was detected in 321 (2.58%; 95% CI: 2.31-2.87%) specimens, with slightly higher prevalence in the HIV positive individuals (2.94%; 95% CI: 2.5-3.46%) than in the HIV negative individuals (2.35%; 95% CI: 2.04-2.71%). Notably, the median age of HCV RNA negative individuals was 28 years while the median for positive individuals was 54. Phylogenetic classification of sequences from N=97 specimens identified HCV genotypes 1 (20%), 2 (17%), and 4 (63%). HPgV-2 antibodies were detected in N=28 (10.61%; 95% CI: 7.44-14.9%) of the HCV RNA positive specimens, with higher prevalence in the HCV-HIV co-infected group (13.08%; 95% CI: 7.96-20.77%) than the HCV mono-infected group (8.92%; 95% CI: 5.39-14.41%). HPgV-2 RNA was detected in N=6 specimens by RT-PCR and/or next generation sequencing, including N=2 HIV co-infected specimens. Classification of the obtained HPgV-2 sequences indicates they are closely related to strains identified previously in the United States.
Conclusion: In the largest HCV surveillance study to date in Cameroon, we find that the prevalence of HCV is relatively low in our study population compared to the results of smaller previous studies. The discovery of HPgV-2 in South Cameroon expands the geography of this virus to the African continent, indicating it may be more widespread than previously appreciated.

629 PREVALENCE AND CORRELATES OF HPGV INFECTION AMONG PWID WITH HIV INFECTION IN INDIA

Nandagopal Paneerselvam[1], Thongadi R. Dinesha[1], Shanmugam Saravanan[1], Allison M. McFall[2], Pachamuthu Balakrishnan[1], Aylur K. Srikrishnan[1], Sunil S. Solomon[2], Shruti H. Mehta[2]
[1]YR Gaitonde Center for AIDS Research and Education, Chennai, India, [2]Johns Hopkins Hospital, Baltimore, MD, USA

Background: Human Pegivirus (HPgV) shares overlapping transmission routes with HIV as it is transmitted through percutaneous and sexual routes. Previous studies have shown that HPgV infection is associated with reduced disease progression among HIV-infected individuals. However, most of these data are from resource-rich settings with non-clade C HIV infection. We estimate the prevalence of HPgV infection and its association with disease progression among HIV-infected people who inject drugs (PWID) in Chennai, India.
Methods: We tested stored plasma samples from 154 HIV-infected PWID who were recruited and followed as part of a community-based cohort of PWID in Chennai, India (the Chennai HIV, HCV and EeRal study (CHHEERS)) from 2012-2016. Samples from the baseline study visit were screened for HPgV infection using Real Time PCR. We compared baseline characteristics of persons who were positive and negative for HPgV using the Fisher's exact test for dichotomous or categorical characteristics and the Mann-Whitney rank sum test for continuous characteristics, with a particular focus on HIV disease parameters including CD4, HIV plasma viral load, and antiretroviral therapy (ART).
Results: All PWID in this cohort were male and the median age was 40 (interquartile range [IQR]:36–43). The median CD4 cell count was 357 (IQR: 226-489), nearly half (47%) were currently taking ART, of whom 38% had suppressed HIV viral load. The prevalence of HPgV infection was 23% (95% confidence interval: 17-31%). There were no statistically significant differences between HPgV positive and HPgV negative persons at baseline in terms of HIV viral load (80% and 78% with detectable viral load, respectively ;p = 0.92) and CD4 cell counts (median 357 and 347, respectively, p=0.77) even after accounting for ART. However, at 24 months of follow-up the median CD4 count among those on ART was significantly higher among HPgV positives compared to those who were negative for HPgV(p=0.01) (Figure 1).
Conclusion: We observed a high prevalence of co-infection with HPgV among a cohort of HIV-infected PWID in India. The HPgV infected patients exhibited a superior response to ART with better recovery of CD4cells. Further evaluation of these relationships in a larger sample size might shed light on the role of HPgV infection among PWID with HIV infection.

Figure1



630 HEPATITIS C VIRUS AND INCIDENT TYPE 1 AND TYPE 2 MYOCARDIAL INFARCTION IN HIV

Jessica Williams-Nguyen[1], Robin M. Nance[1], Sara Lindström[1], Susan Heckbert[1], Inga Peter[2], Matthew Budoff[3], W. C. Mathews[4], Joseph J. Eron[5], Peter W. Hunt[6], Richard D. Moore[7], Michael J. Mugavero[8], Mari Kitahata[1], Michael Saag[8], Heidi M. Crane[1], Joseph Delaney[1]
[1]University of Washington, Seattle, WA, USA, [2]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [3]Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, USA, [4]University of California San Diego, San Diego, CA, USA, [5]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [6]University of California San Francisco, San Francisco, CA, USA, [7]Johns Hopkins University, Baltimore, MD, USA, [8]University of Alabama at Birmingham, Birmingham, AL, USA

Background: Persons living with HIV (PLWH) are at increased risk of cardiovascular events including Type 1 (atheroembolic) and Type 2 (oxygen supply-demand mismatch) myocardial infarction (MI), potentially due in part to chronic inflammatory processes. Evidence is inconclusive on the role of chronic coinfection with hepatitis C virus (HCV), common in PLWH, in modulating the risk of MI. This analysis sought to understand whether HCV in PLWH is associated with increased MI risk or differences in risk by MI type.
Methods: The CFAR Network of Integrated Clinical Systems (CNICS) is a multi-center HIV cohort with comprehensive clinical data including centrally adjudicated MI. We estimated the association between HCV and time to incident Type 1 MI (T1MI) and Type 2 MI (T2MI) using Cox regression models with multiple imputation to accommodate missingness in covariates. Estimates were adjusted for age, sex, site, race, ethnicity, smoking, substance use, measures of cholesterol, diabetes, treated hypertension, statin use, nadir CD4 count and HIV viral load.
Results: Among 24,755 PLWH, 2,280 (9.2%) were positive for HCV infection at baseline and there were 332 T1MI and 328 T2MI during a median of 4.2 years of follow-up. HCV was not associated with overall MI (adjusted hazard ratio (aHR) 1.20, 95% Confidence Interval (CI): 0.94-1.52). In subtype analysis, HCV was associated with risk of T2MI (aHR 1.51, 95% CI: 1.12-2.05) but not T1MI (aHR 0.86, 95% CI: 0.57-1.28). In further analyses examining adjudicated causes of T2MI, HCV was not associated with T2MI attributed to cocaine use (aHR 1.04, 95% CI: 0.41-2.60) but was associated with a 2-fold greater risk of T2MI attributed to sepsis (aHR 2.01, 95% CI: 1.22-3.29).
Conclusion: HCV status in PLWH is associated with T2MI but not with classical, plaque-rupture-event T1MI. In particular, we found an association between HCV status and T2MI attributed to sepsis suggesting that HCV-infected PLWH have a higher risk of developing sepsis or T2MI as a complication of sepsis. This could be explained by consequences of HCV infection, such as liver dysfunction and chronic inflammation, or differences in sepsis risk factors between HCV-infected and uninfected individuals. Our analysis of MI subtypes allowed us to obtain a more detailed understanding of the cardiovascular risks associated with HCV in PLWH and may thereby facilitate future treatment and prevention efforts.

Table. Association between chronic Hepatitis C infection status among persons living with HIV and myocardial infarctions overall and by subtype

Model	Number of events	Unadjusted HR (95% CI)	Fully adjusted HR (95% CI)
All MI	667	**1.77 (1.44-2.19)**	1.20 (0.94-1.52)
T1MI	337	1.01 (0.70-1.45)	0.86 (0.57-1.28)
T2MI	330	**2.69 (2.07-3.49)**	**1.51 (1.12-2.05)**
T2MI due to cocaine use	37	**2.61 (1.19-5.71)**	1.04 (0.41-2.60)
T2MI due to sepsis	119	**3.57 (2.38-5.36)**	**2.01 (1.22-3.29)**

Bold type indicates statistical significance at alpha=0.05. Fully adjusted models included age, sex, history of injecting drug use, site, diabetes, statin use, hypertension, ever smoker, race, ethnicity, men who have sex with men, hepatitis B virus, ART use at baseline, nadir CD4+ cell tablcount, HIV viral load at baseline, body mass index, total cholesterol, HDL cholesterol, triglycerides, amphetamine use, cocaine use, opiate use, marijuana use, alcohol use score. MI: mycocardial infarction, T1MI: Type 1 MI, T2MI: Type 2 MI, HR: hazard ratio, CI: confidence interval

631 ERADICATION OF HCV: EFFECTS ON CARDIOVASCULAR RISK AND PRECLINICAL ATHEROSCLEROSIS

Ana Carrero[1], **Juan Berenguer**[1], Victor Hontanon[2], Jordi Navarro[3], José Hernández-Quero[4], Maria J. Galindo[5], Carmen Quereda[6], Ignacio Santos[7], María J. Téllez[8], Enrique Ortega[9], José Sanz[10], Javier Bermejo[1], José M. Bellón[1], Juan González-García[2]

[1]General University Hospital Gregorio Marañón, Madrid, Spain, [2]La Paz University Hospital, Madrid, Spain, [3]Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, [4]Hospital Universitario San Cecilio, Granada, Spain, [5]Hospital Clinic of Valencia, Valencia, Spain, [6]Hospital Ramon y Cajal, Madrid, Spain, [7]Hospital Universitario de La Princesa, Madrid, Spain, [8]Hospital Universitario Clínico San Carlos, Madrid, Spain, [9]Hospital General de Valencia, Valencia, Spain, [10]Hospital Universitario Príncipe de Asturias, Madrid, Spain

Background: We previously showed that eradication of HCV in HIV/HCV-coinfected patients was associated a near-significant increase in the risk of cardiovascular events (Hepatology 2017; 66:344). We compared changes in 10-year Framingham cardiovascular risk (10y-CVR) and changes in noninvasive tests for preclinical atherosclerosis in coinfected patients with and without SVR receiving anti-HCV therapy (anti-HCV Rx).

Methods: We performed a multicenter prospective study between February 2012 and March 2014. Serum lipids, 10y-CVR, arterial stiffness by carotid-femoral pulse wave velocity (PWV), and carotid intima-medial thickness (cIMT) by B-mode ultrasound were assessed at baseline and 96 wk after initiation of anti-HCV Rx. Age at baseline was computed for estimation of 10y-CVR at both time-points.

Results: We recruited 262 patients. Median age, 48 yr; males, 77%; prior IDU, 78%; HCV genotype-1, 65%; median liver stiffness, 13 kPa; anti-HCV Rx, pegylated interferon and ribavirin (PR) plus 1 direct-acting antiviral (DAA) 54%, PR 33%; all-oral DAA, 13%; concomitant ART, 98%. A total of 163 (62%) patients achieved SVR. After the exclusion of patients who died or were lost to follow-up and of those initiating statin therapy during the study period, paired measurements (baseline and wk 96) were available from 227 patients for 10y-CVR, from 128 patients for PWV, and from 49 patients for cIMT. No significant differences were found at baseline in these variables between responders and nonresponders (Table). Significantly higher changes (Δ) in LDL-C and 10y-CVR were observed in responders than in non-responders (Table). No significant differences were found in Δ-PWV or Δ-cIMT between responders and nonresponders (Table).

Conclusion: We found that eradication of HCV in coinfected patients was associated with an increase in 10y-CVR. This change was driven by an increase in serum LDL-C. Eradication of HCV was not associated with improvements in noninvasive tests for preclinical atherosclerosis.

Variable – median (IQR)	Non-SVR	SVR	*P*
LDL-C – mg/dL	N=86	N=141	
Baseline	87 (73;105)	92 (71;109)	0.484
Δ-LDL-C	0 (-12;25)	14 (-3;32)	0.032
10y-CVR – (%)	N=86	N=141	
Baseline	9.5 (4.4;16.3)	9.4 (6;14)	0.885
Δ-10y-CVR	0.2 (-1.9;2.0)	0.9 (-0.8;4.4)	<0.001
PWV – m/s	N=54	N=74	
Baseline	7.4 (6.8;9.1)	7.8 (6.5;8.9)	0.279
Δ-PWV	0.1 (-0.9;1.1)	0.3 (-0.8;1.3)	0.635
cIMT - mm	N=18	N=31	
Baseline	0.62 (0.57;0.78)	0.64 (0.61;0.71)	0.079
Δ-cIMT	0.02 (-0.02; 0.1)	0.03 (-0.02; 0.11)	0.198

632 RISK OF DIABETES IN HCV-HIV PATIENTS IS ASSOCIATED WITH CIRRHOSIS, NOT WITH HCV

Aurélien Provoost[1], Moustapha Drame[1], **Laurent Cotte**[2], Lise Cuzin[3], Rodolphe Garraffo[4], David Rey[5], François Raffi[6], Isabelle Poizot-Martin[7], Pascal Puglièse[8], Firouze Bani-Sadr[1]

[1]CHU de Reims, Reims, France, [2]Hospices Civils de Lyon, Lyon, France, [3]CHU de Toulouse, Toulouse, France, [4]CHU de Nice, Nice, France, [5]Hôpitaux Universitaires de Strasbourg, Strasbourg, France, [6]CHU de Nantes, Nantes, France, [7]Assistance Publique–Hopitaux Marseille, Marseille, France, [8]Nice University Hospital, Nice, France

Background: Both HIV and hepatitis C (HCV) infections have been reportedly associated with a higher risk of diabetes mellitus (DM) but results are conflicting. The aim of this study was to determine whether there is an association between chronic HCV and the incidence of DM, and to study the role of factors such as cirrhosis, IFN-based HCV therapy, sustained virologic response (SVR) and chronic hepatitis B (HBV) infection among patients living with HIV (PLHIV) followed in a large French multicenter cohort in the combination antiretroviral therapy (cART) era.

Methods: All PLHIV followed up in the Dat'AIDS cohort were eligible. Patients with preexisting DM or a diagnosis of DM within six months following HIV diagnosis, patients with spontaneous HCV cure or with no HCV serology were excluded. Cox models for survival analysis were used to study the time to occurrence of DM.

Results: Among 28,699 PLHIV, 4,004 patients had chronic HCV-infection. The mean duration of HIV and HCV follow-up was 12.4±7.9 and 12.5±8.1 years, respectively. DM occurred in 969 (3.4%) patients overall. By multivariate analysis, increasing age (>50 years, HR 9.9, 95% CI 7.94-12.34, p<0.0001), elevated body mass index, cirrhosis (HR 2.26, 95% CI 1.79-2.85; p <0.0001), AIDS status (HR 1.35 95% CI 1.17-1.56; p<0.0001), nadir CD4 cell count ≤ 200/mm^3 (HR 1.49, 95% CI 1.29-1.73; p <0.0001) and detectable HIV viral load (HR 1.32 95% CI 1.05-1.65; p=0.017) were predictors of DM, whereas longer cART duration was associated with a lower risk of DM (HR 0.84 95% CI 0.83-0.85 p<0.0001). Chronic HCV and HBV-infection, IFN-based HCV therapy and lipodystrophy were not associated with DM. In a subanalysis among HCV-infected patients, SVR was not related to DM (HR 1.09 (95% CI 0.76-1.57); p=0.65).

Conclusion: Our study shows that in PLHIV, cirrhosis is associated with an increased risk of DM, but not chronic HCV infection or duration of HCV infection. Furthermore, in the late cART era, the duration of cART was no longer associated with a higher risk of DM. Apart from HIV factors related to immunodeficiency (AIDS status, low nadir CD4 cell count and detectable HIV viral load), PLHIV share the same traditional risk factors for DM, such as age and BMI, as compared to the general population

633 HCV AND LIVER DISEASE INCREASE RISK OF NEUROCOGNITIVE IMPAIRMENT IN HIV+ INDIVIDUALS

Ilaria Mastrorosa, Carmela Pinnetti, Patrizia Lorenzini, Alessandra Vergori, Gabriele Fabbri, Pietro Balestra, Maria Maddalena Plazzi, Martina Ricottini[1], Rita Bellagamba, Stefania Cicalini, Rita Maddaluno, Mauro Zaccarelli, Adriana Ammassari, Andrea Antinori

Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy

Background: HCV may be implicated in the pathogenesis of neurocognitive impairment (NCI), but its precise contribution in the setting of the HIV infected (HIV+) population is still controversial. HCV-mediated liver injury may itself contribute to NCI. We investigated the effect of HCV infection and liver function (Lf) on neurocognition.

Methods: From a prospective, monocenter, observational study conducted from January 2000 to July 2017 on neuropsychological (NP) evaluations, we selected HIV+ patients (pts) with known HCV status: negative serology (HCV-), positive serology (HCV+), viremic (RNA+), aviremic (RNA-). A comprehensive battery of 14 tests on 5 different domains was used to classify HIV-associated neurocognitive disorders (HAND) according to Frascati's criteria. NPZ8 was used as summary measure of z-scores of NP tests. Fibrosis 4 score (Fib4) was calculated as measure of Lf. Chi-square and K-Wallis tests were used for statistical comparisons. Stepwise backward multivariable logistic regression was employed to investigate predictors of HAND.

Results: Excluding pts with confounding factors for HAND diagnosis, we analyzed 1,305 pts: 953 HCV-, 109 HCV+RNA-, 243 HCV+RNA+. Male 79%, median age 45 yrs (IQR 38-52), median education 13 yrs (IQR 8-13), IDUs 17%,

median CD4 nadir 215/mm^3 (IQR 98-336) and current 491/mm^3 (IQR 285-710), on antiretroviral therapy (ART) 82%, HIV RNA <50 copies/mL 59%. Table 1 depicts HAND prevalence and NPZ8 according to HCV status (1a) and to Fib4 score strata in all pts (1b) and in HCV+RNA+ pts (1c). A higher prevalence of HAND together with lower median NPZ8 scores were found in HCV+ pts (with or without HIV RNA) and with higher Fib4. In HCV+RNA+ pts, frequency of HAND was similar across Fib4 stages. Adjusting for demographics and clinical variables (age, education level, current and nadir CD4 count, HIV-RNA, mode of HIV transmission, years from HIV test, ART, Fib4), HCV+RNA+ was associated to higher risk of HAND [OR 1.51(1.06-2.13), p 0.021]. When excluding the variable age from the model, Fib4 >3.25 had higher risk of HAND [OR 2.04(1.15-3.61), p 0.015].

Conclusion: Our results show that both, HCV co-infection and worse liver function scores were associated with detrimental neurocognitive performance in HIV+ pts. Notably, among pts with actively replicating HCV, NCI was not influenced by liver function scores. Now that curative anti-HCV therapy is available, these findings need further investigation.

1a All patients N=1305	HCV- N=953	HCV+RNA- N=109	HCV+RNA+ N=243	
Unimpaired	**684 (71.8%)**	**62 (26.9%)**	**137 (56.4%)**	***p* at *chi-square* < 0.001**
HAND	**269 (28.2%)**	**47 (43.1%)**	**106 (43.6%)**	
ANI	140 (14.7%)	21 (19.3%)	47 (19.3%)	
MND	100 (10.5%)	23 (21.1%)	47 (19.3%)	
HAD	29 (3.0%)	3 (2.8%)	12 (4.9%)	
NPZ8, median (IQR)	-0.19 (-0.72; 0.25)	-0.31 (-1.01; 0.06)	-0.57 (-1.18; 0.09)	***p* at *K-Wallis* < .001**

1b All patients N=1305	Fib4 <1.45 N=754	Fib4 1.45-3.25 N=196	Fib4 >3.25 N=73	
Unimpaired	**561 (74.4%)**	**121 (61.7%)**	**37 (50.7%)**	***p* at *chi-square* < 0.001**
HAND	**193 (25.6%)**	**75 (38.3%)**	**36 (49.3%)**	
ANI	111 (14.7%)	39 (19.9%)	18 (24.7%)	
MND	64 (8.5%)	30 (15.3%)	17 (23.3%)	
HAD	18 (2.4%)	6 (3.1%)	1 (1.4%)	
NPZ8, median (IQR)	-0.19 (-0.77; 0.27)	-0.57 (-1.37; -0.02)	-0.83 (-1.49; -0.36)	***p* at *K-Wallis* < 0.001**

1c HCV+RNA+ patients N=243	Fib4 <1.45 N=76	Fib4 1.45-3.25 N=56	Fib4 >3.25 N=44	
Unimpaired	**44 (57.9%)**	**39 (69.6%)**	**25 (56.8%)**	***p* at *chi-square* = 0.303**
HAND	**32 (42.1%)**	**17 (30.4%)**	**19 (43.2%)**	
ANI	17 (22.4%)	13 (23.2%)	9 (20.4%)	
MND	12 (15.8%)	3 (5.4%)	9 (20.4%)	
HAD	3 (4.0%)	1 (1.8%)	1 (2.3%)	
NPZ8, median (IQR)	-0.30 (-0.99; 0.39)	-0.43 (-1.16; 0.07)	-0.61 (-1.26; -0.20)	***p* at *k-wallis* = 0.210**

Table 1. HIV-associated neurocognitive disorders (HAND) prevalences and median NPZ8 scores according to HCV status (1a), to Fibrosis 4 score (Fib4) in all patients (1b) and in HCV+RNA+ patients (1c). For the abbreviations see text.

634 PORPHYRIA CUTANEA TARDA EVOLUTION IN HCV+/HIV+/- PATIENTS POST TREATMENT WITH HCV DAA

Lucio Jesus Garcia-Fraile Fraile, Pablo Rodríguez, Luisa Consuelo García Buey, Concepción Alonso Cerezo, Ignacio d. Santos Gil
Hospital Universitario de La Princesa, Madrid, Spain

Background: PCT is an extrahepatic manifestation found in HCV patients. Former treatment was based on phlebotomies and chloroquine, not always able to get a maintained improvement on symptoms. We want to analyse PCT evolution after achieving HCV eradication with DAA.

Methods: Retrospective study via medical histories review of PCT patients treated with DAA in our hospital (Infectious & Digestive Units). We collected baseline characteristics: age, sex, risk group[RG], HIV infection (in these, baseline CD4 cell count and HIV viral load[VL]). Referred to HCV: genotype, VL, fibrosis stage by fibroscan, DAA regimen and virological response.
For PCT: prevalence of associated risk factors (hypertension[HT], diabetes mellitus[DM], dyslipidemia[DL], smoking, alcohol, and genetic polymorphisms for hemochromatosis [HFE] and activity of uroporphyrinogendecarboxylase [UROD]), clinical diagnosis and previous treatment. We followed the evolution of the disease after classic treatment, comparing it with that after achieving HCV virological response. SPSS22.0

Results: 13 patients: mean age 57 y.o.; 9 males; RG: 6 former IDU, 1 MSM; 8 HIV co-infected (among these: 7 with HIV suppressed VL, median CD4 cell count: 663 cells/ml). HCV genotype: 5 G1a, 5 G1b, 1 G3, 2 G4; fibrosis stage: F1-2: 7, F3: 3 and F4: 3; DAA regimen: SOF/LDV 5, OMB/PTV/DSB 5, OMB/PTV 1, SOF+DAC 1, SOF+SIM 1; all achieved sustained virological response at 12thweek after DAA. Risk factors for PCT: 12 smokers, 4 active alcohol consumption, 1 HT, 1 DL, no DM. Genetic tests performed in 8 patients: UROD activity normal in 8; C282Y heterozygosis in 1/8 and H63D heterozygosis in 6/8. Baseline total/fractionated porphyrins in urine were high in the 6 patients in which were available. PCT Symptoms&Evolution: blisters in photo-exposed skin in 11, scarring in 4, malar hypertrichosis in 1. PCT treatment: phlebotomy in 10, chloroquine in 5. With PCT treatment 10/13 improved skin activity (4 complete resolution), 3 symptomatic: 2 worsened and 1 without changes. After HCV eradication by DAA (among 9 remaining symptomatic patients) 8 (6 totally/ 2 subtotally) improved their symptoms but in 1 patient skin symptoms restarted. 3/13 stopped their PCT treatment but 1 restarted phlebotomies.

Conclusion: PCT is not rare among our HCV patients. It is interesting the association found to H63D polymorphisms. Classic could fail to control it, but after viral eradication with DAA regimens skin activity stopped in all but one of our patients.

635 INFLAMMATION AND IMMUNE ACTIVATION MARKERS IN HEPATITIS C INFECTION AND CLEARANCE

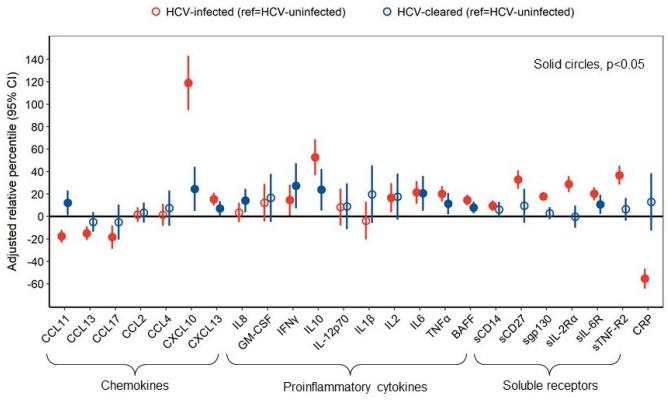
Ruibin Wang[1], Chloe Thio[1], Otoniel Martínez-Maza[2], Steven Wolinsky[3], Yue Chen[4], Eric C. Seaberg[1]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]University of California Los Angeles, Los Angeles, CA, USA, [3]Northwestern University, Chicago, IL, USA, [4]University of Pittsburgh, Pittsburgh, PA, USA

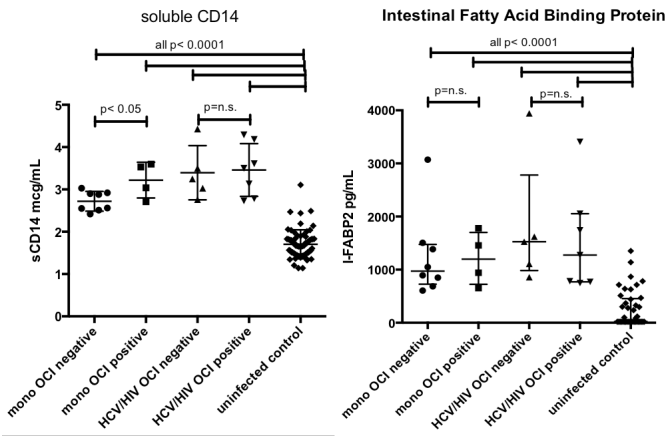
Background: Hepatitis C virus (HCV) coinfection leads to an increased risk of liver disease and mortality among people living with HIV. While some inflammatory cytokines and chemokines are elevated in HCV infection, their relation to an effective immune response resulting in HCV clearance is unclear. We examined serum levels of 23 markers of inflammation and immune activation and a liver-derived acute phase reactant, C-reactive protein (CRP), for association with acute HCV infection and spontaneous clearance in a cohort of HIV-infected men who have sex with men (MSM) from the Multicenter AIDS Cohort Study (MACS).

Methods: We included 1,887 MSM with known HCV status who contributed inflammation marker measurements at 12,028 person-visits from 1984 to 2009. HCV status was determined by anti-HCV and HCV RNA and categorized into three groups: HCV-uninfected (reference group), infected and cleared. Serum biomarker levels were quantified with two multiplex assay platforms. CRP was measured with high-sensitivity immunophelometric assay. To compare the levels of biomarkers across three HCV groups, we used conventional generalized gamma models with robust variance to account for repeated biomarker measurements, adjusting for age, race, hepatitis B infection, body mass index, injection drug use, smoking, alcohol use, HIV serostatus, antiretroviral therapy use and plasma HIV RNA levels.

Results: Among HCV-infected men, serum levels of a number of pro-inflammatory cytokines and chemokines were significantly elevated. In contrast, CRP and three chemokines that are involved in antibody production including CCL17, CCL11 and CCL13 were down-regulated. Following spontaneous HCV clearance, most biomarkers were normalized. However, several pro-inflammatory markers, including BAFF, IL6, IFNγ, TNFα, IL10, CXCL13 and soluble IL6 receptor (sIL6R), remained elevated even after the clearance of HCV infection.

Conclusion: Our results suggest that HCV infection is characterized by a complex dysfunction of cytokine/chemokine network, representing an immune hyperactive state. In contrast, lower CRP levels in HCV-infected men likely reflect decreased CRP production due to HCV-induced liver damage. After HCV clearance, several markers involved in immune activation (IFNγ, IL10, CXCL13 and sIL6R) remain higher than levels present in HCV-uninfected men. Further examination of the immune response during early phase of HCV infection and how it impacts disease establishment and progression is needed.





636 IMPACT OF OCCULT HCV INFECTION (OCI) ON SYSTEMIC IMMUNE ACTIVATION AFTER DAA THERAPY

David M. Asmuth[1], Annie Y. Chen[2], Netanya S. Utay[3], Natalie Torok[1], Patricia L. Poole[1], Joy Vongspanich[1], Kathleen R. Haight[1], Anoma D. Sumasunderam[3], Enkhmaa Byambaa[1], Xiao-Dong Li[1], Stuart T. Cohen[1], Lars Berglund[1], Mark Holodniy[4], Tomasz I. Michalak[2]

[1]University of California Davis, Davis, CA, USA, [2]Memorial University of Newfoundland, St. John's, NL, Canada, [3]University of Texas at Houston, Houston, TX, USA, [4]Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA

Background: OCI is the presence of low level HCV detection in plasma or cells when commercial assays report undetectable viral loads and was well described in the IFNα-era following sustained virologic response (SVR). The occurrence and frequency of OCI following Directly Acting Agent (DAA) therapy has not been reported. Further, the relationship between OCI and persistent immune activation following SVR is unknown.

Methods: HCV/HIV co- and HCV monoinfected patients (pts) with prolonged SVR following DAA Rx were enrolled. 4 mL of plasma underwent 300,000g ultracentrifugation for 22 hrs. Extracted RNA from the plasma pellet and $5x10^6$ PBMC underwent 2 rounds of PCR amplification using HCV 5'-UTR primers applying stringent precautions/controls in validated methods. Signal specificity was confirmed by nucleic acid hybridization (NAH) with a 5'-UTR-E2 ^{32}P probe. Sensitivity of the RT-PCR/NAH assay is∠10 viral equivalents/mL or∠2.5 ve/µg RNA (≈4 IU/mL or 1 IU/µg RNA, respectively). NS5A is sequenced for DAA resistance. Biomarkers of inflammation were measured using ELISA and Luminex kits. Nonparametric statistical methods are reported (median, IQR).

Results: 12 HCV/HIV pts on chronic ART and 12 HCV-monoinfected pts with a median of 13.5 (9.5, 17) months since SVR12 provided a single blood sample (ie, 16.5 mo since any DAA). HCV/HIV pts had 663 T-cells (426, 916) and∠20 HIV load. All but 1 were genotype (GN) 1 and all received either 12 or 24 weeks of sofosbuvir with ledipasvir except 1 who received ribavirin (GN 2). 50% in each cohort had documented cirrhosis. 7/12 (58%) co-infected and 4/12 (33%) mono-infected pts had HCV RNA positive-strand detected from plasma and/or PBMCs. Overall, only 3 were discordant with OCI in cells but not plasma (n=2) or plasma but not cells (n=1). In total, 3 had detectable HCV RNA negative-strand. sCD14 and I-FABP were higher than uninfected pts (p<0.0001) and mono-infected OCI positive pts had higher sCD14 than OCI negative pts (P<0.05). Others were not increased. Cirrhosis status did not impact OCI detection or biomarkers.

Conclusion: These findings support the hypothesis that persistent OCI following DAA could contribute to systemic immune activation observed in these pts. Since B-cells and monocytes are known to harbor HCV, sorted cells and/or identification of the tissue reservoir may reveal higher OCI frequency. Despite OCI not leading to relapse historically, its impact on HCV-related comorbidities/HCC in cured pts needs further investigation.

637 POTENTIAL FOR SERUM MICRO-RNAs TO PREDICT FIBROSIS REGRESSION DURING HBV TREATMENT

Cody Orr[1], Rob Myers[2], David Gong[2], Biao Li[2], Zhaoshi Jiang[2], John Flaherty[2], Anuj Gaggar[2], G. Mani Subramanian[2], **Eric G. Meissner**[1]

[1]Medical University of South Carolina, Charleston, SC, USA, [2]Gilead Sciences, Inc, Foster City, CA, USA

Background: Long-term anti-viral therapy of patients with chronic hepatitis B virus (HBV) infection results in regression of fibrosis and cirrhosis in many, but not all patients. Fibrosis regression likely reduces the risk of hepatic decompensation and hepatocellular carcinoma. We asked whether serum micro-RNAs (miRNAs) could serve as biomarkers reflective of fibrosis regression.

Methods: We used serum collected from subjects with chronic HBV infection and biopsy proven cirrhosis (Ishak score 5 or 6) who were treated for 5 years with tenofovir disoproxil fumarate (TDF) in clinical trials NCT00117676 and NCT00116805. In these trials, 71/96 subjects had biopsy-proven regression of cirrhosis at year 5. Serum samples from 14 subjects with fibrosis regression and 14 patients without fibrosis regression were available at baseline, year 1, and year 5 of treatment. mi-RNAs were isolated from serum and analyzed by quantitative PCR (qPCR) for 179 species using the Exiqon platform. Hemolyzed samples were excluded (n=3). Data were normalized to housekeeping miRNA species and then analyzed using non-parametric assumptions.

Results: qPCR detected an average 159 miRNAs per sample, with 45 miRNAs detected in all samples. A comparison of patients with and without cirrhosis regression identified a number of miRNAs that differed at baseline (miR-421, miR-454-3p, miR-15b-5p, miR-141-3p), at year 1 of treatment (miR-199a-5p, miR-223-3p), and at year 5 of treatment (miR-199a-3p, miR-423-3p, miR-142-3p, miR-let-7d-5p). In addition, several species had differential change between baseline and 1 year of treatment (miR-21-5p, mir-29a-3p, miR-22-3p, miR-425-3p, miR-30a-5p) and between baseline and year 5 of treatment (miR-103a-3p, miR-107, miR-34a, miR-885) in the two groups. Multiple of the identified miRNA species, including mir-21 and miR-199a-5p, have plausible mechanistic relationships to pathways associated with stellate cell activation and known mechanisms of fibrogenesis.

Conclusion: In cirrhotic patients with chronic HBV infection treated with TDF, a number of serum mi-RNAs differ both before and after treatment based on fibrosis regression. Further validation will determine their potential clinical utility as biomarkers.

638 HEPATIC EXPRESSION OF HSA-MIR-125A-5P AND FIBROSIS IN OVERT AND OCCULT HBV INFECTION

Lorenzo Onorato[1], Aniello Russo[1], Giorgio de Stefano[2], Carmine Minichini[1], Mario Starace[1], Pietro Filippini[1], Loredana Alessio[1], Nunzia Farella[2], Nicoletta Potenza[1], Evangelista Sagnelli[1], Nicola Coppola[1]

[1]Second University of Naples, Caserta, Italy, [2]AORN dei Colli, Naples, Italy

Background: MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression at post-transcriptional level; hsa-miR-125a-5p, a microRNA expressed in human liver, was shown to bind a specific sequence of S gene of HBV, inhibiting the expression of HBsAg in vitro. We aimed to correlate the hepatic expression pattern of hsa-miR-125a-5p with the concentrations of

HBV-DNA in liver tissue and the progression of fibrosis in 74 consecutive patients with overt or occult HBV infection.

Methods: We enrolled all the consecutive HBsAg positive treatment naive patients who underwent a diagnostic liver biopsy (overt HBV group) between April 2007 and April 2015 in one of the three liver units participating in the study. Moreover, of the 68 HBsAg negative patients with hepatocellular carcinoma who underwent a liver biopsy in the same period, those with a positive HBV-DNA in liver tissue were enrolled (occult HBV group). HIV coinfected patients were excluded from the analysis. For each patient we collected a plasma sample and two fragments from the extremities of liver biopsy. Tissue concentrations of HBV-DNA and hsa-miR-125a-5p were analysed by real-time quantitative PCR. Necroinflammatory activity and fibrosis were evaluated according to the Ishak score.

Results: 64 HBsAg positive and 10 HBsAg negative patients were included in the study. In the overt HBV group, 54.7% showed a mild fibrosis, 26.6% a moderate fibrosis, while the remaining had a cirrhosis. All patients in the occult HBV group were cirrhotic. Patients with more advanced fibrosis showed a higher mean age as compared to those with mild ($p<0.00001$) or moderate fibrosis ($p<0.00001$). Similarly, patients with occult B infection were older than HBsAg positive patients. Liver concentrations of miR-125a-5p were significantly higher in patients with cirrhosis as compared to patients with mild ($p=0.0002$) or moderate fibrosis ($p=0.0006$). Moreover we found an inverse correlation, although not statistically significant, between the tissue HBV-DNA levels and the staging of fibrosis. Eventually, patients with higher liver HBV-DNA concentrations showed a slightly lower microRNA expression ($p=0.19$).

Conclusion: This study demonstrates a strong correlation between the tissue expression of hsa-miR-125a-5p and the progression of liver damage in a group of patients with occult or overt HBV infection. However further studies are needed to investigate the role of this miRNA in the pathogenesis of HBV infection.

	HBsAg positive patients			Occult HBV infection	p			
	Staging 0-2	Staging 3-4	Staging 5-6		P1*	P2*	P3*	P4*
N° patients	35	17	12	10				
Age (mean ± SD)	40.3 (11.7)	40.8 (10.3)	68.0 (3.5)	67.0 (10.6)	0.87	**<0.00001**	**<0.00001**	**0.00003**
Males, n° (%)	21 (60)	14 (82.3)	11 (91.7)	8 (80.0)	0.11	0.04	0.47	0.73
AST/ULN(mean ± SD)	0.77 (0.44)	1.55 (1.8)	0.96 (0.62)	1.75 (1.06)	0.09	0.49	0.25	0.06
ALT/ULN (mean ± SD)	1.06 (0.93)	2.46 (2.83)	1.11 (1.02)	1.66 (1.08)	0.06	0.9	0.11	0.66
PT% (mean ± SD)	90.1 (18.9)	90.7 (11.4)	82.3 (13.4)	88.1 (8.9)	0.88	0.16	0.12	0.48
HAI>6, n° (%)	2 (5.7)	10 (59.0)			**0.0002**			
Plasma HBV-DNA UI/ml (mean ± SD)	2.83 E+6 (1.62 E+7)	1.29 E+7 (4.13 E+7)	3.1 E+5 (7.9 E+5)	9.3 E+3 (2.69 E+4)	0.35	0.32	0.22	0.11
Liver HBV-DNA cp/cell (mean ± SD)	5.09 (20.1)	0.81 (1.85)	0.07 (0.16)	0.06 (0.07)	0.25	0.17	0.13	0.06
miR-125a-5p AU (mean ± SD)	1.39 (0.94)	2.43 (2.18)	9.75 (4.42)	7.4 (5.59)	0.07	**0.0002**	**0.0006**	0.09

Footnotes: P1: Staging 0-2 vs 3-4; P2: Staging 0-2 vs 5-6; P3: Staging 3-4 vs 5-6; P4: occult vs overt HBV infection

639 CIRCULATING MICRORNAs IN HIV PATIENTS REVEAL SPECIFIC SIGNATURES FOR LIVER DAMAGE

Miguel Angel Martinez[1], Sandra Franco[1], Daniela Buccione[2], Beatriz Mothe[1], Lidia Ruiz[1], Maria Nevot[1], Ana Jordan-Paiz[1], Raquel Pluvinet[2], Susanna Aussó[2], Rosa M. Morillas[2], Lauro Sumoy[2], Cristina Tural[2]

[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [2]Hospital Germans Trias i Pujol, Barcelona, Spain

Background: HIV-1-induced inflammation and/or long-term antiretroviral drug toxicity may contribute to liver disease evolution. MicroRNAs (miRs) are potential disease biomarkers and therapeutic targets. Here, we investigated circulating plasma miRs among HIV-1 infected patients and their association with liver injury.

Methods: Large-scale deep sequencing analysis of small RNA expression was performed on plasma samples from 101 HIV-1 patients with elevated ALT, focal nodular hyperplasia or HCV coinfection. Twenty one healthy uninfected donors and 22 HCV monoinfected patients were also analyzed.

Results: A total of 1425 different miRs were identified. When compared with healthy donors, monoinfected HIV-1 or HCV patients showed significant (fold change> 2 and adjusted $p< 0.05$) altered expression of 25 and 70 miRs, respectively. Of the 25 altered miRs found in HIV-1 patients, 19 were also found in the HCV mono-infected patients. Indeed, 13 of the 14 miRs more highly upregulated (ranging a 9.3-3.4 fold increase) in HCV monoinfected patients (miR-193b-5p, miR-483-5p, miR-1224-5p, miR-125b-1-3p, miR-885-5p, miR-100-5p, miR-192-5p, miR-592, miR-193b-3p, miR-125b-2-3p, miR-629-5p, miR-99a-5p and miR-203a-3p) were upregulated in HIV-1 monoinfected patients. These 13 miRs were also upregulated in HIV-1-HCV coinfected patients. Importantly, these 13 miRs significantly and positively correlated ($p< 0.05$) with ALT and AST levels with most of the study samples including healthy donors. Two of the former miRs, miR-99a-5p and miR-100-5p, were significantly upregulated in HIV-1-HCV coinfected patients who progressed to liver cirrhosis, although at the time of sampling all compared coinfected patients had liver fibrosis-0. Finally, the comparison of miR profiles of HIV-1 monoinfected patients with elevated ALT or focal nodular hyperplasia with HIV-1 monoinfected patients displaying normal levels of ALT showed significantly altered expression of 25 and 7 miRs, respectively. The two more highly overexpressed miRs in these two cohorts were miR-122-3p and miR-193b-5p. The levels of these 2 miRs significantly correlated with liver fibrosis progression in our cohort of HCV monoinfected patients ($p< 0.05$).

Conclusion: These results reveal that HIV-1 infection affects liver miR metabolism, even in the absence of co-infection with hepatotropic viruses, and highlights the potential of miRs as biomarkers in the progression of liver injury in HIV-1 infected patients.

640 MIRNA PROFILE OF HCV SPONTANEOUS CLEARANCE INDIVIDUALS SHOW PREVIOUS HCV INFECTION

Óscar Brochado Kith[1], Alicia Gómez Sanz[1], Luis M. Real[2], Javier Crespo[3], Pablo Ryan[4], Juan Macías[2], Joaquín Cabezas[3], Juan A. Pineda[2], María T. Arias-Loste[3], Isabel Cuesta[1], Sara Monzón-Fernández[1], Luz M. Medrano[1], María Á. Jimenez-Sousa[1], Salvador Resino[1], **Amanda Fernández-Rodríguez**[1]

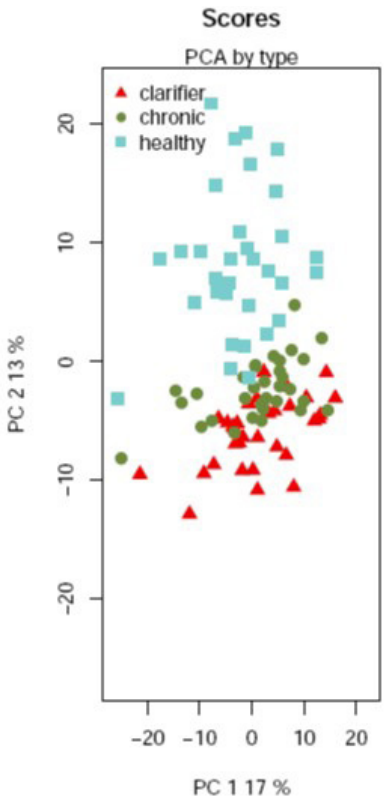
[1]Institute de Salud Carlos III, Majadahonda, Spain, [2]Hospital Universitario de Valme, Seville, Spain, [3]Hospital Universitario Marqués de Valdecilla, Santander, Spain, [4]Hospital Universitario Infanta Leonor, Madrid, Spain

Background: Hepatitis C virus (HCV) usually progress to chronic infection, but a small percentage of patients clarify the virus spontaneously. Factors involved in HCV clarification seem to be related to interaction between HCV and host innate/adaptive immune system. However, little is known about the cost for the immune system after HCV infection. Genomic background of patients plays also a key role in the antiviral immune response against HCV, being the microRNAs (miRNA) essential. These small RNAs are post-transcriptional regulators of gene expression, which play a key role in the innate and adaptive immune response and they are actively involved in the HCV cycle. In this study, we analyzed the miRNA profile of peripheral blood mononuclear cells (PBMCs), from individuals that spontaneously clarified HCV, chronic patients and healthy donors, to evaluate the effects of HCV infection on immune system.

Methods: We have sequenced the miRNA profiles from PBMCs of 96 individuals: 32 HCV chronic patients, 32 individuals that spontaneously clarified HCV, and 32 healthy donors. Library was performed with TruSeq smallRNA (Illumina), and sequenced in an Illumina HiSeq 2500 with 1x50 bp SE reads. Quality control of the reads was evaluated with FastQC. Adapters were removed by Cutadpat. Different methods were used for miRNA quantification, normalization, and differential expression analysis (mirDeep2, edgeR, DESeq and NOIseq). Principal Component Analysis (PCA) was performed. A fold change higher than 2 and false discover rate (FDR) of 5%, were considered.

Results: We did not find any differentially expressed miRNAs between HCV spontaneous clarifiers and chronic patients. However, both groups showed similar expression differences with healthy donor individuals (9 and 8 miRNAs respectively). PCA also confirmed that spontaneous clarifier's patients were more similar to HCV chronic patients than healthy donors (Figure). The potentially altered molecular pathways by these miRNAs (miRPath) belongs manly to fatty acids pathways, which seem to be repressed in donors. MIRNAs related to chronic myeloid leukemia were also altered, showing higher expression within chronic patients. Finally, some miRNAs involved in the strogen signaling pathways were impaired in chronic patients.

Conclusion: It seems that the HCV infection leaves a fingerprint in the immune system that do not vanish after HCV clarification. PBMC´s microRNA expression profile of spontaneously clarified individuals and HCV chronic patients were similar



641 INCREASED RATES OF HEPATIC STEATOSIS IN YOUNG ADULTS WITH LIFE-LONG HIV INFECTION

Julia A. Aepfelbacher[1], Julia Purdy[2], Aviva Mattingly[1], Kirsten Zambell[2], Chloe S. Chaudhury[1], Colleen Hadigan[1]
[1]NIAID, Bethesda, MD, USA, [2]NIH, Bethesda, MD, USA

Background: Liver disease is a leading cause of morbidity in persons living with HIV (PLWHIV), however little is known about the liver health of adults infected with HIV early in life. Transient elastography permits effective, non-invasive assessment of liver steatosis and fibrosis. As this unique population with life-long HIV ages, concerns over hepatic and metabolic health gain increasing importance.

Methods: Young adults who acquired HIV early in life (i.e. perinatal or transfusion) (n=46) and healthy controls (n=9) completed fasting transient elastography and laboratory tests as part of a natural history cohort study. Liver stiffness and controlled attenuation parameter (CAP) measurements were obtained using the Echosens FibroScan 502™. A CAP score >248 dB/m was used to define hepatic steatosis. Anthropometrics, BMI, lipid panel, glucose, CD4 and HIV viral load were measured. We used non-parametric statistics for between group comparisons.

Results: PLWHIV had a median age of 26 years (25/46 male), mean CD4 count 524±370 cells/mm^3, 61% HIV VL<40 copies/mL and median ART exposure 19 years. Hepatic steatosis was present in 35% of young adults with HIV and 0% controls (p=0.03), however, fibrosis scores did not differ between groups (HIV 5.8±2.7 vs. controls 6.3±2.5 kPa, p=0.4). Overweight/obesity (BMI > 25kg/m^2) was common in PLWHIV (HIV 54% vs. 22% controls p=0.08). PLWHIV had significantly higher waist to hip ratio compared to controls (p=0.0002). This ratio was not significantly correlated with CAP score within the HIV group, whereas waist circumference was (r=0.42, p=0.01). Among those with HIV, CAP score was also positively correlated with BMI (r=0.33, p<0.05), glucose (r=0.40, p=0.01), and cholesterol (r=0.55, p=0.0004), but not related to CD4 count, viral suppression or ART duration. In a multivariate regression including HIV status, BMI, glucose and cholesterol, cholesterol was a significant independent predictor of CAP score (p=0.007) with a trend (p=0.06) for HIV status.

Conclusion: Our study is the first to demonstrate increased rates of hepatic steatosis in young adults with life-long HIV. Hepatic steatosis was noted in association with modifiable metabolic disturbances including dyslipidemia and increased BMI. Larger cohorts and longitudinal follow-up are needed to better understand the role of HIV in this phenomenon and to pursue strategies targeting associated metabolic risk factors.

642 CARDIOMETABOLIC RISK PROFILES IN HIV AND NONALCOHOLIC FATTY LIVER

Alyson Kaplan[1], Donald Chute[1], Tracey G. Simon[1], Samson Okello[2], Hui Zheng[1], Raymond T. Chung[1], Kathleen E. Corey[1]
[1]Massachusetts General Hospital, Boston, MA, USA, [2]Mbarara University of Science and Technology, Mbarara, Uganda

Background: Among the general population, nonalcoholic fatty liver disease (NAFLD) is an independent risk factor for cardiovascular disease (CVD). However, the cardiometabolic risk profiles (CMP) of NAFLD among persons living with HIV (PLWH) are unknown. We sought to determine the CMP of PLWH with NAFLD.

Methods: Search of the Partners Research Patient Data Registry identified PLWH with and without NAFLD. NAFLD was defined as fatty infiltration of the liver on imaging or steatosis on biopsy. The absence of NAFLD was defined as normal liver imaging or histology. Those with significant alcohol use or viral hepatitis were excluded. Multivariable logistic regression modelling was used to determine risk factors for an adverse CMP defined as the presence ≥3 of the following: hypertension (HTN), triglycerides ≥ 150 mg/dL, HDL<50 mg/dL in women and <40 in men mg/dL and diabetes; and for CVD, defined as the presence of coronary artery disease (CAD) or cerebral vascular accidents. As the number of CVD cases was small (N=22) only NAFLD and 1 additional covariate were included in each CVD model.

Results: 102 adults with NAFLD and 139 without NAFLD were identified. Adults with NAFLD had significantly higher BMIs than those without NAFLD (31 kg/m2 ± 6.3 vs. 28 kg/m2 ± 5.3, P<0.001). There was no difference by group in age, gender, race, tobacco use or diabetes. NAFLD was associated with an adverse CMP compared to those without NAFLD, with a higher prevalence of HTN (52% vs 35%, p=0.008), lower HDL (40 mg/dL ± 15 vs. 51 mg/dL ± 19, p<0.001), and higher triglyceride levels (255 mg/dl ± 276 vs. 141 mg/dl ± 75, p<0.001). There was no difference in hemoglobin A1C, LDL or total cholesterol levels between groups. CAD and CVD were more common in those with NAFLD (CAD: 9% vs 4%, p=0.089 and CVD: 14% vs. 6%, p=0.034). NAFLD was independently associated with an adverse CMP after adjustment for age, gender, tobacco use and BMI (OR 2.4, p=0.02) and an increased risk of CVD (OR 3.02, p=0.02) after adjustment for BMI and for diabetes.

Conclusion: Among PLWH, the presence of NAFLD is independently associated with adverse cardiometabolic risk profiles and CVD. Further evaluation is needed to understand the relationship between HIV, NAFLD and cardiovascular disease.

	HIV and NAFLD (N=102)	HIV Controls (N=139)	P value
Age, years (mean ± SD)	54 ± 9.6	55 ± 6.8	0.34
Female, n (%)	24 (24%)	33 (24%)	0.97
BMI, kg/m3 (mean ± SD)	30.98 ± 6.3	27.78 ± 5.3	<0.0001
Race			
Black, n (%)	15 (15%)	37 (27%)	0.138
White, n (%)	61 (60%)	72 (52%)	
Hispanic, n (%)	13 (13%)	18 (13%)	
Other, n (%)	13 (13%)	12 (9%)	
Diabetes Mellitus			
Yes, n (%)	20 (20%)	18 (13%)	0.161
No, n (%)	82 (80%)	121 (87%)	
HTN			
Yes, n (%)	53 (52%)	48 (35%)	0.008
No, n (%)	49 (48%)	91 (65%)	
Smoking			
Yes, n (%)	11 (11%)	23 (17%)	0.218
No, n (%)	89 (89%)	115 (83%)	
Total Cholesterol, mg/dL (mean ± SD)	182 ± 45	188 ± 43	0.30
HDL, mg/dL (mean ± SD)	40 ± 15	51 ± 19	<0.0001
LDL, mg/dL (mean ± SD)	101 ± 36	109 ± 35	0.116
Triglycerides, mg/dL (mean ± SD)	255 ± 276	141 ± 75	<0.0001
HgbA1C, % (mean ± SD)	4.3 ± 0.68	5.0 ± 6.96	0.29
Coronary Artery Disease			
Yes, n (%)	9 (9%)	5 (4%)	0.089
No, n (%)	93 (91%)	133 (96%)	
Cardiovascular Disease			
Yes, n (%)	14 (14%)	8 (6%)	0.034
No, n (%)	88 (86%)	131 (94%)	

643 UNANTICIPATED INCREASES IN FATTY LIVER IN HIV NAFLD PATIENTS WITH EPLERENONE

Chloe S. Chaudhury[1], Julia Purdy[2], Chia-Ying Liu[2], Caryn G. Morse[2], Takara L. Stanley[3], David E. Kleiner[4], Colleen Hadigan[1]
[1]NIAID, Bethesda, MD, USA, [2]NIH, Bethesda, MD, USA, [3]Massachusetts General Hospital, Boston, MA, USA, [4]National Cancer Institute, Bethesda, MD, USA

Background: Nonalcoholic fatty liver disease (NAFLD) is common in HIV, often seen in association with metabolic syndrome, however there are no approved therapies for NAFLD. Promising mouse models demonstrate the efficacy of mineralocorticoid receptor (MR) antagonists for attenuation of the effects of fatty liver disease, including marked reductions in fasting glucose, insulin, steatosis, and inflammation in mice fed a high-fat diet receiving an MR antagonist.

Methods: The aim of this open-label proof-of-concept study was to determine the effect of the MR antagonist eplerenone on hepatic fat in 20 HIV+ patients with steatosis, defined as hepatic fat ≥ 5% by magnetic resonance spectroscopy (MRS). Five subjects received eplerenone (25 mg daily x 1 week followed by 50 mg daily x 23 weeks). Laboratory tests were done at each visit, and the primary endpoint, change in hepatic fat content, was determined by MRS at baseline and week 24. An additional MRS was performed 1-2 months after drug discontinuation.

Results: We observed unexpected significant increases in hepatic fat at the week 24 (mean increase 13.2 ± 8.1%, p=0.02) (See Figure 1). There was a trend to return to baseline hepatic fat levels during the 'washout' (mean -9.6 ± 9.5%, p=0.08). In two participants with pre- and post-eplerenone liver biopsies, steatosis grade increased confirming the MRS observations. Surprisingly, the increases in steatosis were accompanied by a tendency for transaminase values to decrease (ALT mean change -14 ± 17 IU/L, p=0.14). There were no consistent improvements in HbA1c, fasting glucose, total cholesterol, triglycerides, or blood pressure. Initial rise in aldosterone was observed as expected, however, three subjects' aldosterone levels returned to near baseline by week 24.

Conclusion: The unexpected observation of increased hepatic steatosis with administration of eplerenone led to a pause in enrollment and early termination of the investigation. While limited due to the small number of participants and the open-label design, the present study provides compelling data to suggest that MR antagonism, at least with eplerenone, is not a reasonable approach to treat NAFLD in HIV or in the general population. Additional research is needed to determine the pathophysiologic mechanism behind these unanticipated observations.

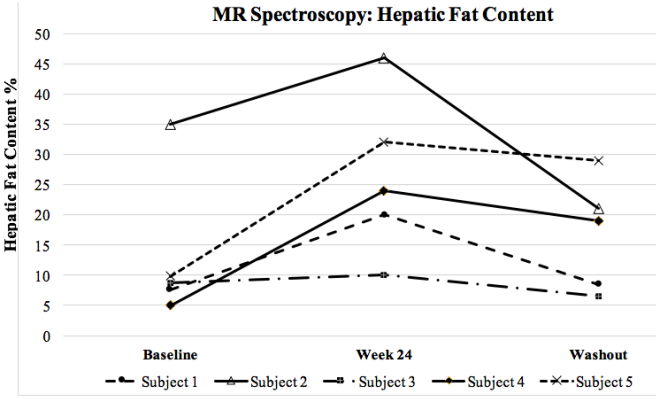


Figure 1. Hepatic fat content by MR spectroscopy in participants at baseline, after 24 weeks Eplerenone 50 mg daily, and 1-2 months after stopping drug (washout). Paired t-test of Baseline to Wk 24, p=0.02; Wk 24 to Washout p=0.08.

644 FAILURE RATE OF ULTRASOUND SURVEILLANCE OF HEPATOCELLULAR CARCINOMA IN HIV+ PATIENTS

Nicolás Merchante[1], Esperanza Merino[2], Francisco Rodríguez-Arrondo[3], Boris Revollo[4], Sofía Ibarra[5], Maria J. Galindo[6], Marta Montero[7], Miguel García-Deltoro[8], Antonio Rivero-Juárez[9], Marcial Delgado-Fernández[10], Francisco Téllez[11], Maria J. Rios-Villegas[12], Jose J. Portu[13], Juan A. Pineda[1]
[1]Hospital Universitario de Valme, Seville, Spain, [2]Hospital General Universitario de Alicante, Alicante, Spain, [3]Hospital Donostia, San Sebastián, Spain, [4]Hospital Germans Trias i Pujol, Barcelona, Spain, [5]Hospital de Basurto, Basurto, Spain, [6]Hospital Clinic of Valencia, Valencia, Spain, [7]Hospital Universitario y Politecnico La Fe, Valencia, Spain, [8]Hospital General de Valencia, Valencia, Spain, [9]Hospital Universitario Reina Sofia, Cordoba, Spain, [10]Hospital Regional Universitario de Málaga, Málaga, Spain, [11]Hospital Universitario de Puerto Real, Cadiz, Spain, [12]Hospital Universitario Virgen Macarena, Sevilla, Spain, [13]Hospital de Txagorritxu, Vitoria, Spain

Background: Surveillance of hepatocellular carcinoma (HCC) by hepatic ultrasound (US) every 6 months is recommended in HIV-infected patients with cirrhosis. However, there are no specific studies addressing the performance of such strategy in this population. As it has been reported that HCC could have a more aggressive course in the HIV-infected patient, the effectiveness of this surveillance policy needs to be evaluated in this specific scenario. The objective of this study was to assess the proportion of HIV-infected patients diagnosed of HCC soon after a normal surveillance US.

Methods: The GEHEP-002 multicentric cohort (ClinicalTrials.gov ID: NCT02785835) recruits HCC cases diagnosed in HIV-infected patients from 32 centers from Spain. For this analysis, HCC cases diagnosed within an US screening program were selected. Surveillance failure was defined as the diagnosis of an HCC within the first 3 months after a previous surveillance US not showing hepatic nodules. The characteristics of HCC cases after surveillance failure were compared with the remaining HCC cases diagnosed by screening.

Results: 186 (54%) out of 341 HCC cases recruited in the GEHEP-002 have been diagnosed within an US screening program. Of them, 16 had a normal US in the preceding 3 months. Thus, the rate of HCC diagnosis after US surveillance failure was 8.6%. HCC was associated with HCV infection in these 16 cases. HCV genotype 3 infection was responsible for 5 (31%) out of the 16 cases after surveillance failure vs 43 (25%) among the remaining 180 cases diagnosed by screening (p=0.5). Two (12%) cases of those occurring after surveillance failure and 19 (11%) among the remaining cases were diagnosed after the consecution of SVR (p=0.7). There was a trend for a higher frequency of multicentric presentation [9 (60%) vs 74 (44%), p=0.2] and portal thrombosis [6 (37%) vs 40 (23%), p=0.2] among HCC cases after surveillance failure. Thus, 10 (62.5%) of them were diagnosed at advanced stage (BCLC stage C or D) whereas this occurred in 76 (45%) of the remaining cases (p=0.1).

Conclusion: A significant proportion of HIV-infected patients are diagnosed of HCC soon after a previous normal surveillance US. HCC cases after US surveillance failure tend to show more advanced presentation at diagnosis. A HCC surveillance policy based on the performance of an US every 6 months might be insufficient in HIV-infected patients with cirrhosis.

645 HIV+ PERSONS WITH CIRRHOSIS RECEIVE INADEQUATE SCREENING FOR ESOPHAGEAL VARICES

Chiara Saroli Palumbo, Amine Benmassaoud, Thomas Pembroke, Bertrand Lebouché, Philip Wong, Marc Deschenes, Marina Klein, Peter Ghali, Giada Sebastiani
McGill University Health Centre, Glen site, Montreal, QC, Canada

Background: HIV positive (HIV+) people are at increased risk of developing cirrhosis and its complications, including variceal hemorrhage. The Baveno VI consensus provides guidance as to which patients with cirrhosis should be screened for esophageal varices, and which can safely forego esophagogastroduodenoscopy (EGD), based on transient elastography (TE) and platelet values. We aimed to determine whether Baveno VI consensus guidelines are appropriately applied in HIV+ as compared to HIV negative (HIV-) individuals with liver disease.

Methods: A prospective cohort study was conducted since 2015, which included HIV+ and HIV- persons who underwent TE as part of a routine screening program for liver disease. Liver cirrhosis was defined as TE measurement >13kPa. Baveno VI guidelines (TE measurement ≥20kPa and platelets ≤150,000) were applied to identify those at very low risk of having varices, and who could avoid screening with EGD. Multivariable logistic regression analysis was used to investigate independent cofactors associated with deviation from the Baveno VI guidelines. Diagnostic accuracy screening according to Baveno VI guidelines as compared to universal EGD was computed.

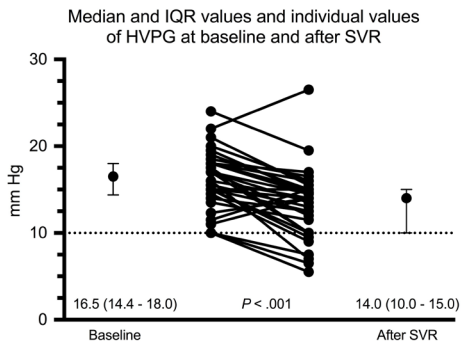
Results: 725 HIV+ (mean age 49 years, 75.2% men; 35% with fatty liver, 21% HIV/HCV co-infected) and 785 HIV- patients (mean age 51 years, 59% men; 36% with fatty liver, 38% with HCV) were included. Prevalence of cirrhosis in the whole cohort was 19%. Overall, 78.8% HIV+ and 73.8% HIV- patients met the Baveno VI guidelines for not requiring screening EGD. In the remaining cases who required screening, EGD was performed in only 22.7% of HIV+ as compared to 87.4% of HIV- patients (p<0.001). Incidence of variceal bleeding was higher in

HIV+ than HIV- patients (5.8% vs 1.9%, p<0.05). In HIV+ patients, the Baveno VI guidelines had a sensitivity 0.82, specificity 0.62, positive predictive value 0.26, negative predictive value 0.95 for the diagnosis of esophageal varices as compared to universal EGD, which were similar to HIV- patients. In multivariable analysis, after adjustment for age, gender, BMI and anti-HCV positivity, being HIV+ was the strongest factor associated with failing to screen when indicated by Baveno VI guidelines (aOR=10.0, 95% CI 7.5-13.5; p<0.0001).
Conclusion: Despite the Baveno VI guidelines performing well in HIV+ patients, they are significantly less likely to receive standard of care screening for esophageal varices than HIV- patients, placing them at higher risk of fatal complications from hemorrhage.

646 MEDIUM-TERM EFFECTS OF DAA THERAPY ON HVPG IN PATIENTS WITH HCV-ASSOCIATED CIRRHOSIS

Cristina Diez[1], **Juan Berenguer**[1], Luis Ibañez[1], Elba L. Herrera[2], Leire Pérez Latorre[1], María V. Catalina[1], Victor Hontanon[3], Diego Rincón[1], Teresa Aldámiz-Echevarría[1], Javier Martínez[4], José M. Bellón[1], José L. Calleja[2], Agustín Albillos[4], Juan González-García[3], Rafael Bañares[1]
[1]General University Hospital Gregorio Marañón, Madrid, Spain, [2]Hospital Puerta de Hierro, Madrid, Spain, [3]La Paz University Hospital, Madrid, Spain, [4]Hospital Ramon y Cajal, Madrid, Spain

Background: In patients with liver cirrhosis (LC), hepatic venous pressure gradient (HVPG) is the most accurate predictor of liver-related outcomes. Little is known about the effects of therapy (Rx) with DAA on HVPG in patients with HCV-related LC. We assessed changes in HVPG following SVR after DAA -Rx in HCV- monoinfected patients (HIV-) and HIV/HCV- coinfected patients (HIV+) with LC.
Methods: Prospective study (4 centers) with patients initiating all-oral DAA Rx between during Jan-Dec 2015. HVPG was measured at baseline and 48 wk after completion of Rx. Inclusion criteria: i) Compensated LC (c-LC) or decompensated LC (d-LC) defined as prior clinical decompensation or Child-Pugh score > 6; ii) clinically significant portal hypertension (CSPH) defined as an HVPG ≥ 10 mmHg; iii) achievement of SVR; iv) no Rx with non-selective betaß-blockers initiated during the study period. Main endpoint: reduction in HVPG to < 10 mmHg. Secondary outcome: decrease in HVPG ≥ 20% or reduction in HVPG to ≤ 12 mm Hg (goal associated with reduced liver complications in patients with variceal bleeding undergoing pharmacological treatment of portal hypertension).
Results: Of 44 patients with LC and paired HVPG measurements, 34 met the 4 inclusion criteria. Main characteristics: median age 53 yr; 22 males, 21 HIV+, 18 previously treated, 17 with d-LC; median MELD score 8; median liver stiffness (LS) 34 kPa. HVPG decreased from 16.5 (IQR 14.4-18.0) at baseline to 14.0 (IQR 10.0 -– 15.0) mmHg at wk 48; (P<.001) (Figure); with a median decrease of 3.1 (IQR 2.0-4.9) mm Hg. No significant differences in the decrease in HVPG decline were observed between HIV- and HIV+. The main outcome endpoint was achieved by 6 patients (18%) and was more frequent in c-LC than in d-LC (35.3 % vs 0 %; P=0.018). The secondary endpoint was achieved by 16 patients (47%); 10 with c-LC (58.8%) and 6 with d-LC (35.3%); P=.303. Of note, HVPG increased from baseline in 4 patients (11.8%). The spearman rho correlation coefficient between changes in HVPG and changes in LS was 0.237, P=.191.
Conclusion: Our findings suggest that, in the medium term, SVR after DAA Rx in patients with LC and CSPH is associated with a decrease in HVPG that is sufficient to reduce the risk of liver complications. However, the frequent persistence of CSPH despite SVR, especially in patients with more advanced disease, indicates a persistent risk of decompensation. The correlation between change in LS and reduction in HVPG was very weak.



647 TRANSPLANT FREE SURVIVAL IN HIV ASSOCIATED NON-CIRRHOTIC PORTAL HYPERTENSION

Kathryn Childs[1], Lauren Hookham[1], Corinna Psomadakis[2], Rosa Miquel[1], Ruth Byrne[1], Mary Cannon[1], Kosh Agarwal[1], Mark Nelson[2], Chris Taylor[1], Abid Suddle[1]
[1]King's College Hospital, London, UK, [2]Chelsea and Westminster Hospital, London, UK

Background: In the last decade there have been numerous reports of patients with HIV presenting with non-cirrhotic portal hypertension (NCPH). We aimed to describe the natural history and clinical outcome in patients from 2 centres who together represent the largest published cohort.
Methods: This is an observational cohort study. Demographics, laboratory, radiological and histological data were obtained on patients at 2 London centres with non-cirrhotic portal hypertension. This was defined by the presence of portal hypertension and either a biopsy or Fibroscan which excluded cirrhosis AND the absence of any other form of liver disease.
Results: 44 patients were identified. From the time of diagnosis of NCPH the median follow up (FU) time was 6.6 yrs (3.3, 8.5) with a total FU period of 310 patient yrs. Characteristics shown in table 1. All patients had been exposed to didanosine (DDI). 28 patients underwent biopsy, 10 showed features of nodular regenerative hyperplasia or portal obliterative venopathy but many showed non-specific inflammation or steatosis. No patient had greater than F3 (Ishak) fibrosis, 24/28 were F0-F2. 27/44 patients developed portal vein thrombosis, 16 were anticoagulated. During 9.5 patient years of FU under anticoagulation, no major bleeding events occurred. At 5 years of NCPH follow up, 5 patients had died (3 liver cause), 1 had undergone orthoptic liver transplantation (OLT). After 10 years of FU, 7 had died (4 liver death), 5 had undergone OLT of whom 1 died. This gives a 5 year all-cause death and transplant free survival rate of 86% and a 10 year survival rate of 73%. 5 year liver death and transplant free survival rate of 91% and a 10 year survival rate of 79.6% 5 patients were transplanted. The indication for OLT was encephalopathy in 3 cases, recurrent ascites in 1 case and synthetic failure in 1 case. In the last case, the diagnosis of NRH was made on histology of the explanted liver. 1 patient died shortly post-transplant of gut ischaemia related to superior mesenteric vein thrombosis. Total follow up post OLT is 8.6 years.
Conclusion: We report a large cohort with a long duration of follow up for HIV associated NCPH. This is a serious condition with 27% of patients having died or undergone transplantation at 10 years. Anticoagulation was safe in this group. Many presented with subtle derangements of liver function, it is vital that HIV care providers maintain a high degree of clinical suspicion so patients can receive appropriate investigation and management.

Characteristic		N = 44 N(%)/Median (IQR)
Gender	M	26 (59%)
	F	18 (41%)
Ethnicity	Caucasian	20 (45%)
	Black African	24 (55%)
Age at presentation		45.4 (40.6, 50.4)
Presenting feature	Variceal bleed	14
	Ascites	9
	Derangement of LFTs	18
	Other (jaundice, anaemia)	3
History of DDI exposure		44/44 (100%)
Portal Vein Thrombosis		27/44 (63%)
HIV viral load <50 copies/ml		40/44 (90%)
CD4 cells/ml		291 (188, 393)

648 MR ELASTOGRAPHY DETECTS HIGHER LIVER FIBROSIS IN UNCONTROLLED HIV INFECTION

Marianna K. Baum[1], Sabrina S. Martinez[1], Richard L. Ehman[2], Kenneth E. Sherman[3], Pedro J. Greer[1], Jun Chen[2], Robert Laird[1], Angela Laird[1], Leslie Seminario[1], Angelique Johnson[1], Alhanoof Alohaly[1], Mukesh Mudgal[1], Alicia Sneij[1], Javier Tamargo[1], Adriana Campa[1]
[1]Florida International University, Miami, FL, USA, [2]Mayo Clinic, Rochester, MN, USA, [3]University of Cincinnati, Cincinnati, OH, USA

Background: Magnetic Resonance elastography (MRE) is a non-invasive, highly accurate method to assess hepatic fibrosis which is needed for therapeutic decisions or predicting disease outcomes. Studies to date have reported contradictory results regarding association between HIV mono-infection and liver fibrosis, possibly due to the difficulty in obtaining liver biopsies and using less accurate non-invasive indicators of liver disease in this population. The objective of this study was to examine the relationship between the extent of liver fibrosis in HIV mono-infected and non-infected adults.
Methods: After consenting 176 HIV mono-infected and 113 HIV/HBV/HCV un-infected adults from the Miami Adult Studies in HIV (MASH) cohort, demographics were collected. CD4 cell count and HIV viral load was obtained from medical charts. Controlled HIV viral load was defined as having <400 copies/mL. MRE was conducted on a 3T Siemens MAGNETOM Prisma MRI and mean stiffness of the liver was calculated through an inversion algorithm that generates elastogram/stiffness maps of the tissue in kilopascals. Statistical analyses were completed using frequencies, Wilcoxon Two-Sample test and regression models.
Results: The median age was 54 years (IQR: 49-59), 54.55% were male and 67.16% were African American. In those with HIV, 11% had detectable HIV viral load. Within the group infected with HIV, those who had undetectable HIV viral load had lower mean liver stiffness compared to those with detectable HIV viral load [2.266 kPa (IQR=2.480-1.970) vs. 2.237 kPa (IQR=2.450-1.950), P=0.025). Those who had detectable HIV viral load had a significantly higher mean liver stiffness compared to the uninfected group [2.691 kPa (IQR=3.080-2.180) vs. 2.237 kPa (IQR=2.450-1.950), P=0.024]. In a regression analysis, those with detectable HIV viral load had significantly higher mean liver stiffness (β=0.389, SE=0.180, P=0.033) after controlling for age, BMI, and CD4 cell count.
Conclusion: MRE, an accurate, non-invasive method to detect liver fibrosis in a cohort of HIV infected and HIV/HBV/HCV uninfected adults, shows that detectable HIV viral load is associated with more advanced liver fibrosis than when HIV viral load is undetectable or when patients are not infected. These results indicate a deleterious effect of the HIV virus on the liver and confirm earlier reported analyses using FIB-4 to estimate liver fibrosis in similar cohorts.

649 HIV AND CANCER RISK IN CONTEXT OF HIGH ART COVERAGE IN BOTSWANA

Scott Dryden-Peterson[1], Neo Tapela[2], Isaac Nkele[1], Oaitse John[1], Gita Suneja[3], Surbhi Grover[4], Memory Bvochora-Nsingo[5], Malebogo Pusoentsi[2], Joseph Makhema[1], Mompati O. Mmalane[1], Mukendi Kayembe[2], Shahin Lockman[1]
[1]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [2]Botswana Ministry of Health, Gaborone, Botswana, [3]Duke University, Durham, NC, USA, [4]Botswana–UPenn Partnership, Gaborone, Botswana, [5]Life Gaborone Private Hospital, Gaborone, Botswana

Background: Antiretroviral therapy (ART) has reduced incidence of Kaposi's sarcoma and several types of lymphoma. However, the impact of ART on risk of developing other cancers is less certain, particularly in sub-Saharan Africa where the great majority of HIV-infected individuals live. Botswana has nearly achieved the UNAIDS 90-90-90 targets. We sought to estimate the excess risk for cancer among people living with HIV in Botswana in the setting of high ART coverage.
Methods: We prospectively enrolled consenting patients presenting for specialized oncology care at the four principal treatment centers in Botswana (October 2010 to September 2017). Patients with unknown HIV status were tested. Cancer diagnoses were abstracted from clinical and pathologic records. After finding similar time to diagnosis and similar cancer stage, we assumed non-differential case capture by HIV status. We utilized population-representative data from the Botswana AIDS Incidence Survey (2013) to estimate age- and sex-standardized incidence ratios (SIR).
Results: A total of 2700 patients with cancer were enrolled, including 1477 (54.7%) with HIV and 1140 (42.2%) without HIV. Eighty-three patients (3.1%) with unknown HIV status were excluded from further analyses. The majority (68.2%) of cancer patients were women. For HIV-infected patients, median current CD4 cell count was 355 cells/μL (IQR 213 to 543) and 1189 (82.5%) were on ART at the time of their cancer diagnosis (median ART duration 4.8 years [IQR 1.2 to 8.8 years]). Of the 1075 with an available measurement (90.4%), 1028 (95.6%) had HIV viral load < 1000 copies/mL. Patients living with HIV were 3.3-fold more likely to develop cancer (95%CI 3.1 to 3.5) and excess risk was similar for men (SIR 3.5, 95%CI 3.2 to 3.9) and women (SIR 3.2 95%CI 3.0 to 3.4). With exception of breast and head and neck cancer, HIV was significantly associated with increased risk for all cancer types; estimated SIRs for individual cancers are shown in the Table. HIV infection accounted for an estimated 39.3% of cancer cases (population attributable fraction).
Conclusion: With ART coverage exceeding 80%, more than a third of cancer cases are attributable to HIV infection in Botswana. Cancers in HIV-infected populations remain a large public health challenge and strategies to mitigate this burden are urgently needed.

Cancer Type	Cases	SIR (95%CI) *HIV-infected vs. HIV-uninfected*	P-value
Cervix	661	5.7 *(5.2 to 6.3)*	<.001
Kaposi sarcoma	324	80.2 *(71.5 to 88.9)*	<.001
Non-Hodgkin lymphoma	123	5.5 *(4.3 to 6.7)*	<.001
Head and neck	165	1.3 *(0.98 to 1.7)*	0.063
Anus	84	4.3 *(3.2 to 5.5)*	<.001
Vulva and vagina	85	31.6 *(24.6 to 38.6)*	<.001
Penis	61	26.0 *(19.1 to 32.9)*	<.001
Hodgkin lymphoma	51	3.7 *(2.3 to 5.0)*	<.001
Breast	453	1.0 *(0.85 to 1.2)*	0.77
Esophagus	76	1.9 *(1.2 to 2.5)*	0.015
Other	516	1.2 *(1.05 to 1.4)*	0.016

Table: Standardized incidence ratios for cancer types and 95% confidence intervals (95%CI)

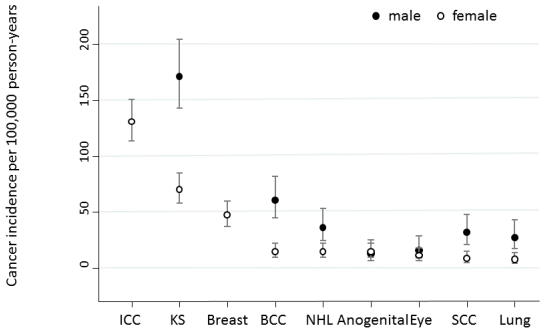
650 SOUTH AFRICAN HIV CANCER MATCH STUDY: A PILOT STUDY TOWARDS PRECISION PUBLIC HEALTH

Mazvita Sengayi[1], Wenlong C. Chen[1], Adrian Spoerri[2], Elvira Singh[1], Matthias Egger[2], Julia Bohlius[2]
[1]National Health Laboratory Service, Johannesburg, South Africa, [2]Institute of Social and Preventive Medicine, Bern, Switzerland

Background: Precision Public Health capitalizes on large population-based data to provide targeted interventions for well-defined populations. We use machine learning to create a national cohort of HIV-positive people with cancer outcomes in South Africa.
Methods: For this pilot study we retrieved laboratory test results for HIV-ELISA, CD4 cell counts and HIV-RNA from one South African province (Northern Cape) stored at the central data warehouse of the National Health Laboratory Service (NHLS) for the period 2004-2013. We used machine learning (dedupe; https://github.com/dedupeio/dedupe) to identify records belonging to the same person and created a cohort of unique HIV-positive persons. This cohort was then linked to the National Cancer Registry. Linkage variables included first names, surnames, date of birth and sex. Persons with ≥2 CD4 cell count measurements were included for analysis. We calculated cancer incidence rates per 100,000 person-years from the date of first CD4 cell count to cancer diagnosis or last CD4 cell count date, whichever came first. We present cancer incidence rates stratified by sex.
Results: We retrieved 653,071 laboratory records and created a cohort of 212,746 unique HIV-positive persons; 80,204 were included in incidence analyses. 66% were female, median age was 32 years (IQR 25-40) and median first CD4 cell count was 310 cells/μL (IQR 169-493). We identified 1,410 cancers, 63% (n=889) were incident. Overall cancer incidence per 100,000 person-years was 518 in men and 367 in women. The five cancers with the highest incidence rates were Kaposi sarcoma, cervical cancer, breast cancer, basal cell carcinoma of the skin and Non Hodgkin Lymphoma (Figure). After completion of the pilot study, we will use 49 million NHLS laboratory test results covering all South African provinces to create the national South African HIV Cancer Match Study.
Conclusion: Machine learning allows to create a national HIV cohort with cancer outcomes based on large laboratory and cancer registry data. The spectrum of cancers seen in this pilot study is similar to those in previous South

African studies. However, incidence rates are much lower, probably reflecting the poorer access to cancer diagnosis in this province. The South African HIV Cancer Match Study will allow to identify disadvantaged populations in need of targeted interventions, a step towards Precision Public Health.

Figure: Cancer Incidence in HIV-positive Men and Women, Northern Cape Province, South Africa



Legend: ICC Invasive Cervical Cancer, KS Kaposi Sarcoma, BCC Basal Cell Carcinoma, NHL Non Hodgkin Lymphoma, Anogenital (vulva, vagina, anus and penis), SCC Squamous Cell Carcinoma of the Skin

651 STILL HIGH RISK OF VIRUS-RELATED CANCER DESPITE 20 YEARS OF cART IN ICONA COHORT

Pierluca Piselli[1], Diego Serraino[2], Alessandra Bandera[3], Andrea Antinori[1], Enrico Girardi[1], Claudia Cimaglia[1], Alessandro Tavelli[4], Francesca Bai[5], Gianmaria Baldin[6], Andrea Calcagno[7], Antonella D'Arminio Monforte[5], Antonella Cingolani[6]
[1]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, [2]CRO Aviano National Cancer Institute, Aviano, Italy, [3]San Gerardo Hospital, Monza, Italy, [4]Icona Foundation, Milan, Italy, [5]University of Milan, Milan, Italy, [6]Catholic University of the Sacred Heart, Rome, Italy, [7]University of Turin, Turin, Italy

Background: The advent of combination antiretroviral therapy (cART) in 1996, led to a decreased incidence of several cancers, in particular AIDS-defining malignancies (ADMs, i.e. Kaposi sarcoma-KS, Non-Hodgkin lymphoma-NHL and Invasive Cervical Cancer-ICC), and among non-AIDS defining malignancies (NADMs) of virus-related e.g. Hodgkin's lymphoma (HL) or anal cancer. In our study, we quantified the incidence of cancer in a Large Italian cohort of ART-naïve persons with HIV or AIDS (PWHAs) HIV-diagnosed in the last 20 years (ICONA cohort).

Methods: Person years (PY) at risk of cancer in the ICONA cohort (1996-2016) were computed from 30 days after first HIV-diagnosis to cancer diagnosis, death, drop out or last follow-up. The risk of cancer was assessed through sex- and age-standardized incidence ratios (SIR) computed by dividing the observed cases with expected ones from Italian cancer registries. Age- and sex-standardized incidence rates (ASR) were computed using the entire cohort as reference population and stratified for calendar periods.

Results: Among 11761 PWHAs (77% males) during 69,221 PYs (median follow-up 4.8 years) with a median time at diagnosis of 2.3 years, 432 single new cancers were diagnosed in 421 enrolled individuals (3.6%), with overall incidence of 6.1 cases/103 PYs. ADMs represent most cancers (N=221, 51.2%), with a median time at cancer diagnosis of 0.9 years (4.2 among NADMs). Overall, significantly increased SIRs were observed for ADMs (SIR=18.4), and for virus-related NADMs (SIR=4.27), and overall for all virus-related cancers (SIR=11.0), but not for virus unrelated NADMs. (Fig.1 left panel). A reduced ASR over time was observed for KS and ICC from the first period ($p<0.001$) then remaining stable, but not for NHL, while a trend to an increasing incidence for virus-related NADMs was found in the first decade. ASR for virus unrelated NADMs remained overall stable [Fig.1 (right panels)].

Conclusion: A substantial higher incidence of cancer compared to general population was observed. Despite a decline over time for ADMs, risk of virus-related cancers remains elevated in the modern treatment era, possibly due either to sexual transmission of the causative virus or to persistent inflammation/immune activation. For not virus related cancers the incidence was comparable to that of general population and may represent an ageing effect, strongly suggesting additional efforts aimed at cancer prevention and screening among PWHAs.

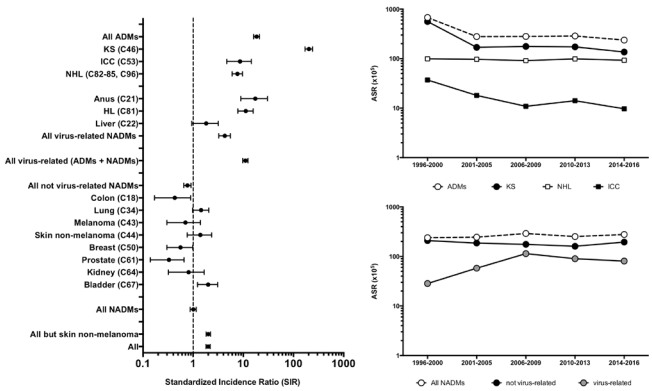


Figure 1. Standardized incidence ratio (SIR) for selected cancers (left panel). Age and sex standardized rates (ASR) per 10^5 population per calendar period for AIDS Defining Malignancies (ADMs, upper right panel) and non AIDS-Defining Malignancies (lower right panel). ADMs: AIDS-defining malignancies; NADMs: non AIDS-defining malignancies; ICC: Invasive cervical cancer; HL: Hodgkin's Lymphoma;

652 CANCER STAGE, TREATMENT, AND SURVIVAL COMPARING HIV CLINIC ENROLLEES AND SEER

Keri Calkins, Geetanjali Chander, Corinne Joshu, Anthony T. Fojo, Richard D. Moore, Bryan Lau
The Johns Hopkins University, Baltimore, MD, USA

Background: The effect of HIV on cancer stage, treatment, and survival is unclear and differences may be driven by immune suppression and/or access to care. We compared cancer outcomes among people with HIV (PWH) enrolled in care to the general US population, with a sub-analysis stratified by CD4 count.

Methods: We compared cancer stage at diagnosis, receipt of any cancer treatment, and restricted mean survival time (RMST) between 255 cancer cases in PWH enrolled in the Johns Hopkins HIV Clinical Cohort (JHHCC) and similar cases sampled from the NCI's Surveillance, Epidemiology and End Results Program (SEER), presumed to be largely HIV negative. We performed G-computation using random forest methods to estimate the effect of HIV on stage and treatment risk differences (RD) and on RMST differences, adjusting for demographic and cancer covariates. We also stratified the JHHCC by CD4 cell count ≤200 and >200 cells/mm^3, to examine effect modification by immune status at cancer diagnosis.

Results: The probability of localized cancer was 0.30 among PWH in JHHCC, while it was 0.07 in SEER (Risk difference (RD)= 0.24 [95% CI= 0.17, 0.31]). Similarly, the probability of distant cancer was 0.45 in JHHCC versus 0.07 in SEER (RD=0.38 [95% CI= 0.31, 0.43]). Among those in JHHCC with ≤CD4 200, 74% received any cancer treatment compared to 80% of SEER (RD=-0.06 [95% CI= -0.24, -0.02]), but there was no difference in cancer treatment overall or at higher CD4 levels. Table 1 provides a comparison of mortality after cancer diagnosis between JHHCC and SEER. Model 1 accounted for age, sex, race, year of diagnosis, and cancer type; while model 2 also adds CD4 count at cancer diagnosis. PWH had evidence of reduced survival of all cancers after adjusting for the model 1 covariates (RMST Difference= -3.4 months [95% CI= -7.1, -0.2]). The observed difference was larger when examining PWH with CD4 ≤200 adjusting for the model 2 covariates (-10.6 months [95% CI=-18.3, -4.9]). Differences in survival were no longer significant when stage and treatment were added to the models.

Conclusion: PWH are more likely to be diagnosed with cancer at earlier and later stages than the general US population, suggesting that HIV may contribute to faster progression and that engagement in HIV care may improve earlier detection. Survival differences were largely explained by cancer stage and treatment, although there is some evidence of lower rates of cancer treatment and higher mortality in those with low CD4 counts.

Table 1. Five year restricted mean survival time (RMST) among those enrolled in JHHCC and SEER.

Cancer Types	Model	JHHCC RMST Months	(95% CI)	SEER RMST Months	(95% CI)	RMST Difference Months	(95% CI)
All Cancers	Model 1[a]	32.9	(30.2, 35.9)	36.3	(34.1, 39.3)	-3.4	(-7.1, -0.2)
	Model 1+ Stage[b]	33.3	(30.2, 35.9)	33.1	(31.4, 37.8)	0.2	(-5.5, 2.4)
	Model 1+ Stage+ Treatment[c]	33.3	(30.3, 41.0)	34.8	(32.4, 40.0)	-1.5	(-5.1, 3.4)
CD4 ≤200	Model 2[d]	26.2	(20.3, 32.3)	36.8	(33.5, 42.4)	-10.6	(-18.3, -4.9)
	Model 2+ Stage[e]	28.0	(20.3, 32.1)	32.5	(28.3, 38.9)	-4.5	(-15.0, 0.2)
	Model 2+ Stage+ Treatment[f]	26.2	(20.2, 32.1)	33.0	(28.3, 38.8)	-6.8	(-14.8, 0.1)
CD4 >200	Model 2	36.6	(33.0, 44.4)	35.5	(33.1, 41.8)	1.1	(-3.3, 5.2)
	Model 2+ Stage	35.3	(33.1, 40.7)	33.1	(32.0, 38.4)	2.1	(-2.1, 5.5)
	Model 2+ Stage+ Treatment	36.6	(33.1, 40.7)	35.1	(32.0, 38.5)	1.6	(-2.1, 5.4)

[a] Model 1 includes cancer type, age, sex, race, and year of diagnosis.
[b] Model 1 + stage includes cancer type, age, sex, race, year of diagnosis, and cancer stage (localized, regional, distant, or unstaged).
[c] Model 1 + stage + treatment includes cancer type, age, sex, race, year of diagnosis, cancer stage, any chemotherapy, any radiation, and any surgery.
[d] Model 2 includes cancer type, age, sex, race, year of diagnosis, and CD4 cell count at diagnosis.
[e] Model 2 + stage includes cancer type, age, sex, race, year of diagnosis, CD4 cell count at diagnosis, and cancer stage.
[f] Model 2 + stage + treatment includes cancer type, age, sex, race, year of diagnosis, CD4 cell count at diagnosis, cancer stage, any chemotherapy, any radiation, and any surgery.

653 RISK OF NON-AIDS-DEFINING CANCERS AMONG VETERANS WITH WELL-CONTROLLED HIV INFECTION

Aaron P. Thrift, Kathryn E. Royse, Peter A. Richardson, Suchismita Raychaudhury, Roxanne Desiderio, Donna L. White, Jennifer R. Kramer, Elizabeth Chiao

Baylor College of Medicine, Houston, TX, USA

Background: The introduction of combined antiretroviral therapy has revolutionized HIV-infection management, resulting in improved outcomes and survival for HIV-infected individuals. However, as individuals with HIV are living longer and aging, their risk of mortality from cancer has increased. We aimed to examine risk of non-AIDS-defining cancers (NADC) in a large contemporary cohort of patients with well-controlled HIV infection during the antiretroviral therapy era.

Methods: This was a retrospective cohort study from a total of 121 facilities in the Veterans Health Administration. Veteran patients with HIV diagnosis between 1 October 1999 and 31 December 2016 were included and followed until cancer diagnosis, death or 12/31/2016. NADCs were identified using the VA Clinical Cancer Registry, and included esophageal, stomach, lung, head and neck, colorectal, prostate, liver, anal, oropharyngeal, and Hodgkin lymphoma. We compared the incidence rate of all NADCs combined in veterans with HIV with those in a matched cohort (4:1 matched on age, sex, and date of HIV-matched diagnosis) of veterans without HIV infection. We also report incidence rates separately for esophageal, stomach, lung, and prostate cancers.

Results: We identified 46,765 patients with HIV infection who met our study eligibility criteria. Most were men (96.9% of follow-up time) and aged 40 to 59 years at HIV infection (65.7%). Further, African Americans (48.2%) and whites (40.9%) were the two largest race/ethnicity groups. During 430,595 person-years of follow-up, 4020 patients develop a NADC (all cancers combined), yielding an incidence rate of 9.34 per 1,000 person-years (95% confidence interval [CI] 9.05-9.63). Incidence rates were highest among persons aged >70 years and Asians. The incidence rate of all NADCs combined was almost 5-fold higher among the HIV cohort relative to the non-HIV cohort (incidence rate, 1.96 per 1,000 person-years). Among HIV-infected patients, risk of esophageal, stomach, lung and prostate cancer were 2.93-fold (0.17 vs. 0.06 per 1,000 person-years), 2.86-fold (0.12 vs. 0.04 per 1,000 person-years), 4.64-fold (2.22 vs. 0.48 per 1,000 person-years), and 3.52-fold (2.71 vs. 0.75 per 1,000 person-years) higher relative to the non-HIV cohort, respectively.

Conclusion: People with HIV infection are at increased risk for developing common NADCs compared to age-matched controls in the antiretroviral therapy era. Further research is needed to understand the reasons for this increased risk.

654 TRENDS IN INCIDENCE OF KAPOSI SARCOMA AMONG MALES IN ALL 50 UNITED STATES, 2000-2013

Aaron P. Thrift, Donna L. White, Harrison Nguyen, Kathryn E. Royse, Jennifer R. Kramer, Elizabeth Chiao

Baylor College of Medicine, Houston, TX, USA

Background: Kaposi sarcoma (KS) is the most common neoplasm of people living with HIV today. Although the overall incidence of KS has been reported to be declining in the US, KS has strong racial/ethnic, age, and regional diversity in incidence trends.

Methods: We analyzed KS incidence data from the US Cancer Statistics (USCS) registry for the years 2000-2013. The USCS registry is the official data source for federal government–reported cancer incidence statistics and covers 97% of the US population. Women were excluded because of the low numbers of KS cases in certain geographic regions. We also restricted our analyses to the 20 to 54 year-old age-group as prior validation studies indicated that ~94% of KS cases in this age-range are HIV-related. We calculated adjusted incidence rates and assessed annual trends among sociodemographic and geographic subgroups using joinpoint regression analysis.

Results: During the study period, 11,712 men were diagnosed with KS. The overall incidence of KS among men decreased from 1.42/100,000 in 2000 to 0.92/100,000 in 2013, decreasing by 3.60% (95% confidence interval [CI], -4.00% to -3.13%) annually. The average annual percentage change (AAPC) between 2000 and 2013 was higher in Hispanics (AAPC, -5.72%; 95% CI, -7.19% to -4.23%) than in non-Hispanic whites (AAPC, -4.53%; 95% CI, -5.32% to -3.74%) and in Blacks (AAPC, -3.70%; 95% CI, -4.34% to -3.06%). While KS incidence decreased by 5.39% per year among 30-44-year-old individuals (95% CI, -7.19% to -4.23%), the incidence of KS increased among 20-29-year-old individuals (AAPC, 2.48; 95% CI, 0.83% to 4.16%) and remained stable among 45-54-year-old individuals (AAPC, -0.26; 95% CI, -0.95% to 0.44%). Between 2003 and 2013, KS incidence rates were highest in Georgia (2.69/100,000), New York (2.07/100,000), California (1.91/100,000), Florida (1.81/100,000) and Texas (1.32/100,000). While overall incidence decreased in New York (AAPC, -4.64%; 95% CI, -6.65% to -2.45%), California (AAPC, -4.95%; 95% CI, -6.65% to -3.21%), Florida (AAPC, -7.56%; 95% CI -9.43% to -5.65%) and Texas (AAPC, -4.43%; 95% CI -7.29% to -1.49%) between 2003 and 2013, incidence rates remained stable in Georgia (AAPC, 2.35%; 95% CI -1.14% to 5.96%).

Conclusion: Geographic and racial disparities in KS incidence remain. Georgia has the highest incidence rates, and, unlike in other high incidence states where incidence has decreased, the incidence of KS has remained unchanged in Georgia.

655 KNOWLEDGE OF KAPOSI SARCOMA (KS) AND HIV AMONG TRADITIONAL HEALERS IN ZIMBABWE

Suzanne P. Fiorillo[1], Francis Jaji[2], Maxwell Matimba[2], Thomas Campbell[1], Margaret Borok[2]

[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [2]University of Zimbabwe, Harare, Zimbabwe

Background: Traditional healers play a major role in providing health care in Africa and many HIV-infected people seek care from traditional healers while simultaneously receiving Western-style medical care. This pluralistic practice can result in treatment delays, late diagnosis and higher mortality rates for HIV-related conditions, including Kaposi sarcoma (KS). This study aimed to evaluate traditional healer knowledge of HIV and KS and the perceptions of people with KS who have sought care from traditional healers.

Methods: Between September 2015 and February 2016, traditional healers were invited to attend one of 11 informational sessions conducted by KS medical experts at 8 clinics in Zimbabwe. Healers were asked to complete a survey about their knowledge and experience in treating KS and HIV. KS clients were asked to complete a survey about their perceptions towards traditional healers. Qualitative results were organized into themes and analyzed.

Results: Data were obtained from 406 traditional (30%), faith (32%) and herbalist (38%) healers. Faith and herbal healers were more likely to be older and more educated than traditional healers (both $p<0.0001$). Among healers, 76% claimed familiarity with KS and had treated clients with the disease. Over half (55%) of healers had positive opinions toward medical treatment only for KS and HIV, and 20% of healers recommended that both traditional and medical practitioners work together in treating the diseases. Healers were more knowledgeable of the accepted medical treatment for HIV but had limited knowledge of treatment options for KS. Healers would more often recommend traditional medicines; such as herbs, supplements, dietary concoctions or spiritual guidance, for treating KS than for HIV. Surveys from 395 KS clients were obtained, with 115 (29%) having visited a healer before. Those who had visited a healer were more likely to be rural rather than urban dwellers (OR 1.6; $p=0.05$) and 82% visited a healer specifically for KS consultation; 17% were 'somewhat', 'very' or 'definitely' satisfied with the care received from a healer whereas 94% had the same satisfaction with the care received at the medical clinic.

Conclusion: Traditional healers are often the first care provider for many seeking KS treatment and a collaborative approach toward care should be considered. Even though knowledge of medical treatment of HIV has increased, better understanding of KS disease by traditional healers could help with earlier diagnosis and linkage to medical care.

656LB INTERIM SAFETY ANALYSIS OF CITN-12: PEMBROLIZUMAB IN PATIENTS WITH HIV AND CANCER

Thomas S. Uldrick[1], Priscila H. Gonçalves[2], Steven Fling[1], Brinda Emu[3], Marc S. Ernstoff[4], Judith Kaiser[1], Matthew Lindsley[2], Lisa Lundgren[1], Kathryn Lurain[2], Rob Gorelick[5], Frank Maldarelli[2], Elad Sharon[2], Robert Yarchoan[2], Martin "Mac" A. Cheever[1]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [2]National Cancer Institute, Bethesda, MD, USA, [3]Yale University, New Haven, CT, USA, [4]Roswell Park Cancer Institute, Buffalo, NY, USA, [5]National Cancer Institute, Frederick, MD, USA

Background: Anti-PD-1 and anti-PD-L1 antibodies are becoming mainstays of cancer therapy. The safety of pembrolizumab, an anti-PD-1 humanized monoclonal antibody, is being evaluated in patients with HIV and cancer. The effect of anti-PD-1 therapy on HIV reservoirs is unknown.

Methods: Cancer Immunotherapy Trials Network (CITN)-12 is a multicenter study of pembrolizumab in patients with HIV and advanced cancers. Three CD4 defined cohorts (C) are accruing; C1: 100-199, C2: 200-350, and C3: >350 cells/uL. Eligibility: >4 weeks antiretroviral therapy (ART), HIV viral load <200 copies/mL. Treatment: pembrolizumab 200mg intravenously every 3 weeks for up to 2 years. Primary objective: assess safety and tolerability by summarizing CTCAEv4 graded adverse events (AEs) and evaluating HIV viral load (VL) and CD4 counts. Immune mediated AEs are managed using standard guidelines. We performed an interim analysis of treatment emergent adverse events at least possibly related to pembrolizumab (rTEAEs), serious AEs, and CD4 counts on therapy. Plasma HIV VL was measured by an HIV gag single copy assay (SCA).

Results: 17 patients were accrued starting April 2016 and followed through May 2017. Characteristics: 1 woman, 16 men; median age 56 years (range 43-77); Cancers: lymphoma (3), Kaposi sarcoma (1), anal (5), tonsil (1), lung (2), bladder (1), hepatocellular (1), pancreatic (1), cholangiocarcinoma (1). Safety was observed over 100 total cycles, median 4 (range 1-20). 82 rTEAEs were observed and comparable between cohorts. 93% were grade 1-2. Ten primary serious AEs were observed, 2 possibly attributable to pembrolizumab, both in the setting of progressive malignancy. Immune mediated AEs: subclinical hypothyroidism 6 (35%), pneumonitis (2) and liver test elevations (2). Median CD4 increased over time, changes did not reach statistical significance. HIV remained suppressed on ART in all patients. In a subset of 14 patients, baseline median HIV VL by SCA was 0.8 copies/mL (range: <0.3-9.9); In an evaluation of plasma HIV kinetics over the first two cycles, no significant increases from baseline were noted.

Conclusion: Pembrolizumab has an acceptable safety profile to date in patients with cancer and suppressed HIV on CITN-12, with no evidence of increased HIV VL over 6 weeks of therapy. Anti-PD1 therapy is appropriate for FDA approved indications in HIV-infected patients. Studies evaluating HIV latency reversal and HIV-specific immunity are underway.

657 SUPPRESSIVE ART ASSOCIATED WITH EFFECTIVE TREATMENT OF CERVICAL PRECANCER

Christina Carlander[1], Philippe Wagner[2], Astrid van Beirs[3], Aylin Yilmaz[4], Kristina Elfgren[5], Joakim Dillner[1], Anders Sönnerborg[1], Pär Sparén[1]

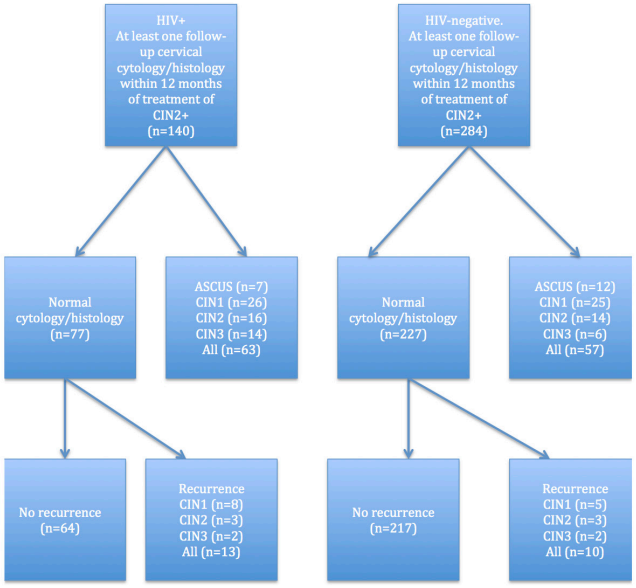
[1]Karolinska Institute, Stockholm, Sweden, [2]Uppsala University, Uppsala, Sweden, [3]Linköping University, Linköping, Sweden, [4]Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden, [5]Karolinska University Hospital, Stockholm, Sweden

Background: It is uncertain what effect suppressive antiretroviral therapy (ART) (HIV-RNA<50 copies/mL) has on the results of CIN2+ treatment among women living with HIV (WLWH). We conducted a matched register-based national cohort study with the aim of analyzing: 1) if WLWH in Sweden have a poorer outcome after treatment of CIN2+ than HIV-negative women 2) to identify predictors of CIN2+ treatment failure and recurrence.

Methods: The Swedish National HIV Registry and the Swedish Population Registry were linked with the Swedish National Cervical Screening Registry. We identified all WLWH, living in the Counties of Stockholm and Gothenburg sometime between 1983 and 2014, with a diagnosis of cervical intraepithelial neoplasia grade 2 or worse (CIN2+). For each WLWH we randomly selected two HIV-negative women, living in the same counties sometime between 1983 and 2014, diagnosed with CIN2+, matched for country of birth. Additional data, such as surgical method, was collected from medical records. Treatment failure was defined as the presence of an abnormal cervical cytology/histology at initial follow-up. Recurrence was defined as the presence of CIN1+ subsequent to an initial normal follow-up. Logistic regression and Cox regression were used to estimate the effect of predictors of treatment failure and recurrence respectively. All models were adjusted for age and birth region.

Results: A total of 140 WLWH and 284 HIV-negative women were treated for CIN2+ and had at least one follow-up cervical cytology/histology within one year and were not treated with a hysterectomy. WLWH were three times more likely to have a treatment failure (odds ratio (OR) 3.3 (95% CI 2.1-5.2) and five times more likely to recur (hazard ratio 5.0 (95% CI 2.1-11.6) than HIV-negative women. Suppressive ART at time of treatment of CIN2+ was associated with reduced odds of treatment failure (OR 0.4 (95% CI 0.2-0.8)). Advanced immunosuppression (CD4+T-cell/μL<200) at time of treatment of CIN2+ was associated with almost nine times higher odds of treatment failure than a CD4 count ≥500 (OR 8.9 (95% CI 2.9-27.7).

Conclusion: To our knowledge this is the first study to show that suppressive ART and CD4 counts ≥500 at time of treatment are both associated with an effective treatment of CIN2+. An early HIV diagnosis, immediate ART and continuum of care are all essential to reach successful CIN2+ treatment.



658 LEEP TREATMENT OF EXTENSIVE CERVICAL INTRAEPITHELIAL NEOPLASIA IN HIV-INFECTED WOMEN

Sharon A. Greene[1], Hillary M. Topazian[2], Hugo De Vuyst[3], Christine J. McGrath[1], Barbra A. Richardson[1], Grace John-Stewart[1], Anthony Cagle[1], Evans Nyongesa-Malava[1], Nelly Yatich[1], Catherine Kiptinness[1], Sameh Sakr[4], Nelly R. Mugo[1], Michael H. Chung[1]

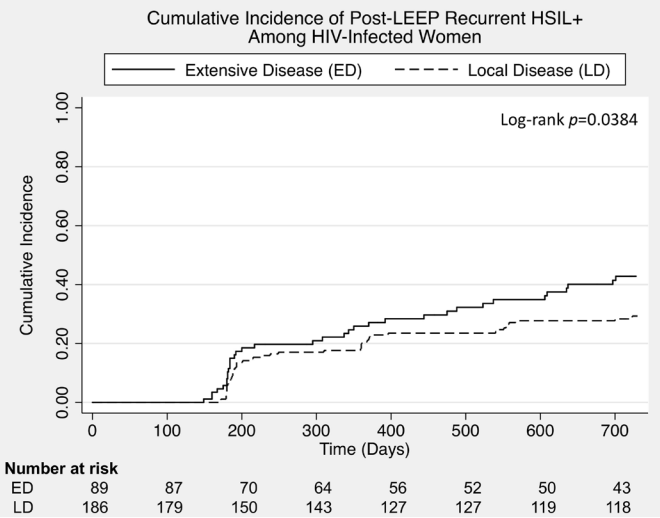
[1]University of Washington, Seattle, WA, USA, [2]Harvard University, Cambridge, MA, USA, [3]International Agency for Research on Cancer, Lyon, France, [4]Coptic Hospital, Nairobi, Kenya

Background: WHO guidelines recommend loop electrosurgical excisional procedure (LEEP) in resource-limited settings for histologically confirmed cervical intraepithelial neoplasia 2/3 (CIN2+) regardless of HIV status or extent of lesion. We determined the incidence and correlates of recurrence following LEEP among HIV-infected women with CIN2+.

Methods: From June 2011 to July 2014, HIV-infected women enrolled at the Coptic Hope Center for Infectious Diseases in Nairobi, Kenya underwent cervical cancer screening with Papanicolaou (Pap) smear. Women with high grade squamous intraepithelial lesions (HSIL) and CIN2+ diagnosed by colposcopy-directed biopsy or endocervical curettage (ECC) were treated with LEEP. Recurrence of pre-cancerous cervical disease was defined as HSIL+ on Pap smear taken every 6 months for 2 years. Outcomes were compared between women with biopsy-confirmed CIN2+ lesions limited to the ectocervix (ECL) and ECC-confirmed CIN2+ lesions indicating endocervical involvement (ENL) using Chi-square tests and Cox proportional hazards regression.

Results: Among 275 women who received LEEP at baseline, 186 women with ECL had a median age of 37 years, [interquartile range (IQR), 31-44], 92% were on antiretroviral therapy (ART), 34% had low CD4 (<250 cells/μl) and 69% were treated for CIN3. Eighty-nine women with ENL had a median age

of 40 (IQR 36-46), 89% were on ART, 28% had low CD4 and 81% were treated for CIN3. The rate of HSIL+ recurrence was 16.7 per 100 woman-years for ECL and rose to 27.8 for ENL. Women with ENL were significantly more likely to be ≥40 years, compared to women with ECL (53% vs 39%, P=0.034) and report younger age of sexual debut, ≤16 years (39% vs 26%, P=0.059). At the end of follow-up, women with ENL experienced significantly higher recurrence than those with ECL (40% vs 27%; P=0.030). Women treated for ENL were 56% more likely to experience recurrence than women with ECL (Hazard Ratio: 1.56, 95% confidence interval: 1.02-2.39; P=0.039). Recurrence among women with ENL was associated with age ≥40 years (P=0.031) and antecedent pathology of CIN3 (P=0.052), but not with low CD4 <250 cells/μl (P=0.364) or ART use (P=0.975).
Conclusion: Pre-cancerous lesions with endocervical involvement among HIV-infected women were more likely to occur in older women and were 36% less likely to be successfully treated with LEEP compared to lesions limited to the ectocervix. Immune status and ART did not modify recurrence risk after LEEP in HIV-infected women with endocervical involvement.



659 GENE PROFILE INFORMS HPV GRADE BUT NOT RELAPSE AFTER LEEP IN ART-SUPPRESSED HIV+HPV+

Emmanouil Papasavvas[1], Andrew V. Kossenkov[1], Livio Azzoni[1], Nicola M. Zetola[2], Agnieszka Mackiewicz[1], Brian Ross[1], Matthew Fair[1], Surya Vadrevu[1], Doreen Ramogola-Masire[2], Cindy Firnhaber[3], Luis Montaner[1]
[1]Wistar Institute, Philadelphia, PA, USA, [2]Botswana–UPenn Partnership, Gaborone, Botswana, [3]University of the Witwatersrand, Johannesburg, South Africa

Background: No intrinsic human papillomavirus (HPV)-associated gene expression signature able to distinguish between high risk (HR) HPV infection, cervical histopathology, or recurrence following loop electrosurgical excision of the transition zone of cervix (LEEP) has been identified. Human immunodeficiency virus 1 (HIV-1) infection alters the course of HPV-associated oncogenesis, while the role of antiretroviral therapy (ART) in this process is controversial. We performed a cross-sectional study to assess the impact of the transcriptional profile of the cervical microenvironment on cervical histopathology, and on recurrence/relapse of pre-malignant lesions following LEEP in ART-suppressed HIV+HPV+ women.
Methods: Gene array analysis was performed on RNA isolated from paraffin-embedded cervical tissue collected from ART-suppressed HIV+HPV+ women from: A) South Africa: 55 women recruited in three groups: HR (-) (group 1, n=16) and HR (+) (group 2, n=15) HPV with negative cervical histopathology, and HR (+) (group 3, n=24) HPV with Cervical Intraepithelial Neoplasia (CIN) grade 1/2/3. B) Botswana: 28 women with CIN2/3 lesion grade who underwent LEEP, recruited in two groups based on a 12-month follow-up: women with (n=13) and without (n=15) lesion recurrence/relapse. Tissue in this cohort was collected at the time of LEEP. All gene groups identified had false discovery rate (FDR) <15%, and fold change >1.5.
Results: Neoplasia-associated genes (n=272 genes) were a feature of dysplasia independently of the presence of HR types, as suggested by enrichment in cervical CIN 1/2/3 dysplasia for MCM2, SMC1B, CXCL6, MMP12, POU4F1, IL-1A, IL-8, and TCAM1 among other genes. This finding was also supported by the identification of group-specific genes: group 1-specific genes (n=22, e.g. ITIH5, PCBP4, NANOS1, PARP1) and group 2-specific genes [n=81, e.g. PTPRD, EYA4, TNMD, SFRP5, TIGIT, CDKN1A, UHRF1, IL-21R, CDC42, EGR3, SIRPG, CCL22, NR4A3, E2F8, SELL, CTLA4, ATF3, FCRL3). No significant difference in gene expression was found in dysplastic lesions from women with or without recurrence/relapse, despite a trend for enrichment of neoplasia-associated genes observed in women with recurrence/relapse following LEEP.
Conclusion: An enrichment in neoplasia-associated cervical gene expression was detected as an indicator of cervical dysplasia independently of high-risk HPV type infection, or of the potential for recurrence/relapse after LEEP excision in ART-suppressed women.

660 IMPACT OF SINGLE-DOSE NANOVALENT VACCINE FOR HIV-HPV COINFECTION IN SOUTH AFRICA

Nicholas Tan, Monisha Sharma, Ruanne V. Barnabas
University of Washington, Seattle, WA, USA

Background: Women in sub-Saharan Africa have high dual burden of HPV and HIV infections, which can interact to increase cervical cancer (CC) risk. The 9-valent HPV (9vHPV) vaccine has high demonstrated effectiveness against HPV types causing 90% of CC. Additionally, one dose of the 9vHPV vaccine has the potential to achieve greater coverage at lower costs than a two-dose schedule. However, the potential impact of the single-dose 9vHPV vaccine in a high HIV prevalence setting has not been estimated while accounting for HPV-HIV interactions.
Methods: We adapted a dynamic HIV transmission model to include HPV acquisition and CC pathogenesis and projected the impact of a single dose 9vHPV preadolescent vaccination in KwaZulu-Natal, South Africa. We report the health impact of HPV vaccination separately for HIV-negative women and HIV-positive women stratified by HIV treatment and CD4 count status.
Results: At 90% coverage of females age 9 years with 80% lifelong vaccine efficacy, single dose HPV vaccination was projected to reduce both CC incidence and mortality by 56% at 70 years after the start of the vaccination program. Mortality reductions were highest in HIV-positive females at high CD4 counts (60%). Health benefits were reduced when assuming waning protection at 20 years, with a 30% reduction in CC and a 31% reduction in CC-associated mortality.
Conclusion: Single dose 9vHPV vaccination is projected to avert substantial CC burden in South Africa and similar high HIV prevalence settings. Results were dependent on assumptions of vaccine coverage, efficacy, and waning.

661 COST-EFFECTIVENESS OF CERVICAL CANCER SCREENING IN WOMEN WITH HIV IN SOUTH AFRICA

Nicole G. Campos[1], Naomi Lince-Deroche[2], Carla J. Chibwesha[3], Cindy Firnhaber[4], Pamela Michelow[5], Gesine Meyer-Rath[6], Lise Jamieson[2], Suzette Jordaan[7], Vivien Tsu[8], Jose Jeronimo[9], Jane Kim[1]
[1]Harvard University, Cambridge, MA, USA, [2]Health Economics and Epidemiology Research Office, Johannesburg, South Africa, [3]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [4]Clinical HIV Research Unit, Johannesburg, South Africa, [5]National Health Laboratory Service, Cape Town, South Africa, [6]Boston University, Boston, MA, USA, [7]National Health Laboratory Service, Johannesburg, South Africa, [8]PATH, Seattle, WA, USA, [9]Global Coalition Against Cervical Cancer, Arlington, VA, USA

Background: Women with HIV face increased risk of human papillomavirus (HPV) acquisition and persistence, cervical intraepithelial neoplasia, and invasive cervical cancer. WHO guidelines recommend cervical cancer screening every three years for these high-risk women, but the cost-effectiveness of different screening strategies has not been established.
Methods: To evaluate the health impact and cost-effectiveness of screening among women with HIV in South Africa, we modified a mathematical model of HPV infection and cervical disease to reflect co-infection with HIV. The model was calibrated to epidemiologic data from HIV-infected women in South Africa (i.e., age-specific prevalence of HPV; proportion of HPV type-specific infections in CIN3 and cervical cancer). Clinical and economic data were drawn from in-country data sources. The model was used to project reductions in the lifetime risk of cervical cancer, discounted life expectancy, discounted lifetime costs, and incremental cost-effectiveness ratios (ICERs) of alternative Pap and HPV DNA testing algorithms beginning at HIV diagnosis. We considered screening performed at 1-, 2-, or 3-year intervals. Strategies with an ICER below South Africa's per capita GDP (2016 US$5,270) were considered 'cost-effective.'

Results: HPV testing followed by treatment (test-and-treat) at 2-year intervals was the most effective strategy that was also cost-effective, reducing lifetime cancer risk by 56.6% with an ICER of US$3,010 per year of life saved (YLS) (Table). Other cost-effective strategies included Pap testing (referral threshold: HSIL+) at 1-, 2-, and 3-year intervals, and HPV test-and-treat at 3-year intervals. Pap (referral threshold: ASCUS+), HPV testing with 16/18 genotyping, and HPV testing with Pap or visual triage of HPV-positive women were less effective and more costly than alternatives (i.e., dominated). HPV test-and-treat was consistently the most effective strategy that was also cost-effective as costs, test performance, visit compliance, cryotherapy eligibility, and treatment effectiveness were varied. The ICER for HPV test-and-treat at 2-year intervals fell to $1,500/YLS when the cost of HPV testing was reduced to $20/test.
Conclusion: Screening HIV-infected women with an HPV test-and-treat approach is cost-effective in South Africa. If resources are available, this population may benefit from screening more frequently than every 3 years. Price reductions in HPV tests would further improve cost-effectiveness.

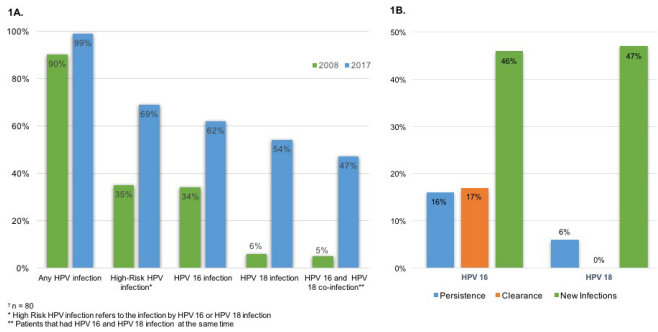
Screening strategy	Lifetime cost (US$, discounted)	Life expectancy (discounted)	ICER (US$/YLS)
No screening	2,227	19.937	--
Pap (HSIL+), 3y	2,272	20.069	340
Pap (HSIL+), 2y	2,294	20.094	900
HPV (test-and-treat), 3y	2,338	20.119	1,780
HPV (visual triage), 3y	2,351	20.110	dominated
Pap (HSIL+), 1y	2,358	20.127	2,420
Pap (ASCUS+), 3y	2,362	20.096	dominated
HPV (test-and-treat), 2y	2,393	20.138	3,010
HPV (visual triage), 2y	2,403	20.129	dominated
Pap (ASCUS+), 2y	2,403	20.117	dominated
HPV (16/18 gen), 3y	2,405	20.072	dominated
HPV (Pap triage), 3y	2,412	20.097	dominated
HPV (Pap triage), 2y	2,461	20.115	dominated
Pap (ASCUS+), 1y	2,474	20.141	dominated
HPV (16/18 gen), 2y	2,478	20.091	dominated
HPV (visual triage), 1y	2,523	20.149	dominated
HPV (test-and-treat), 1y	2,551	20.158	8,020
HPV (Pap triage), 1y	2,552	20.135	dominated
HPV (16/18 gen), 1y	2,669	20.115	dominated

662 CLEARANCE, PERSISTANCE, AND NEW HPV INFECTIONS IN A MEXICAN MSM - HIV COHORT

Ofelia M. Rosales Del Real[1], Rocio Mendez Martinez[2], Yanink Caro-Vega[1], Norma E. Rivera-Martínez[1], Alejandro M. García-Carrancá[2], Juan Sierra-Madero[1], Brenda Crabtree-Ramírez[1]
[1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Instituto Nacional de Cancerología, Mexico City, Mexico

Background: Incidence of anal cancer has been increasing in people living with HIV over the years despite the use of cART. Human Papillomaviruses (HPVs) cause genital warts and cancers in men. Information about the natural history of HPV infection in terms of persistence and clearance in men who have sex with men (MSM) is scarce, and that information is needed for prevention strategies. We aim to estimate the proportiuon of patients with clearance, persistence and new cases of anal HPV infection among MSM population at a tertiary site of care in Mexico City.
Methods: From a previous study of HPV prevalence in MSM population conducted in 2008 at "Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán" we invited patients retained in care 9 years after. All participants signed informed consent and answer a sexual risk behavior questionnaire applied also in 2008. We obtained anal exudate to extract DNA and amplified HPV sequences with consensus primers, with subsequent detection of specific types of HPV with commercial kit INNO-LiPA HPV Genotyping Extra II (FUJIREBIO) to compare with previous detection in 2008 in order to determinate persistence, clearance and new infections by HPV serotypes. Descriptive proportions were used to asses clearance, persistence and new cases of specific anal HPV infection in the study population.
Results: From the 328 participants in 2008, 275 were retained, 125 were offered to enter to the study and 80 had HPV results. The 80 patients included were on cART had a median CD4 count of 598 cell/mm^3 (RIC 533-693) and 97.5% had viral suppression (defined as <50 copies/mL). Prevalence of any HPV infection increased from 90% in 2008 to 99% in 2017 Detailed HPV infection serotype can be seen in Figure 1(A). Clearance of HPV infection was seen only in 14 cases in type16, but not for type 18. There were 18 persistent high-risk HPV infections, 13 in type 16 and 5 in type 18, with a proportion of new infections of HPV of 46% for type 16 and 47% for type 18; Figure 1(B).
Conclusion: The lack of clearance, high persistence and new high-risk HPV infection in MSM- HIV infected population with high CD4 cell counts and virological suppression, indicates the urgent need of prevention strategies.

Figure 1 A. Proportion of HPV anal infections by serotype, in 2008 and 2017 †. B. Persistence, Clearance and New High-risk HPV infections †.



† n = 80
* High Risk HPV infection refers to the infection by HPV 16 or HPV 18 infection
** Patients that had HPV 16 and HPV 18 infection at the same time

663 AGE-SPECIFIC PREVALENCE OF VACCINE-PREVENTABLE ANAL HPV INFECTION IN HIV-INFECTED MSM

Alessandra Latini[1], Maria Gabriella Dona[1], Manuela Colafigli[1], Mauro Zaccarelli[2], Maria Benevolo[3], Francesca Rollo[3], Domenico Moretto[1], Amalia Giglio[1], Antonio Cristaudo[1], Massimo Giuliani[1]
[1]San Gallicano Dermatology Institute, Rome, Italy, [2]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, [3]Regina Elena National Cancer Institute, Rome, Italy

Background: The availability of prophylactic HPV vaccines provides a unique opportunity to prevent HPV and related diseases in HIV-infected patients, who are particularly susceptible to anal infections and at high-risk for anal cancer. We aimed to assess the age-specific prevalence of the HPV genotypes included in the quadrivalent (qHPV) and nonavalent (nHPV) HPV vaccines in HIV-infected MSM.
Methods: HIV-infected MSM (≥18-year-old) attending the HIV/AIDS Unit of the S. Gallicano Dermatological Institute in Rome, Italy, were recruited from September 2009 to March 2016. They were not vaccinated for HPV infection and had no signs or symptoms of ano-genital HPV-related disease. Data on medical history, socio-demographic factors and sexual behavior were collected through face-to face interviews. Anal samples were collected using a Dacron swab and dispersed in PreservCyt (Hologic). HPV-DNA detection and genotyping was carried out using the Linear Array® HPV Genotyping Test (Roche Diagnostics).
Results: Three hundred thirteen subjects were eligible. Median age was 41 years (IQR:34-48). Median age at first same sex intercourse was 19 years (IQR:17-22) and the median number of lifetime and recent sex partners were 60 (IQR:20-200) and 3 (IQR:1-6), respectively. At baseline, 88.0% of the patients were on cART, 78.0% were aviremic and the median CD4+ count was 596/mm^3 (IQR: 430-722). Overall anal HPV prevalence was 95.2% (95% CI: 68.2–77.0). At least one of the qHPV types was detected in 49.5% (CI 95%: 43.8-55.2) of the patients, and 71.2% (CI 95%:65.9-76.2) harbored at least one of the types included in the nHPV vaccine. MSM aged 25-29 years harbored the highest prevalence of both qHPV and nHPV types (67.7% and 93.5%, respectively). The lowest prevalence was observed in MSM ≥45 years (40.8% and 60.0% for qHPV and nHPV, respectively). A significant linear decrease in the prevalence of both qHPV (chi-square=4.33; p=0.040) and nHPV types (chi-square=14.37; p<0.001) was observed (i.e. from 18-24 age group to ≥45).
Conclusion: The prevalence of anal HPV infection among successfully treated HIV-infected MSM is dramatically high. Compared to the qHPV vaccine, a substantially higher proportion of patients could benefit from vaccination with the nHPV vaccine. Based on the observed age-specific distribution of nHPV types, the potential benefits of vaccination appear to be achievable across all ages, but particularly in HIV-infected MSM younger than 30 years of age.

664 ABLATION OUTCOMES FOR HIV INFECTED AND UNINFECTED PATIENTS WITH ANAL DYSPLASIA

Keith M. Sigel, Yuxin Liu, Michael Gaisa
Icahn School of Medicine at Mt Sinai, New York, NY, USA

Background: Human papilloma virus (HPV) associated high-grade intraepithelial lesions (HSIL) are the putative anal cancer (AC) precursors and are highly prevalent in HIV infected (HIV+) patients. Screening and local ablation of anal HSIL has been proposed for high-risk patients but is associated with substantial recurrence rates. Using data from a large AC screening cohort, we evaluated long-term outcomes following HSIL ablation.

Methods: We identified 427 participants in our anal dysplasia screening program with histologically confirmed HSIL who were treated with electrocautery ablation. Using high-resolution anoscopy, surveillance was conducted within 12 months to assess treatment response. HSIL identified in the same anatomic region of the anal canal as the previously ablated index lesion was defined as persistent, whereas new HSIL independent from the index lesion were defined as metachronous. We also defined overall recurrence as the presence of either persistent or new metachronous lesions on follow-up. Baseline demographic information, sexual behaviors, smoking, HIV biomarkers, and number of HSIL were abstracted from a clinical database. Using unadjusted and multivariable analyses, we then examined frequency of outcomes and predictors of HSIL recurrence.

Results: Our cohort largely consisted of men who have sex with men (93%) and 91% of subjects were HIV+. HSIL persistence after ablation was 39% (Table 1; 95% confidence interval [CI]: 34%-43%) and did not differ significantly by HIV status or sexual behavior. No invasive cancers were detected on follow-up. Metachronous HSIL at follow-up was found in 27% (95% CI: 23%-31%) of subjects. The combined outcome of persistent or metachronous HSIL (overall recurrence) occurred in 53% and was more frequent in HIV+ persons (56% vs. 28%; p=0.001). 194 (45%) subjects had more than one HSIL lesion on baseline examination; this group had a higher risk of HSIL persistence than those with solitary lesions (48% vs. 32%; p=0.001). No other factors were associated with risk of HSIL persistence, including age, race/ethnicity, smoking, and (among HIV+ subjects) baseline HIV viral suppression and CD4 count. HIV infection was associated (odds ratio 3.2; 95% CI: 1.5-6.9) with overall recurrence of HSIL after adjustment for baseline number of lesions.

Conclusion: In our cohort, over a third of anal HSIL persisted after electrocautery ablation. HIV+ patients with multiple index lesions at baseline are at a higher risk of recurrence and may require careful surveillance.

	N	Persistent HSIL		Metachronous HSIL		Either Persistent or Metachronous HSIL ("Overall Recurrence")	
		n (%)	p	n (%)	p	n (%)	p
HIV+	391	157 (40)	0.1	112 (29)	0.009	218 (56)	0.001
HIV-	36	10 (28)		3 (8)		10 (28)	

665 PATTERNS OF REPEATED ANAL CYTOLOGY TESTING AMONG HIV-POSITIVE AND HIV-NEGATIVE MSM

Hilary Robbins[1], Dorothy J. Wiley[2], Ken Ho[3], Michael Plankey[4], Susheel Reddy[5], Nancy Joste[6], Teresa Darragh[7], Elizabeth Breen[2], Stephen Young[6], **Gypsyamber D'Souza**[1]
[1]Johns Hopkins Hospital, Baltimore, MD, USA, [2]University of California Los Angeles, Los Angeles, CA, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA, [4]Georgetown University, Washington, DC, USA, [5]University of Chicago, Chicago, IL, USA, [6]University of New Mexico, Albuquerque, NM, USA, [7]University of California San Francisco, San Francisco, CA, USA

Background: Men who have sex with men (MSM) are at increased risk for anal cancer, and this risk is further elevated among HIV-positive MSM. In cervical cancer screening, patterns of repeated cytology are used to identify low- and high-risk women, but little is known about these patterns for anal cytology among MSM.

Methods: We analyzed data from MSM in the Multicenter AIDS Cohort Study (MACS) who were offered anal cytology testing annually (HIV-positive, n=708) or every 2 years (HIV-negative, n=796) for 4 years. After excluding men with anal dysplasia treatment during testing, at least 2 valid cytology results were available for 474 HIV-negative and 502 HIV-positive MSM, and at least 3 results for 328 HIV-positive MSM. We used inverse probability weighting to address possible selection bias.

Results: Following a single negative cytology, the frequency of the next cytology remaining negative was lower among HIV-positive MSM with CD4≥500 (74%) or CD4<500 (68%) than HIV-negative MSM (83%) (p<0.001). Alternatively, after a single abnormal cytology, the frequency of the next cytology remaining abnormal was highest among HIV-positive MSM with CD4<500 (70%) compared to CD4≥500 (53%) or HIV-negative MSM (46%) (p=0.003). Among HIV-positive MSM, 37-38% had 3 consecutive negative results, while the proportion with 3 consecutive abnormal results was larger among CD4<500 (22%) than CD4≥500 (10%) (p=0.008).

Conclusion: Many HIV-positive MSM have consistently negative anal cytology over a four-year period. Following abnormal anal cytology, a repeated cytology is commonly negative in HIV-negative and HIV-positive MSM, although persistent cytological abnormality is more likely among HIV-positive MSM with CD4<500.

666 EFFECTIVENESS OF A SCREENING PROGRAM FOR ANAL CANCER PREVENTION IN HIV-INF. PATIENTS

Boris Revollo, Sebastia Videla, Arelly Ornelas, Roger Paredes, Josep Coll, Marta Piñol, Francesc García-Cuyás, Antoni Tarrats, David Parés, Ross Cranston, Bonaventura Clotet, Guillem Sirera
Fundació Lluita Contra la Sida, Badalona, Spain

Background: Anal cancer screening is key to detection and treatment of precancerous lesions in HIV-infected patients but its impact on survival is debated. We compared the incidence of invasive anal squamous cell carcinoma (IASCC) in HIV-infected patients included in a single-center anal cancer screening program (screening cohort) with that from subjects from the same center who where not included in the program (non-screening cohort).

Methods: All subjects were HIV-1 infected adults from single tertiary care center in Catalonia, Spain, and all had at least 6 months of clinical follow up between January 2005 and December 2014. Subjects included in the screening program received an anal cytology every 6 to 12 months. High-resolution anoscopy and directed biopsy were performed for those with ASCUS, LSIL or HSIL anal cytology. AIN lesions on biopsy were treated. The incidence of IASCC was estimated and compared with that of subjects who declined to participate in the screening cohort but had followed at least 2 regular clinical visits during one year within the same study period.

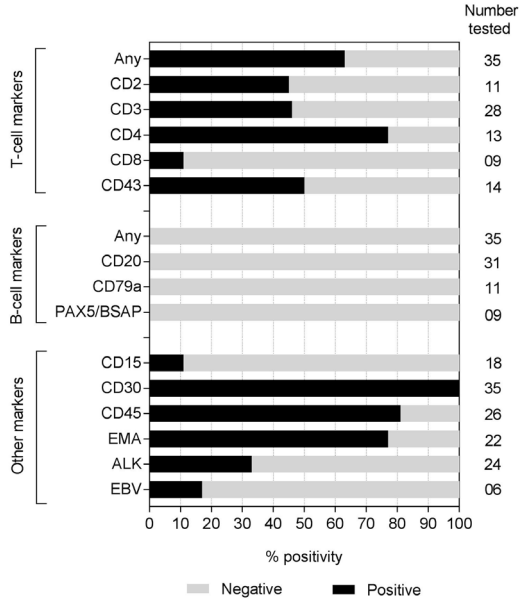
Results: 3343 subjects (1546 men who have sex with men (MSM), 914 men who have sex with women (MSW), 723 women, and 160 men with no data on sexual orientation) were included, 1916 of them (57%) followed the prospective anal cancer screening (median 4.4 person-years of follow-up) and the remaining 1427 (43%) did not (median 5.7 person-years of follow-up). Both cohorts were well balanced in terms of age, gender, duration of HIV-1 infection, time on antiretroviral therapy, CD4+ T-cell counts and HIV-1 RNA at the first study visit and nadir CD4+ T-cell counts. Subjects in the screening cohort were predominantly MSM (62.1% MSM, 14.7% MSW) whereas those in the non-screened cohort where predominantly MSW (25% MSM, 44.3% MSW) (p<0.001). Ten IASCC were diagnosed during the study follow-up: 2 (both MSM) in screening cohort and 8 (4 of them in MSM, 2 in women and another 2 in MSW) in non-screening cohort. The cumulative incidence was 0.01% (95%CI: 0.03-0.4%) and 0.6% (95%CI: 0.3-1.1%) respectively, p-value: 0.023. The incidence rate was 0.02 per 100 person-years in the screening cohort and 0.09 per 100 person-years in non-screening cohort, p-value: 0.151.

Conclusion: Engagement on an anal cancer-screening program is associated with lower incidence of IASCC. Women and MSW might also benefit from such program.

667 ANAPLASTIC LARGE CELL LYMPHOMA IN HIV-INFECTED INDIVIDUALS

Parag Mahale[1], Dennis D. Weisenburger[2], Amy R. Kahn[3], Lou Gonsalves[4], Karen Pawlish[5], Lori Koch[6], Mirabel Tirado-Gomez[7], Christina A. Clarke[8], Glenn Copeland[9], Georgetta Alverson[9], Meredith S. Shiels[1], Eric A. Engels[1]
[1]NCI, Rockville, MD, USA, [2]City of Hope National Medical Center, Duarte, CA, USA, [3]New York State Department of Public Health, Albany, NY, USA, [4]Connecticut Department of Public Health, Hartford, CT, USA, [5]New Jersey Department of Health, Trenton, NJ, USA, [6]Illinois Department of Public Health, Springfield, IL, USA, [7]Puerto Rico Department of Health, San Juan, PR, USA, [8]GRAIL, Inc, Menlo Park, CA, USA, [9]Michigan Department of Health and Human Services, Lansing, MI, USA

Background: HIV-infected (HIV+) people have elevated risk of several non-Hodgkin lymphoma (NHL) subtypes due to loss of immune control of Epstein-Barr virus (EBV) infection. HIV+ people reportedly have a high risk for anaplastic large cell lymphoma (ALCL), a rare CD30+ T-cell NHL. However, ALCL is morphologically similar to variants of diffuse large B-cell and Hodgkin lymphoma, which may be misclassified as ALCL. Herein, we evaluated pathology reports of ALCL cases in HIV+ people to confirm the diagnosis and determined risk factors for ALCL.
Methods: We used data from the HIV/AIDS Cancer Match Study (HACM) (1996-2012), which links US HIV and cancer registries. When available, deidentified pathology reports of ALCL cases were acquired by participating cancer registries and evaluated by a hematopathologist. Immunohistochemistry or flow cytometry results for expression of CD30, T and B cell surface markers, anaplastic lymphoma kinase (ALK) protein, and EBV status of tumors were extracted. Risk of confirmed ALCL in HIV+ people relative to the general population was calculated as a standardized incidence ratio (SIR). ALCL risk factors among HIV+ people were evaluated using Poisson regression.
Results: We identified 132 ALCL cases in HIV+ people. Based on review of 39 pathology reports, 35 (90%) were confirmed as ALCL. All confirmed ALCL cases were CD30+, none was positive for any B-cell marker, and 22 (63%) were positive for at least one T-cell marker (see Figure). Only 8 cases (33%) were ALK+ ALCLs. EBV was detected in 1 of only 6 tumors tested (17%). Risk of confirmed ALCL was strongly elevated among HIV+ people compared to the general population (SIR=6.9; 95%CI=5.4-8.6). ALCL incidence was highest among 40-49-year-olds (adjusted incidence rate ratio [aIRR]=3.8 vs. 0-29-year-olds), lower among females (aIRR=0.7), and was lower among non-Hispanic blacks compared to whites (aIRR=0.6). Risk was also significantly higher among HIV+ people who had AIDS compared to those who did not (aIRR=2.2). ALCL incidence declined sharply with increasing CD4+ T-cell count (aIRR=0.18 for CD4+ T-cell count ≥500 cells/μL vs. <200 cells/μL).
Conclusion: Our pathology review confirmed the diagnosis of ALCL for most cases identified in cancer registries. ALCL is rare, but risk is highly elevated among HIV+ people and is especially increased among those with AIDS or a low CD4+ T-cell count, supporting a role for immunosuppression. Based on limited data, EBV does not appear to contribute to ALCL in HIV+ individuals.



Abbreviations: CD, cluster of differention; PAX5, Paired box protein-5; BSAP, B-cell lineage specific activator protein; EMA, epithelial membrane antigen; ALK, anaplastic lymphoma kinase; EBV, Epstein-Barr virus

668 CNS-IPI AS RISK MODEL FOR CNS RELAPSE IN HIV-ASSOCIATED DIFFUSE LARGE B-CELL LYMPHOMA

Alessandra Bandera[1], Davide Dalu[2], Ilaria De Benedetto[1], Elisa Colella[1], Gaia Bombonati[2], Elisa Doni[1], Fulvio Crippa[3], Omar Giglio[4], Maurizio Mena[5], Elisa Suardi[3], Paola Vitiello[6], Carlo Gambacorti Passerini[7], Andrea Gori[7], Luisa Verga[1]
[1]San Gerardo Hospital, Monza, Italy, [2]Luigi Sacco University Hospital, Milan, Italy, [3]University of Milan, Milan, Italy, [4]Sant'Anna Hospital, Como, Italy, [5]Ospedale Civile di Legnano, Legnano, Italy, [6]Ospedale di Circolo di Busto Arsizio, Busto Arsizio, Italy, [7]University of Milano–Bicocca, Milan, Italy

Background: CNS relapse is an important and most often fatal event in patients (pts) affected by Diffuse Large B cell lymphoma (DLBCL). Recently, a risk score (CNS-IPI) predicting CNS relapse has been validated in HIV-negative population with DLBCL. Aim of our study was to evaluate the rate of CNS relapse in HIV+ pts as regard to CNS-IPI score.
Methods: Observational, multicenter, cohort study involving 6 centres in Lombardia, Italy. HIV+ pts with DLBCL diagnosis observed from 2009 to 2015 were included. CNS-IPI was estimated including IPI score plus kidney and/or adrenal glands involvement (scored 1 point if present or 0 if absent). Three levels of CNS relapse risk were defined: low risk (LR: 0-1 points), intermediate risk (IR: 2-3 points), high risk (HR: 4-6 points). Chi-square or Fisher's exact test and Kruskal-Wallis test were used for comparison of discrete and continuous variables, respectively.
Results: Sixty-one HIV+ pts with DLBCL were included. Characteristics of pts at lymphoma diagnosis: 90% male; median age 49 years; median CD4+ T cells 224 cells/mm^3; 70.5% on antiretroviral treatment (ART); 93.4% treated with R-CHOP regimen; 54% with IPI ≥3; 19.7% pts underwent intratechal (IT) prophylaxis. According to CNS-IPI, we defined 13 pts (21.3%) at HR, 38 pts (62.3%) at IR and 10 pts (16.4%) at LR of CNS relapse. Pts belonging to HR group displayed significantly higher number of extranodal sites (84.6% showing 2-4) as compared to IR and LR groups (20% and 0% showing 2-4, respectively, p=0.03). In addition, pts with HR score showed a poor ECOG PS (61.5% with > 2) as compared to intermediate and low CNS relapse risk (20% and 20% with ECOG PS > 2, respectively, p=0.01). No significant associations emerged among HIV-related factors (current and nadir CD4+ T cells, HIV-RNA, use of ART) and CNS-IPI. After a median follow-up of 28 months (range 4-96), 6 pts (9.8%) displayed CNS relapse. CNS relapse was significantly more frequent in CNS-IPI HR pts (4/13, 30.8%) as compared to CNS-IPI IR or LR pts (2/30, 6.7% and 0/10, 0%, respectively, p=0.049) (figure 1). Risk of death was also significantly higher in CNS-IPI HR group (69.2%) as compared to IR and LR groups (33.3% and 0%, respectively; p<0.0001).
Conclusion: Our data support the use of CNS-IPI score as a valuable prognostic tool of CNS relapse in HIV+ pts with DLBCL. CNS directed-investigations and prophylactic interventions could be tailored according to this risk model in future interventional studies.

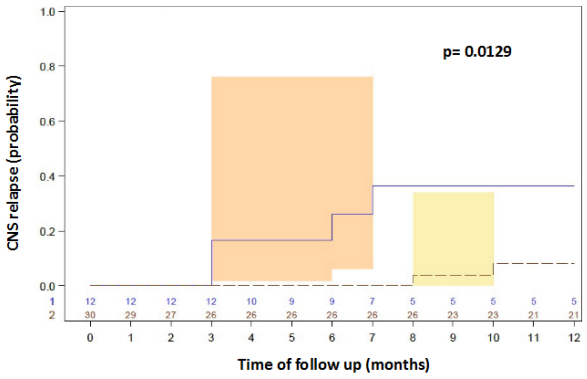


Figure 1. Kaplan-Meyer estimates of CNS relapse probability according to CNS-IPI high risk **(solid line)** and CNS-IPI intermediate risk **(dashed line)**

669 PRESENTATION AND OUTCOME OF BIOPSY-PROVEN HEPATOCELLULAR CARCINOMA BY HIV STATUS

Jessie Torgersen[1], Lesley Park[2], Tamar Taddei[3], Dena M. Carbonari[1], Michael J. Kallan[1], Kisha Mitchell-Richards[4], Xuchen Zhang[3], Kathryn D'Addeo[3], Rajni Mehta[3], Farah Kidwai-Khan[3], Amy C. Justice[3], Vincent Lo Re[1]
[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Stanford University, Stanford, CA, USA, [3]Yale University, New Haven, CT, USA, [4]Greenwich Hospital, Greenwich, CT, USA

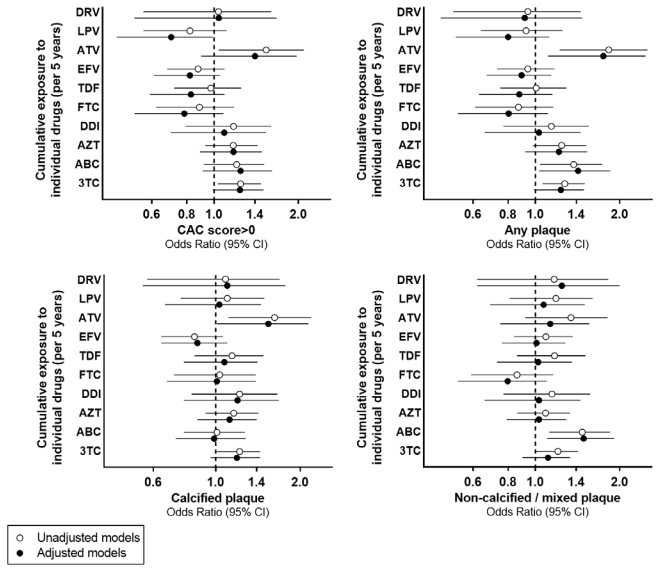
Background: HIV+ patients have a two- to four-fold higher risk of hepatocellular carcinoma (HCC) than uninfected individuals. Despite the

importance of HIV on HCC incidence, few studies have evaluated patients with biopsy-proven HCC to examine differences in background hepatic fibrosis, tumor differentiation, HCC stage, and survival between HIV+ and uninfected persons.
Methods: We performed a cohort study of HIV+ and uninfected patients with HCC diagnosed between 2000 and 2016 within the Veterans Aging Cohort Study (VACS). We identified patients who underwent liver biopsy and collected the reports of pathologists' reviews of these specimens. Demographics, comorbidities, background liver fibrosis on biopsy, tumor characteristics, American Joint Committee on Cancer (AJCC) stage, and survival after biopsy was compared by HIV status. Hepatitis virus co-infection status was determined by laboratory test results. Cox proportional hazards regression was used to determine hazard ratios (HRs) of factors associated with death after biopsy-proven HCC, including HIV, hepatitis B virus (HBV) coinfection, hepatitis C virus (HCV) coinfection, level of alcohol consumption, and advanced hepatic fibrosis present on biopsy.
Results: Among 304 patients (median age, 58.4 years; 99% male; 59% black) with biopsy-proven HCC, 134 (44%) were HIV+ with no significant differences in demographics by HIV status. HIV+ patients more commonly were infected with HBV (14% vs. 3%; p<0.001), but not RNA-confirmed HCV infection (78% vs. 83%; p=0.18). There were no differences in tumor differentiation, prevalence of advanced hepatic fibrosis/cirrhosis, or HCC stage by HIV status. Median survival after diagnosis was shorter for HIV+ than uninfected patients (397 days [IQR: 127, 1127] vs. 565 days [IQR: 202, 1522]; log-rank: p=0.05). After adjustment for age, race, alcohol use, HBV, HCV, advanced hepatic fibrosis, and HCC stage, the risk of death after diagnosis was higher for HIV+ than uninfected persons (HR, 1.33 [95% CI, 1.00-1.78]).
Conclusion: In this sample of patients with biopsy-proven HCC, there were no differences in tumor differentiation, background hepatic fibrosis, or HCC stage between HIV+ and uninfected persons. However, HIV was associated with poorer survival after diagnosis. Future studies should evaluate the impact of HCC treatments by HIV status.

670 ANTIRETROVIRAL DRUGS ASSOCIATED WITH SUBCLINICAL CORONARY ARTERY DISEASE

Helen Kovari[1], Alexandra Calmy[2], Thanh Doco-Lecompte[2], René Nkoulou[2], Alex Marzel[1], Rainer Weber[1], Philipp A. Kaufmann[1], Ronny R. Buechel[1], Bruno Ledergerber[1], Philip E. Tarr[3]
[1]University Hospital Zurich, Zurich, Switzerland, [2]University Hospitals of Geneva, Geneva, Switzerland, [3]University of Basel, Basel, Switzerland

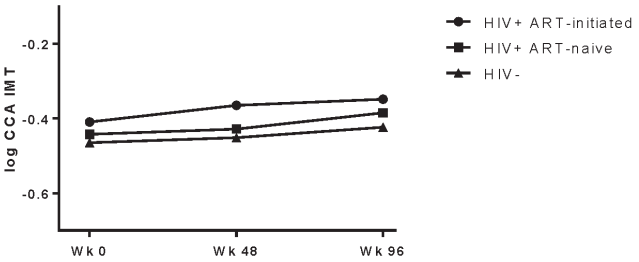
Background: Definite and validated coronary artery disease (CAD) events have been associated with certain antiretroviral therapy (ART) agents. In contrast, the influence of ART drugs on early, subclinical atherosclerosis as determined by coronary artery calcium (CAC) scoring and coronary CT angiography (CCTA) is yet to be elucidated.
Methods: In this prospective study of ≥45 year old Swiss HIV Cohort Study participants, CAC scoring and CCTA were performed. The following subclinical CAD endpoints were analysed separately: CAC score >0, any plaque, calcified plaque, and non-calcified/mixed plaque on CCTA. Logistic regression was used to explore associations between the different CAD endpoints and cumulative exposure to ART, ART classes, and the ten most often used individual drugs. Covariables included sex, age, smoking, hypertension, dyslipidemia, diabetes, CD4 nadir <50 cells/µL, and peak HIV-1 RNA >100'000 copies/mL.
Results: We included 428 participants (mean age 52 years, 86% men, 91% Caucasian, 35% current smokers, 60% homosexual, median CD4 cell count at cardiac imaging 598 cells/µL, 93% on ART, 87% with undetectable HIV-1 RNA). CAC score >0 was recorded in 227 (53%) patients, any plaque in 226 (53%), calcified plaque in 158 (37%), and non-calcified/mixed plaque in 158 (37%) participants, respectively. Cumulative exposure to PIs was associated with calcified plaque (adjusted odds ratio (aOR) per 5 years 1.21 [95% confidence interval, 1.01-1.46]). The associations between cumulative exposure to individual ART drugs and different CAD outcomes are shown in the figure. Adjustment for covariables did only marginally affect point estimates. CAC score >0 was not associated with any individual ART drug. Any plaque was associated with cumulative exposure to regimens containing atazanavir (aOR per 5 years 1.66 [1.11-2.47]), and abacavir (1.38 [1.03-1.85]). Calcified plaque was associated with exposure to atazanavir (1.47 [1.01-2.14]). Non-calcified/mixed plaque was associated with exposure to abacavir (1.45 [1.10-1.91]).
Conclusion: We found an increased risk of coronary artery plaque in patients exposed to regimens containing atazanavir or abacavir independent of CAD risk factors. Atazanavir was associated with calcified plaque whereas abacavir was associated with non-calcified/mixed plaques. Although adjustment for traditional cardiovascular risk factors only marginally affected associations with individual drugs, we cannot fully exclude residual confounding.



671 CAROTID IMT PROGRESSION IS MOST STRIKING IN FIRST 48 WEEKS OF ANTIRETROVIRAL THERAPY

Corrilynn O. Hileman[1], Grace A. McComsey[2]
[1]MetroHealth Medical Center, Cleveland, OH, USA, [2]University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Background: Studies are mixed as to whether common carotid artery intima media thickness (CCA IMT) progression is more accelerated in HIV+ vs. HIV- and the role of contemporary ART and systemic inflammation remain unclear.
Methods: This is a 4-year prospective, observational, cohort study of ART-naïve HIV+ adults and age- and sex-matched HIV- healthy controls designed to evaluate CCA IMT progression measured by high resolution ultrasound annually. Subjects were followed for at least 96 weeks after the last subject enrolled. Mixed effects linear modeling was used to compare CCA IMT measurements over time among HIV+ who remained ART-naïve, HIV+ who initiated ART and HIV-. Potential contributors to CCA IMT progression including traditional cardiovascular disease (CVD) risk factors and soluble markers of systemic inflammation were evaluated.
Results: 130 adults were enrolled (85 HIV+; 45 HIV-). Among HIV+, 44 initiated ART (45% NNRTI; 39% PI; 9% RAL) and 41 remained ART-naïve. Overall, mean age was 39 with 74% men. There were more smokers in HIV+ (56% vs. 18% in HIV-) and higher Framingham risk score (FRS) of 4% vs 3% in HIV-. None had previously diagnosed CVD or diabetes. Mean duration of HIV (5.6 years) and baseline HIV-1 RNA (15,473 copies/ml) were similar among HIV+, but nadir CD4+ was slightly lower in the HIV+ who initiated ART (453 vs. 525 cells/mm^3; p=0.04). Baseline CCA IMT was similar between groups (0.653 ± 0.109 mm). Over time, CCA IMT progressed similarly in HIV+ ART-naïve and HIV- groups (p=0.55); however, there was a trend towards ART-initiation leading to greater CCA IMT over time compared to HIV- (p=0.05)(see figure). Adding baseline FRS, sCD163, IL-6 and hsCRP each in turn attenuated this association. In the HIV+ ART-initiated group, mean absolute change over 48 weeks before and after ART were -0.003 mm (p=0.75 within-group) and 0.039 mm (p=0.01), respectively (p=0.04 between pre-and post-ART 48 week changes). Interestingly, from 48 weeks to 96 weeks post-ART the change declined to 0.013 mm (p=0.52 within-group and p=0.63 between pre- and post-). The only predictor of CCA IMT increase in the first 48 weeks after ART was higher baseline sVCAM-1 (p=0.01).
Conclusion: CCA IMT progressed significantly in the first 48 weeks after ART initiation and the HIV+ ART-initiated group had significantly greater CCA IMT over time when compared to HIV-. Both traditional CVD risk factors and systemic inflammation contributed to this difference.



Symbols represent mean log-transformed CCA IMT by group at each time point. Group by time interaction was not statistically significant.

672 EFFECTS OF ANTIRETROVIRAL THERAPY ON ALLELE-ASSOCIATED LIPOPROTEIN(A) LEVEL IN HIV

Enkhmaa Byambaa[1], Anuurad Erdembileg[1], Chin-Shang Li[1], Robert C. Kaplan[2], Jason Lazar[3], Daniel Merenstein[4], Roksana Karim[5], Bradley E. Aouizerat[6], Mardge H. Cohen[7], Kenneth R. Butler[8], Savita Pahwa[9], Igho Ofotokun[10], Adaora Adimora[11], Elizabeth T. Golub[12], Lars Berglund[1]

[1]University of California Davis, Davis, CA, USA, [2]Albert Einstein College of Medicine, Bronx, NY, USA, [3]SUNY Downstate Medical Center, Brooklyn, NY, USA, [4]Georgetown University, Washington, DC, USA, [5]University of Southern California, Los Angeles, CA, USA, [6]New York University, New York City, NY, USA, [7]Cook County Health & Hospitals System, Chicago, IL, USA, [8]University of Mississippi, Jackson, MS, USA, [9]University of Miami, Miami, FL, USA, [10]Emory University, Atlanta, GA, USA, [11]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [12]Johns Hopkins Hospital, Baltimore, MD, USA

Background: An elevated level of lipoprotein(a) [Lp(a)] is a causal risk factor for cardiovascular disease (CVD). Lp(a) levels are regulated by a size polymorphism in the apolipoprotein(a) [apo(a)] gene. In general, small apo(a) sizes are associated with a high Lp(a) level and an increased CVD risk. HIV infection and antiretroviral therapy (ART) have been shown to increase CVD risk. We demonstrated a significant positive association between Lp(a) level and subclinical atherosclerosis in HIV-seropositive women. Currently, the effects of ART initiation on Lp(a) level in relation to apo(a) size polymorphism remain unclear.

Methods: The effects of ART initiation on Lp(a) levels and allele-specific apo(a) levels (ASL), the Lp(a) level associated with the larger or smaller apo(a) allele in each individual, were assessed in 126 HIV-seropositive women in the Women's Interagency HIV Study. ART effects were tested by a mixed-effects model over three time points (the visit before ART initiation and the first and third visits after ART initiation). Data from 120 HIV-seronegative control women assessed at a single time point were used for comparison.

Results: Mean age of the cohort was 38 ± 8 years; most were African-American (~70%). Pre-ART ASL associated with the larger (median: 4.6 mg/dL vs. 8.0 mg/dL, p=0.024) or smaller (median: 13 mg/dL vs. 19 mg/dL, p=0.041) apo(a) sizes in the HIV-seropositive group were significantly lower compared to those in the HIV-seronegative group. Similarly, pre-ART prevalence of a high (≥30 mg/dL) Lp(a) level was lower in the HIV-seropositive vs. seronegative group (30% vs. 46%, p=0.013). However, post-ART both ASL or prevalence of a high Lp(a) level in the HIV-seropositive group did not differ significantly compared to those in the HIV-seronegative group. The median sizes for the larger or smaller apo(a) isoforms and frequency of a small size apo(a) (≤22 Kringle repeats) were similar across the HIV status. Notably, ART initiation significantly increased: 1) Lp(a) level [from pre-ART level of 18 mg/dL to post-ART level of 24 mg/dL, p<0.0001), and 2) ASL associated with the larger (5 mg/dL to 6 mg/dL, p=0.0003) or smaller (13 mg/dL to 16 mg/dL, p<0.0001) apo(a) sizes.

Conclusion: ART initiation increased Lp(a) level and both ASL in HIV-seropositive women. Lp(a) level, regardless of its strong genetic regulation, can be modulated by HIV and its treatment. ART-induced increases in Lp(a) level could contribute to the higher CVD risk seen in HIV-seropositive individuals.

673 COMPARATIVE IMPACT OF ANTIRETROVIRALS ON HUMAN PLATELET ACTIVATION

Kirk A. Taylor[1], Francesca Rauzi[1], Erica Smyth[1], Mark Nelson[2], Brian Gazzard[2], Michael Emerson[1]

[1]Imperial College London, London, UK, [2]Imperial College Healthcare NHS Trust, London, UK

Background: Some HIV therapeutics in the nucleos(t)ide reverse transcriptase (N(t)RTI) inhibitor class (i.e. abacavir sulphate [ABC]) are reportedly associated with increased risk of cardiovascular events, such as myocardial infarction (MI). Increased MI risk is hypothesised to result from altered platelet reactivity in response to antiretroviral therapy. Thus, it is important to determine the impact of N(t)RTIs, including newly emerging therapeutics, such as tenofovir alafenamide (TAF), upon platelet aggregation as part of the process of determining their potential cardiovascular risk profile.

Methods: *In vitro*: Platelets were isolated from healthy, HIV-negative, donors and aggregation assessed *in vitro* using a 96-well plate assay. Platelets were pre-incubated with plasma C_{max} concentrations of N(t)RTIs and stimulated by platelet agonists (ADP, collagen, TRAP6 or thrombin). Platelet activation (granule release and integrin activation) was further assessed by multi-colour flow cytometry. *In vivo*: Collagen-evoked radiolabelled platelet aggregation was monitored in mice following i.p. administration of N(t)RTIs.

Results: Platelet aggregation in response to ADP, collagen or TRAP6 was unaffected by incubation with ABC, TAF or TDF (tenofovir disoproxil fumarate). Equivalent plasma concentrations of tenofovir (TFV) or carbovir triphosphate (Cbv-TP) also did not lead to altered platelet aggregation in vitro. Treatment with Cbv-TP, but not TFV, led to a reversal of NO-mediated inhibition of platelet aggregation. ABC significantly enhanced expression of platelet activation markers whereas TAF and TDF had no effect (see Table 1). These increases demonstrate increased degranulation, indicating enhanced platelet activation and potentially a pro-thrombotic impact, in the presence of ABC. *In vivo* studies showed normal platelet aggregation responses in the presence of TAF or TDF, whereas ABC potentiated aggregation, again indicative of a pro-thrombotic effect.

Conclusion: The reported increased MI risk in patients prescribed ABC may be driven by pharmacological modulation of the platelet activation response as well as interruption of NO-mediated inhibition of platelet aggregation, resulting in a greater propensity for agonist-induced platelet activation. Unlike earlier clinical studies, our observations are made in the absence of HIV infection, allowing assessment of direct pharmacological impacts of N(t)RIs on platelets.

Table 1: Changes in flow cytometric markers of platelet activation following pre-incubation with antiretrovirals

Antibody	Activation Marker	Agonist-evoked marker expression relative to control (mean ± sem; arbitrary units)		
		ABC	TAF	TDF
PAC-1 (Activated integrin αIIbβ3)	Active conformation of the platelet fibrinogen receptor	+4.0 ± 2.1 (P>0.05)	-1.5 ± 2.1 (P>0.05)	-1.4 ± 1.5 (P>0.05)
CD62P (P-selectin)	Release of platelet alpha granules	+2.2 ± 0.9 (P<0.01)	-0.6 ± 1.2 (P>0.05)	-0.2 ± 1.0 (P>0.05)
CD63 (LAMP-3)	Release of platelet dense granules	+4.2 ± 1.6 (P<0.001)	-0.2 ± 1.0 (P>0.05)	-0.0 ± 1.8 (P>0.05)

674 LEUKOCYTES ARE KEY TO THE PRO-THROMBOTIC EFFECTS OF ABACAVIR

Victor Collado-Diaz[1], Ainhoa Sanchez-Lopez[1], Samuel Orden[2], Maria Amparo Blanch-Ruiz[1], Maria Angeles Martinez-Cuesta[1], Isabel Andujar[2], **Angeles Alvarez**[1], Juan V. Esplugues[1]

[1]University of Valencia, Valencia, Spain, [2]FISABIO, Valencia, Spain

Background: Abacavir (ABC) shares a close structural similarity with endogenous purines like ATP and ADP, which are important signalling molecules in vascular physiopathology. ABC induces platelet-leukocyte-endothelial cell interactions and pro-thrombotic effects through a mechanism involving interference with the purinergic system, specifically ATP-P2X7 receptors. In previous in vitro experiments we have determined that the ATP-P2X7 receptors implicated in the actions of ABC are located primarily in leukocytes. Since the recruitment of leukocytes by platelets is an important phase in the formation of thrombi, the present study was performed to evaluate the role of white cells in the pro-thrombotic effects of ABC in an animal model of thrombosis.

Methods: Male wild-type C57BL/6 mice were pre-treated with ABC (5–7.5 µg/mL intrascrotally 4h) or rofecoxib (0.1 mg/kg, i.p. 2h). To generate leukopenia, some mice were treated with cyclophosphamide (150 mg/kg, i.p., 96h), which reduced the number of circulating leukocytes by almost 90%. Arterioles of the cremaster muscle were visualized with an intravascular microscope and blood flow was analyzed with a Doppler velocimeter. The endothelium-damaging agent ferric chloride was superfused at a concentration of 25 mM, a dose that

does not modify blood flow but predisposes arterioles to thrombosis in the presence of other deleterious vascular agents. In contrast, higher concentrations of ferric chloride (over 75 mM) induced thrombi by themselves, an effect that was maintained in leukopenic mice. Images were recorded until blood flow ceased or for 8 min if no vessel occlusion occurred.

Results: ABC induced dose-dependent vessel occlusion in non-leukopenic mice following superfusion with 25 mM ferric chloride (Figure 1). Rofecoxib – a well characterized vascular deleterious agent - generated levels of thrombosis similar to those produced by ABC when administered in the same setting. However, while the pro-thrombotic effects of rofecoxib were maintained in leukopenic mice, those of ABC were absent.

Conclusion: The pro-thrombotic effect of ABC in vivo depends on the presence of leukocytes, thus demonstrating a key role of these cells in the deleterious vascular effects of this drug. These results support previous research suggesting that ABC induces thrombi formation through a specific mechanism involving leukocyte purinergic P2X7 signalling. This may explain the cardiovascular toxicity associated with the use of ABC in humans.

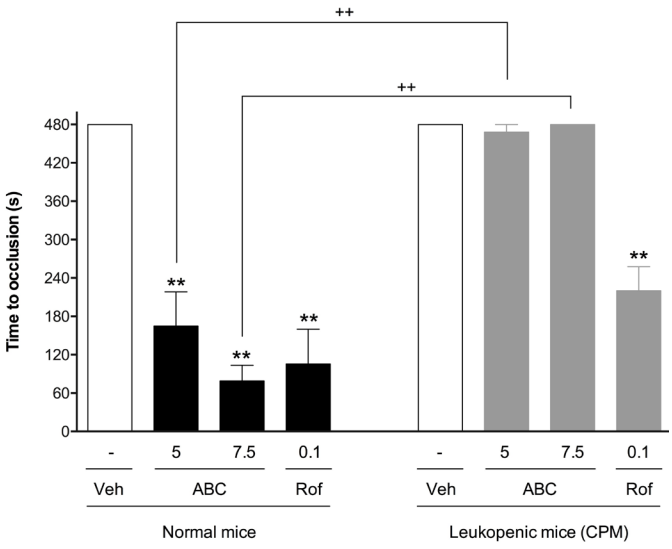


Figure 1. Leukocytes have a role in the pro-thrombotic effect exerted by abacavir. Mice were treated with abacavir (ABC, 5–7.5 μg/mL, intrascrotally, 4h),) rofecoxib (Rof, 0.1 mg/kg, i.p., 2h) or saline (vehicle, Veh). Some mice were pre-treated with cyclophosphamide (CPM, 150 mg/kg, 96 h). Following surgery, the cremasteric arteriole was superfused with a ferric chloride solution ($FeCl_3$, 25 mM) and the time to occlusion of the arterioles was determined. Results are mean ± SEM, n≥4. **p<0.01 vs. corresponding value in vehicle-treated group and $^{++}$p<0.01 vs. corresponding value in non-leukopenic group (ANOVA followed by Newman-Keuls test).

675 EXPLORING CHANGES IN HDL AND MONOCYTE CHOLESTEROL METABOLISM WITH ART INITIATION

Robert T. Maughan[1], Jane A. O'Halloran[1], Alejandro A. Garcia[1], Theodoros Kelesidis[2], Luke O'Brien[1], John Lambert[1], Gerard Sheehan[3], Patrick W. Mallon[1]
[1]University College Dublin, Dublin, Ireland, [2]University of California Los Angeles, Los Angeles, CA, USA, [3]Mater Misericordiae University Hospital, Dublin, Ireland

Background: Dysregulated reverse cholesterol transport (RCT) may contribute to cardiovascular disease pathogenesis in people living with HIV (PLWH). Key components of RCT include cellular cholesterol efflux, the capacity of HDL to accept cholesterol from cells like monocytes/macrophages (M/M) and the oxidative status of HDL (HDLox; increased HDLox reflects impaired HDL function). We previously reported enhanced M/M cholesterol efflux (MCE) and reduced HDLox after antiretroviral therapy (ART) initiation. We aimed to determine how HDLox and MCE interact with HDL efflux capacity (HEC) after ART initiation.

Methods: In a prospective cohort study of PLWH before and after ART initiation compared to HIV- controls matched for age, gender, ethnicity, smoking and hepatitis status, HEC was measured by exposing murine macrophages loaded with fluorescently labelled cholesterol to apolipoprotein B (apoB)- depleted plasma from study subjects. HEC was calculated from total cellular (TC) and supernatant (S) cholesterol measures as [(S/TC+S)*100]. MCE was calculated from the ratio of extra to intracellular cholesterol in subjects' monocytes after exposure to apoA1. HDLox levels were measured using a fluorometric assay normalized to HDL cholesterol. Data are median [IQR]. Mann Whitney and Wilcoxon rank sum tests were used for between and within-group comparisons and Spearman's correlation for bivariate associations.

Results: HIV+ and HIV- groups were well matched (Table) with HIV+ subjects reassessed 17 [13, 18] months post viral suppression with ART (80% TDF/FTC+NNRTI). HEC increased in the HIV+ group after ART initiation (+7.85 [3.47, 17.5]%, p=0.007) approaching levels similar to HIV- controls (p=0.776). Increases in HEC correlated with decreases in HDLox (r=-0.509, p=0.02) and increases in HDL cholesterol (r=+0.545, p=0.013) but not with changes in MCE (r=-0.066, p=0.782). Notably, in the HIV- group, higher HEC correlated with lower MCE (r=-0.61, p=0.004) while in the HIV+ group post-ART, higher HEC correlated with higher MCE (r=+0.499, p=0.025). Changes in HEC were not affected by gender, race, smoking, age, pre-ART HIV RNA, lipids or T cell parameters.

Conclusion: ART initiation is accompanied by increases in HEC and reductions in HDLox to levels seen in HIV- controls, suggesting improvements in HDL function with ART. However, divergent associations between HEC and MCE in the HIV- and HIV+ groups, together with enhanced MCE post-ART indicate ongoing dysregulation of RCT at the M/M cellular level in treated PLWH.

Table. Demographic and laboratory parameters

	HIV negative (n=20)	Pre-ART Initiation (n=20)	p*	Post-ART initiation (n=20)	p†
Age (yrs)	34 (29.5, 44)	34.5 (27, 44.5)	0.752	-	-
Male (n (%))	14 (70%)	14 (70%)	1.0	-	-
Caucasian (n (%))	15 (75%)	15 (75%)	1.0	-	-
Current smoker (n (%))	4 (20%)	3 (15%)	1.0	-	-
CD4+ Count (cells/mm^3)	-	343 (181, 516)	-	627 (458, 836)	0.002
Log HIV RNA (copies/ml)	-	4.64 (3.78, 5.19)	-	1.6 (1.6, 1.6)	<0.001
T. Cholesterol (mmol/L)	4.85 (4.1, 5.7)	4.1 (3.0, 5.2)	0.02	4.5 (3.8,5.2)	0.24
HDL Cholesterol (mmol/L)	1.27 (1.15, 1.76)	0.94 (0.70, 1.08)	<0.001	1.04 (0.9, 1.21)	0.03
HDL cholesterol efflux (HEC)	43.5 (38.2, 45.9)	41.1 (34.8, 41.2)	0.12	42.9 (41.2, 45.2)	0.007
Oxidized HDL (HDLox)	0.82 (0.67, 0.95)	1.23 (0.98, 1.40)	<0.001	0.84 (0.77, 0.99)	<0.001
Monocyte cholesterol efflux (MCE)	1.13 (0.92, 1.35)	1.27 (1.06, 1.50)	0.05	1.89 (1.55, 2.4)	<0.001

Data are median (IQR). p*, p value corresponding to comparisons between HIV negative and Pre-ART groups; p†, p value corresponding to comparison between pre-ART and post-ART timepoints within HIV+ group.

676 FUNCTIONAL STATUS ASSOCIATED WITH CARDIOVASCULAR DISEASE AND DIABETES IN HIV+ ADULTS

Sean G. Kelly[1], Kunling Wu[2], Katherine Tassiopoulos[2], Kristine M. Erlandson[3], Susan L. Koletar[4], Frank J. Palella[5]
[1]Vanderbilt University, Nashville, TN, USA, [2]Harvard University, Cambridge, MA, USA, [3]University of Colorado Denver, Denver, CO, USA, [4]The Ohio State University, Columbus, OH, USA, [5]Northwestern University, Chicago, IL, USA

Background: Age-related frailty and disability contribute to mortality and occur earlier in HIV+ persons, however their associations with other age-related chronic diseases remain unknown. We evaluated associations between frailty and disability and incident non-AIDS related clinical events among participants enrolled in AIDS Clinical Trials Group (ACTG) A5322.

Methods: At A5322 entry, we performed functional status assessments by measuring frailty by Fried's criteria and disability by impairment in Instrumental Activities of Daily Living (IADL). We recorded incident cardiovascular events (CVE: coronary artery disease, myocardial infarction, angina, stroke, cardiomyopathy, peripheral arterial disease, systolic heart failure, arrhythmia, deep vein thrombosis, pulmonary embolism) and diabetes (DM). Multivariable Poisson regression assessed associations between frailty, disability, CVE and DM, as well as effect modification by demographic variables on these associations.

Results: Among 1035 HIV+ participants, all aged ≥40 years, 81% were male, 48% were white, non-Hispanic, 29% were black, non-Hispanic, 46% were pre-frail or frail, and 17% had disability. Median age was 51 years and median duration of follow-up was 3.3 years. Forty-nine CVE were observed. Among black, non-Hispanic persons, being pre-frail/frail was associated with substantially increased risk of CVE (adjusted rate ratio [RR] 5.24, 95% C.I.=1.52,18.1) while being pre-frail/frail was not associated with CVE among persons of other race/ethnicity (white, non-Hispanic: RR=1.40, 95%

C.I.=0.53,3.70; Hispanic/other: RR=1.66, 95% C.I.=0.42,6.46; interaction p-value=0.18). Disability was not associated with CVE (RR= 1.54; 95% CI =0.78,3.05). Sixty-eight incident cases of DM occurred. Disability was associated with incident DM (RR=2.03 [95% C.I.=1.17,3.54]); this association did not vary by race. Being pre-frail/frail was not associated with incident diabetes (RR= 1.45, 95% C.I.= 0.90,2.34). There was no effect modification by sex or age on associations between either disability or frailty and DM and CVE.

Conclusion: Within our cohort of aging HIV+ participants, frailty and disability were common and associated with significantly elevated risk for CVE and DM, respectively. While the association between frailty and CVE was only apparent among black persons, the disability/DM association existed across demographics. Routinely assessing functional status in aging HIV+ persons may optimize risk stratification for serious co-morbid conditions.

677LB CHANGE IN SOLUBLE GLYCOPROTEIN VI (SGPVI) WHEN SWITCHING FROM ABC/3TC TO TAF/FTC

Patrick W. Mallon[1], Robert T. Maughan[1], Alejandro A. Garcia[1], Willard Tinago[1], Aoife Lacey[1], Andrew Lovell[2], Eimear Dunne[3], Elena Alvarez-Barco[1], Alan Winston[2], Frank Post[4], Dermot Kenny[3], Mingjin Yan[5], Moupali Das[5], Martin Rhee[5]
[1]University College Dublin, Dublin, Ireland, [2]Imperial College London, London, UK, [3]Royal College of Surgeons in Ireland, Dublin, Ireland, [4]King's College Hospital NHS Foundation Trust, London, UK, [5]Gilead Sciences, Inc, Foster City, CA, USA

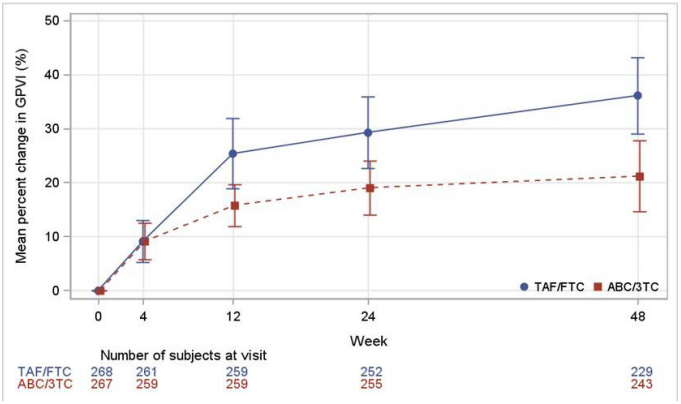
Background: Exposure to abacavir (ABC) has been associated with increased risk of cardiovascular events with altered platelet function implicated. Glycoprotein VI (GPVI), expressed on and shed from platelets, regulates platelet activation in response to collagen exposure. We previously demonstrated increases in soluble GPVI (sGPVI) in virologically-suppressed people with HIV-1 (PWH) switching from ABC to tenofovir disoproxil fumarate (TDF) and recently showed decreased platelet reactivity in response to collagen and increases in GPVI expression on platelets upon switching from ABC / lamivudine (ABC/3TC) to tenofovir alafenamide / emtricitabine (TAF/FTC). Changes in sGPVI when switching from ABC/3TC to TAF/FTC have not been determined.

Methods: In a platelet function substudy within a randomized, double-blind, active-controlled trial of virologically suppressed PWH on ABC/3TC who were randomized to switch to TAF/FTC or remain on ABC/3TC, we quantified sGPVI in platelet-poor plasma taken at weeks 0, 4, 12, 24 and 48 by electrochemiluminescence. The primary endpoint was change in sGPVI to week 48 with the between-group difference compared using mixed effects models with repeated measures.

Results: Of 556 subjects enrolled in the study, 545 (98%) had samples available for analysis. Mean (SD) age was 51 (9.3) years, 82% male, 72% white. Baseline CD4+ count was 712 (284) cells/mm^3 and 99% had HIV-1 RNA <50 copies/ml. Baseline sGPVI (µg/mL, median [IQR]) were similar between groups: TAF/FTC 7.36 (5.2, 12.7) versus ABC/3TC 8.46 (5.27, 14.51), P=0.18. The TAF/FTC group had a significantly greater increase in sGPVI to week 48 (figure), with a +14.7%, (95% CI 4.1, 26.3) difference between groups in change in sGPVI to week 48 by mixed effects models (P=0.005).

Conclusion: Switching away from ABC/3TC to TAF/FTC was associated with greater increases in sGPVI. In combination with the previously demonstrated decreases in platelet reactivity and re-expression of GPVI on platelets in PWH switching from ABC/3TC to TAF/FTC, these data suggest a reversible, inherent platelet dysfunction with ABC/3TC, centered on GPVI function, which may contribute to increased risk of cardiovascular events observed in PWH exposed to ABC.

Figure 1: Mean (SE) percentage change in sGPVI.



678 ELEVATED MICROPARTICLE TISSUE FACTOR ACTIVITY AND CAROTID ARTERY PLAQUE IN HIV+ WOMEN

Juan Lin[1], Xiaonan Xue[1], Kathryn Anastos[1], Mardge H. Cohen[2], Stephen J. Gange[3], Jason Lazar[4], Chenglong Liu[5], Wendy Mack[6], Phyllis Tien[7], Cathy Tilley[8], Howard Hodis[6], Alan Landay[9], Russell Tracy[8], Robert C. Kaplan[1], David B. Hanna[1]
[1]Albert Einstein College of Medicine, Bronx, NY, USA, [2]Cook County Health & Hospitals System, Chicago, IL, USA, [3]The Johns Hopkins University, Baltimore, MD, USA, [4]SUNY Downstate Medical Center, Brooklyn, NY, USA, [5]Georgetown University, Washington, DC, USA, [6]University of Southern California, Los Angeles, CA, USA, [7]University of California San Francisco, San Francisco, CA, USA, [8]University of Vermont, Colchester, VT, USA, [9]Rush University Medical Center, Chicago, IL, USA

Background: Expression of tissue factor (TF) on the surface of activated monocytes may trigger thrombosis, leading to clotting risk, inflammation, and atherosclerosis. TF-positive monocyte-derived microparticles (MP-TF) represent a functionally active form of TF, and its activity has been linked with poor HIV control. We hypothesized that greater MP-TF activity is associated with carotid artery plaque in HIV+ women.

Methods: In our nested case-control study among HIV+ women in the Women's Interagency HIV Study (WIHS), eligible participants underwent B-mode carotid artery ultrasound during 2 study visits occurring 7 years apart. Cases, defined as having at least 1 carotid artery plaque (focal intima-media thickness >1.5 mm) assessed at either visit, were matched 1:2 with available controls, defined as no plaque. Matching was based on age, smoking status, baseline CD4+ count, and antiretroviral therapy (ART) use. Plasma MP-TF activity was assessed by the method of Key et al.. Because the data suggested a threshold effect with case status, MP-TF levels were dichotomized at 0.537 pg/mL, which was determined empirically after examining deciles among values above the minimum detectable limit. Conditional logistic regression estimated the association of MP-TF activity with case status, controlling for demographic and behavioral characteristics, HIV-related factors, cardiometabolic risk factors, and serum inflammation biomarkers (hsCRP, IL-6, sCD14, sCD163, Gal-3, Gal-3BP).

Results: There were 98 cases and 177 controls included (N=275): median age 46, 89% black race or Hispanic ethnicity, 51% smokers, 8% on lipid-lowering therapy, 75% on ART, 44% with undetectable HIV RNA. Mean MP-TF levels were 0.277 pg/mL (SD 0.537) in cases and 0.211 pg/mL (SD 0.719) in controls. After taking into account demographic and behavioral characteristics and HIV-related and cardiometabolic risk factors, elevated MP-TF (>0.537 pg/mL) was significantly associated with greater odds of plaque (adjusted odds ratio [aOR] 3.55, 95% CI 1.09-11.60, p=0.04). The association was attenuated after further adjustment for IL-6 but not for other biomarkers including those denoting monocyte activation (e.g., sCD14). Among those with undetectable HIV RNA (<80 copies/mL, N=121), the association was more pronounced (aOR 10.15, 95% CI 1.38-74.70, p=0.02).

Conclusion: Elevated MP-TF was associated with carotid artery plaque in HIV+ women, suggesting a link between HIV infection, innate immune system perturbation, coagulation, and atherosclerosis.

679 INFLAMMATION ASSOCIATES WITH IMPAIRED ARTERIAL ELASTICITY IN EARLY HIV DISEASE

Tess Peterson[1], Kathy Huppler Hullsiek[1], Nicole Wyman Engen[1], Nagalingeswaran Kumarasamy[2], Pamela Schreiner[1], Jason V. Baker[3]
[1]University of Minnesota, Minneapolis, MN, USA, [2]YR Gaitonde Center for AIDS Research and Education, Chennai, India, [3]Hennepin County Medical Center, Minneapolis, MN, USA

Background: HIV-associated inflammation contributes to higher cardiovascular disease (CVD) risk. It is unclear, however, to what degree CVD pathogenesis is influenced very early in HIV infection before significant disease progression. We evaluated dysfunction of the microvasculature as an early measure of CVD pathogenesis via estimates of small arterial elasticity (SAE) and studied associations with inflammatory biomarkers among a subset of participants in the START trial at baseline (i.e., ART-naïve at CD4 counts > 500 cells/μL).

Methods: Radial artery waveforms were recorded non-invasively using a tonometer, and SAE was estimated from analysis of the diastolic pulse waveform (CR2000, HDI). Biomarkers (see table) were measured from stored plasma samples using immunoassays and analyzed on a $\log_2$ scale. Linear regression was used to evaluate cross-sectional associations between biomarkers and SAE. In addition to individual assessment, biomarkers were also analyzed simultaneously and in adjusted models that included: sex, age, race/ethnicity, CD4 cell count, HIV viral load, smoking, hypertension, body mass index, high-density lipoprotein cholesterol, and total cholesterol.

Results: Among 326 ART-naïve participants, 70% were male, 66% were non-White, 29% were smokers, median (IQR) age was 33 (28, 41), CD4+ cell count was 609 (558, 689) cells/μL, HIV viral load was 4.2 (3.7, 4.7) $\log_{10}$ RNA copies/mL, and SAE was 8.0 (6.3, 9.8) mL/mmHg x100. In univariable models, higher levels of hsCRP, IL-6, sICAM-1, and D-dimer were associated with lower (more impaired) SAE at baseline (Table). After adjustment for age, sex, and race/ethnicity, associations with D-dimer and sICAM-1 were no longer statistically significant, and in fully adjusted models including both demographic and clinical characteristics, hsCRP (ß=-0.18, p=0.031) and IL-6 (ß=-0.56, p<0.001) remained associated with SAE. When all biomarkers were evaluated simultaneously, only IL-6 was independently associated with SAE after full adjustment (ß=-0.52, p=0.003).

Conclusion: These data suggest that higher levels of systemic inflammation contribute to vascular dysfunction even early in HIV disease when CD4 cell counts are high. Only the association between IL-6 and SAE was independent of other measured biomarkers and traditional CVD risk factors. Extending these cross-sectional data to follow-up data in START is needed to determine if early ART with viral suppression influences the contribution of ongoing HIV-associated inflammation to CVD risk.

Table 1. Associations of baseline biomarker levels and small arterial elasticity (SAE; n=326).

Biomarker ($\log_2$)	*Univariable Models*		*Multivariable Model,[a] Markers Studied Individually*		*Multivariable Model,[a] Markers Studied Simultaneously*	
	ß (SE)	P-value	*ß* (SE)	P-value	*ß* (SE)	P-value
hsCRP (μg/mL)	-0.18 (0.09)	0.043	-0.18 (0.08)	0.031	-0.08 (0.13)	0.511
IL-6 (pg/mL)	-0.49 (0.18)	0.006	-0.56 (0.16)	<0.001	-0.52 (0.18)	0.003
SAA (μg/mL)	-0.14 (0.11)	0.210	-0.13 (0.09)	0.175	0.07 (0.14)	0.632
sICAM-1 (μg/mL)	-0.59 (0.29)	0.045	-0.45 (0.26)	0.087	-0.70 (0.42)	0.099
sVCAM-1 (μg/mL)	0.07 (0.31)	0.822	-0.14 (0.28)	0.632	0.57 (0.44)	0.202
D-dimer (μg/mL)	-0.99 (0.19)	<0.001	-0.07 (0.20)	0.738	0.18 (0.21)	0.401
IL-27 (pg/mL)	0.04 (0.10)	0.660	-0.06 (0.09)	0.489	-0.04 (0.09)	0.608

hsCRP, high-sensitivity C-reactive protein. IL-6, interleukin-6. IL-27, interleukin-27. SAA, serum amyloid A. sICAM-1, soluble intercellular adhesion molecule-1. sVCAM-1, soluble vascular adhesion molecule-1. Regression coefficient (*ß*) estimates the difference in SAE per one $\log_2$ unit (or doubling) of each biomarker. SE, standard error of *ß* estimate.

[a] Adjusted for sex at birth, age, race/ethnicity, CD4 count, HIV viral load, smoking, hypertension (systolic BP≥ 140 mmHg, diastolic BP≥ 90 mmHg, or use of BP-lowering therapy), body mass index, high density lipoprotein, and total cholesterol.

680 PERIVASCULAR ADIPOSE INFLAMMATION AND MICROVASCULAR ENDOTHELIAL DYSFUNCTION IN HIV

Cheng Wang, Tian Li, Philena Sun, Cuiwei Wang, Seble Kassaye, Princy Kumar, Jennifer Verbesey, Mary Young, Christopher Wilcox, Dan Wang
Georgetown University, Washington, DC, USA

Background: Perivascular adipose tissue (PVAT) surrounds most vessels in the human body and is a major player in regulating vascular reactivity. We reported previously an enhanced vascular contraction and endothelial dysfunction in subcutaneous microvascular arterioles (SMAs) dissected from a gluteal skin biopsy in HIV infected individuals. This study aims to further examine whether this HIV- associated microvascular dysfunction is caused by impaired PVAT signaling dependent on inflammation and reactive oxidative species signaling (ROS).

Methods: SMAs were obtained from HIV-infected subjects with virally suppressed on antiretroviral therapy (ART) (n=8) and confounding factors-matched HIV-uninfected individuals (n=6). Both groups had no identified other CVD risk factors. The acetylcholine (ACh)-induced endothelium- derived relaxation (EDR), endothelium derived relaxation factor (EDRF), endothelium derived hyperpolarizing factor (EDHF) were recorded ex vivo in PVAT-intact or denuded SMAs by a wire myograph. Microvascular nitric oxide (NO), generation of cellular and mitochondria ROS were quantitated by Fluorescence RatioMaster system. The malondialdehyde (MDA), NO, cytokines and adipokines were measured in homogenate adipose supernatant.

Results: In comparison with the HIV-uninfected, the HIV-infected group had significantly increased (all P<0.05) adipose MDA (15.1 ± 2.5 vs 10.9 ± 2.6 ng/mg protein), PAI-1 (444 ± 42 vs 291 ± 53 pg/mg protein), INFα2 (423±49 vs 286±33 pg/ml/mg protein), IL-1α (5.5±3.8 vs 1.3± 0.7 pg/ml/mg protein) and IL-9 (8.8±1.4 vs 5.1± 0.8 pg/ml/mg protein) and reduced adiponectin (2.1 ± 0.3 vs 3.1 ± 0.4 ng/mg protein).Their PVAT-denuded vessels from HIV group had an impaired responses to ACh-induced EDR (53±2% vs 75±2%), EDRF (26±3% vs 39±2%), NO generation (0.21±0.03 vs 0.58± 0.1 fluoresce unit) and increased cellular ROS (Δ0.32 ± 0.05 vs 0.10 ± 0.02 fluoresce unit) and mitochondria ROS (Δ0.10 ± 0.04 vs 0.18 ± 0.04 fluoresce unit). Whereas, the vessels with PVAT has enhanced EDR, EDRF and NO only in controls. These beneficial effects of PVAT were lost in vessels from HIV-infected group.

Conclusion: HIV-infected individuals have increased intrinsic vascular defects from ROS. They also have adipose inflammation leading to reduction of beneficial microvascular PVAT signaling.To prevent the cardiovascular morbidity of HIV infection, therapeutic targets should include elimination of ROS and inflammation and its extravascular actions on PVAT.

681 PCSK9 LEVELS IN RELATION TO IMMUNE ACTIVATION AND SUBCLINICAL CORONARY PLAQUE IN HIV

Markella V. Zanni[1], **Lauren Stone**[2], Mabel Toribio[2], Dodie Rimmelin[2], Jake A. Robinson[3], Tricia H. Burdo[3], Kenneth C. Williams[4], Kathleen V. Fitch[2], Janet Lo[2], Steven K. Grinspoon[2]
[1]Massachusetts Department of Public Health, Boston, MA, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]Temple University, Philadelphia, PA, USA, [4]Boston College, Chestnut Hill, MA, USA

Background: Proprotein convertase subtilisin /kexin 9 (PCSK9) is known to mediate homeostasis of low density lipoprotein cholesterol (LDL-c), but may also participate in immune reactivity and atherogenesis. A pro-inflammatory milieu stimulates diverse cell types to release PCSK9 into the circulation. Conversely, PCSK9 may elicit pro-inflammatory responses in monocytes/macrophages, with relevance to immune-mediated atherogenesis. In the general population, PCSK9 levels relate to major adverse cardiovascular events, even after controlling for LDL-c levels. We endeavored to assess whether PCSK9 levels would be elevated among asymptomatic individuals with HIV (vs. without HIV) in relation to levels of systemic monocyte activation markers and/or subclinical coronary atherosclerotic plaque parameters.

Methods: We compared PCSK9 levels among asymptomatic individuals with and without HIV. As individuals with HIV are known to have high-level systemic immune activation and an increased subclinical coronary atherosclerotic plaque burden, we therefore assessed whether PCSK9 levels related to levels of systemic monocyte activation markers and/or to subclinical coronary atherosclerotic plaque parameters within each group. Levels of systemic monocyte markers were measured using ELISA and plaque was assessed using coronary computed tomography angiography.

Results: PCSK9 levels were higher among HIV-infected (n=149) vs. matched non-HIV-infected subjects (n=69) [332 (272, 412) ng/mL vs. 304 (257,375) ng/mL; P = 0.047]. Among non-HIV-infected subjects, PCSK9 levels related significantly to age (rho = 0.35; P = 0.003) and to Framingham Point Score (rho = 0.51; P<0.0001). Among HIV-infected subjects, PCSK9 levels related to Framingham Point Score (rho = 0.33; P<0.0001) and LDL-c (rho = 0.16; P = 0.05). Further, among the HIV-infected group, significant positive associations were noted between PCSK9 levels and levels of systemic monocyte activation markers including sCD14 (rho = 0.22; P = 0.009) and sCD163 (rho = 0.23; P = 0.006). PCSK9 levels did not relate to subclinical coronary atherosclerotic plaque parameters either in the group with or without HIV.

Conclusion: Among asymptomatic individuals with HIV, PCSK9 levels are elevated and related to systemic markers of monocyte activation but not to coronary plaque. Additional studies are needed to determine effects of PCSK9 on immune activation and atherogenesis in HIV and to assess whether PCSK9 inhibition reduces immune activation and coronary plaque burden.

682 AN IMMUNOLOGICAL SIGNATURE FOR SUBCLINICAL ATHEROSCLEROSIS IN HIV-1 INFECTION

Tomas Raul Wiche Salinas, Yuwei Zhang, Annie Gosselin, Mohamed El-Far, Inna Bacearnicova, Carl Chartrand-Lefebvre, Madeleine Durand, Cécile Tremblay, Petronela Ancuta

Centre de Research du Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada

Background: Immunological alterations causing gut microbial translocation and chronic immune activation may contribute to accelerated cardiovascular disease (CVD) occurrence in HIV-infected individuals on antiretroviral therapy (ART). Here, we sought to identify an immunological signature associated with subclinical atherosclerosis using samples from the Canadian Cohort of HIV and Aging.

Methods: Blood was available from HIV-infected on ART (HIV+) and uninfected (HIV-) participants, without CVD diagnosis/symptoms at inclusion. Coronary Artery Calcium Score (CACS), total plaque volume (TPV), and low attenuated plaque volume (LAPV, high-risk atherosclerotic lesions) were determined by CT angiography. Markers of microbial translocation (LBP), mucosal damage (I-FABP), immune activation (sCD14), chemokines (CCL20, CX3CL1, CCL25, MIF) were quantified in plasma by ELISA. Flow cytometry identified subsets of CD4+ T-cells (Th1, Th17, Tregs), monocytes (classical, intermediate, non-classical), and plasmacytoid dendritic cells (pDC) and measured expression of chemokine receptors involved in atherosclerotic plaque formation (CCR2, CCR6, CCR9, CX3CR1).

Results: HIV+ (n=71; infection time: 16±8 years; ART duration: 13±8 years; CD4 counts: 551±251 cells/µl; plasma viral load <50 HIV-RNA copies/ml) vs. HIV- (n=26) were similar in age (55±7 vs. 58±8 yrs), Framingham scores (11.1±6.1 vs. 9.9±3.6), and coronary plaque prevalence (42/71 vs. 16/26). However, HIV+ vs. HIV- had higher TPV (369±519 vs. 271±568), LAPV (114±172 vs. 85±171), and CACS (215±385 vs. 174±456; mean±SD). This coincided with increased plasma levels of I-FABP, sCD14, CCL20, and CX3CL1; predominant Th1 and Tregs vs. Th17; reduced frequency of intermediate monocytes with low CCR2 expression; and reduced frequency of CCR9+ pDC. Among HIV+, Th17 frequency negatively correlated with CACS (p=0.011, r=-0.348,), TPV (p=0.005, r=-0.378), and LAPV (p=0.003, r=-0.402); Th17/Th1 ratios negatively correlated with CACS (p=0.03, r=-0.29), TPV (p=0.04, r=-0.27), and LAPV (p=0.05, r=-0.26); and Th7/Tregs ratios negatively correlated with CACS (p=0.034, r=-0.292), TPV (p=0.01, r=-0.346) and LAPV (p=0.006, r=-0.372). Finally, Th17 frequency was negatively correlated with D-dimer levels (p=0.03, r=-0.252).

Conclusion: The paucity of blood Th17 cells correlated with subclinical coronary atherosclerosis in HIV+ individuals on ART. This suggests a link between the "leaky gut" caused by Th17 depletion and the development of HIV-associated CVD.

683 CARDIAC MORBIDITY IN HIV IS ASSOCIATED WITH CHECKPOINT INHIBITOR LAG3

Suresh Pallikkuth[1], Bagavathi Kausalya[2], Rajendra Pahwa[1], Shanmugam Saravanan[2], Li Pan[1], R Vignesh[2], Syed Iqbal[2], Sunil S. Solomon[3], Kailapuri G. Murugavel[2], Selvamuthu Poongulali[2], Nagalingeswaran Kumarasamy[2], Savita Pahwa[2]

[1]University of Miami, Miami, FL, USA, [2]YR Gaitonde Center for AIDS Research and Education, Chennai, India, [3]Johns Hopkins Hospital, Baltimore, MD, USA

Background: Cardiovascular disease (CVD) is a major contributor to mortality and morbidity in HIV infection. Elevated expression of certain checkpoint inhibitor (CPI) molecules (e.g. PD-1, TIGIT, LAG3, TIM3) on T cells is associated with dampened immunity. Recent evidence for expression of receptors for CPI at the tissue level with selective enrichment of LAG3 receptors in the heart point to a control mechanism for organ immune homeostasis, (Rev Immunity 44, 2016). This study was aimed at defining relationship of CPI and CVD in HIV infection.

Methods: Study participants were recruited in YRG CARE, Chennai, India. ART naive viremic, (Gp1, n=102) and ART experienced aviremic (Gp2, n=172) were compared to healthy volunteers (Gp3, n=64) in a cross-sectional analysis of cardiac function (radial pulse wave and c-IMT)and immunologic markers including CPI on CD4 and CD8 T cells (flow cytometry).

Results: In Gp1 findings of CVD were significant (Mann-Whitney' U test) for lower cardiac ejection time, stroke volume, stroke volume index, cardiac output and small arterial elasticity with higher systemic vascular resistance compared to Gp2 and Gp3. Large arterial elasticity was lower in Gp1 comparison to Gp2. Gp1 had significantly (p<0.0001) higher frequencies than Gps 2 and 3 respectively of CD4 T cells expressing LAG3 (Gps 1, 2, 3: 4.9±3.4, 2.5±1.5, 2.4±1.3) and PD1 (Gps 1, 2, 3: 6.2±7.3,1.5±2.5, 0.9±1.6) while those of TIGIT and Tim 3 were equivalent among groups. Shown in table 1 is Pearson Correlation analysis on log 10 transformed data. Frequencies of CD4+ T cells positive for LAG3, PD1, and for dual expression of LAG3 plus PD1 were inversely correlated in Gp1 with cardiac ejection time, cardiac output, cardiac index, stroke volume, stroke volume index and systemic vascular resistance and in Gp 2 with large artery elasticity, and except for PD1, also with small artery elasticity.

Conclusion: In ART naive HIV subjects continuous antigenic stimulation of the immune system results in upregulation of multiple CPI molecules. Our finding of the association of LAG3 and PD1 expressing CD4 cells in cardiac morbidity points to a dominant role of these pathways in regulating cardiac health, given that LAG3 receptors are enriched at the tissue level in the heart. Investigations to understand the immune mechanisms involved could provide insight into potential role of LAG3 immunotherapy (which is in early clinical trials in cancer) in prevention or treatment of cardiac dysfunction in HIV.

Table 1: Correlations between LAG3 and PD1 expressing CD4 T cells and cardiac function

Measures of Cardiac function	CD4+LAG 3+ (%)		CD4+PD1+ (%)		CD4+LAG 3+ PD1+ (%)	
Gp 1 (ART Naïve)	**p value**	**r value**	**p value**	**r value**	**p value**	**r value**
Cardiac ejection time	0.001	-0.33	0.001	-0.33	<0.0001	-0.4
Cardiac output	<0.0001	-0.38	0.001	-0.33	<0.0001	-0.42
Cardiac index	<0.0001	-0.4	<0.0001	-0.39	<0.0001	-0.45
Stroke volume	0.001	-0.33	0.005	-0.29	<0.0001	-0.39
Stroke volume index	<0.0001	-0.34	0.001	-0.33	<0.0001	-0.41
Systemic vascular-resistance	0.004	-0.29	0.01	-0.27	0.002	-0.31
Gp 2 (ART treated)						
Large artery elasticity	0.009	-0.21	0.01	-0.21	<0.0001	-0.19
Small artery elasticity	0.001	-0.26	0.09	-0.14	0.03	-0.17

684LB IMPACT OF METHOTREXATE ON ARTERIAL INFLAMMATION IN PERSONS WITH TREATED HIV

Ahmed Tawakol[1], Heather Ribaudo[2], Amorina E. Ishai[1], Ashley McKhann[2], Daniel H. Solomon[3], Zahi A. Fayad[4], Steven G. Deeks[5], Michael M. Lederman[6], Steven K. Grinspoon[1], James H. Stein[7], Paul M. Ridker[3], Judith S. Currier[8], Priscilla Hsue[5]

[1]Massachusetts General Hospital, Boston, MA, USA, [2]Harvard University, Boston, MA, USA, [3]Brigham and Women's Hospital, Boston, MA, USA, [4]Mt Sinai School of Medicine, New York, NY, USA, [5]University of California San Francisco, San Francisco, CA, USA, [6]Case Western Reserve University, Cleveland, OH, USA, [7]University of Wisconsin–Madison, Madison, WI, USA, [8]University of California Los Angeles, Los Angeles, CA, USA

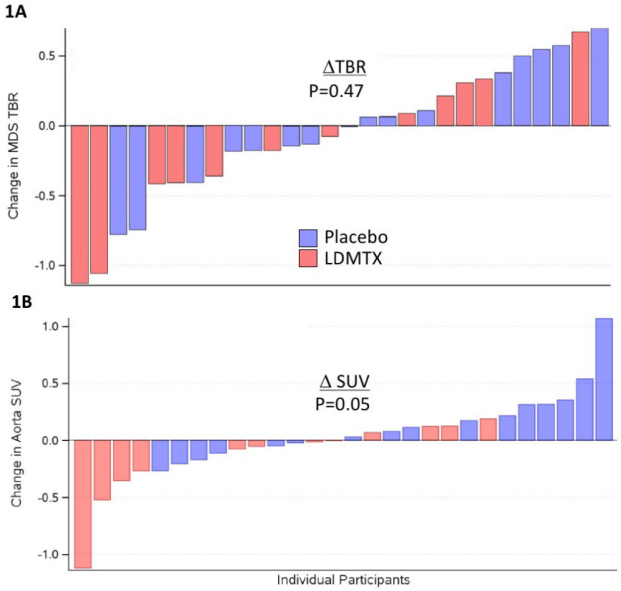
Background: Arterial inflammation, a key driver of atherosclerotic cardiovascular disease (ASCVD), is elevated in individuals living with HIV and is hypothesized to underpin the increased incidence of ASCVD in this population. Low-dose methotrexate (LDMTX) is an anti-inflammatory drug that is associated with lower risk of ASCVD in individuals with rheumatoid arthritis. We evaluated the impact of LDMTX on arterial inflammation in treated HIV infection.

Methods: We conducted a randomized placebo-controlled trial in ART-treated HIV-infected individuals age ≥40 years with or at increased risk for ASCVD and with CD4+ T-cells >400 cells/mm^3. Participants received weekly LDMTX or placebo for 24 weeks; both groups received 1 mg folate daily. Arterial inflammation was assessed using FDG PET/CT imaging at 0 and 24 weeks, and measured as standardized uptake values (SUV). SUV was additionally corrected for background activity, producing target-to-background-ratios (TBR). The primary endpoint was ΔTBR. Additionally, a pre-specified secondary endpoint was ΔSUV (which is less susceptible to variation and may associate better with histological evidence of inflammation). Intent to treat group comparisons used stratified Wilcoxon tests.

Results: A total of 28 individuals, from 8 sites, provided evaluable image sets. Participants had a median [IQR] age of 55 [51, 62] years, 25 were male, and entry CD4+ T cells of 681 [581, 871] /mm^3. For the primary endpoint,

(ΔTBR), we observed a small but non-significant decrease in TBR in the LDMTX group ((ΔTBR: -0.126 [-0.41, 0.258]) relative to placebo (0.026 [-0.176, 0.438], p=0.47, Fig 1A). Higher than anticipated variability in TBR and lower than planned enrollment limited our ability to detect group differences in TBR. For the secondary endpoint (ΔSUV), we observed a significant between-group difference in the LDMTX group relative to placebo (ΔSUV: -0.034 [-0.311, 0.095] vs. 0.096 [-0.081, 0.313], LDMTX vs placebo, p=0.05, Fig 1B). This represented an approx. 2% decrease in SUV (from baseline 2.01) in the LDMTX, and a 5% increase in SUV (from baseline of 1.82) in the placebo group.

Conclusion: LDMTX may reduce arterial inflammation in HIV-infected adults with or at risk for ASCVD, at least as measured by ΔSUV. This finding may explain the apparent beneficial impact of LDMTX on ASCVD risk in chronic inflammatory diseases. The potential effect of LDMTX on arterial inflammation in HIV should be studied in a larger cohort.



685 LIPODYSTROPHY IS AN IMPORTANT DETERMINANT OF MARKERS OF ARTERIAL INFLAMMATION IN HIV

Suman Srinivasa, Kathleen V. Fitch, Martin Torriani, Markella V. Zanni, Patrick Maehler, Sara E. Looby, Janet Lo, Steven K. Grinspoon
Massachusetts General Hospital, Boston, MA, USA

Background: Persons living with HIV(PLWH) well-treated on antiretroviral therapies remain at risk for ensuing arterial inflammation. The exact mechanism for inflammatory-mediated cardiovascular disease (CVD) in HIV remains unclear. HIV lipodystrophy has been associated with advanced metabolic disease. In this regard, visceral adipose tissue (VAT) accumulation and subcutaneous adipose tissue (SAT) loss contribute to a unique and highly inflamed adipose depot. Therefore, we sought to investigate the relationship between adipose depots and specific markers of arterial inflammation to gain insight into the potential link between lipodystrophy and CVD risk.

Methods: 155 PLWH and 71 individuals without HIV(PLWOH) and no known CVD were previously recruited and well-phenotyped for body composition. VAT and SAT were assessed via single slice CT abdomen imaging. Circulating markers of arterial inflammation [lipoprotein-associated phospholipase A2(LpPLA2), oxidized LDL(oxLDL), high sensitivity troponin T(hsTnT), high sensitivity C reactive protein(hsCRP)] were evaluated. Relationships were assessed by Spearman's correlation.

Results: PLWH(mean age 47±1yrs, duration HIV 14±1yrs, duration ART 8±0yrs, CD4+ count 552±24cells/μL, logVL 1.82±0.04copies/mL) were of similar age and sex vs. PLWOH. Despite similar BMI and VAT, PLWH(199[126,288] vs. 239[148,358]cm2,P=.04) had significantly lower SAT compared to PLWOH. Reduced SAT was inversely correlated with LpPLA2(ρ=-0.19, P=.02) and hsTNT(ρ=-0.24, P=.004) among PLWH. Furthermore, increased VAT was significantly and positively related to LpPLA2(ρ=0.25, P=.003), oxLDL(ρ=0.28, P=.0005), hsTNT(ρ=0.28, P=.0007), and hsCRP (ρ=0.32, P=<.0001) among the HIV group. Similar analyses among PLWOH revealed significant relationships between SAT and LpPLA2(ρ=-0.24, P=.05), as well as VAT and LpPLA2(ρ=0.37, P=.002), oxLDL(ρ=0.28, P=.05), and hsCRP (ρ=0.29, P=.002). In separate models simultaneously controlling for VAT, SAT, age, CD4+ count, and viral load among PLWH, reduced SAT was an independent predictor of LpPLA2(P=.006) and increased VAT was an independent predictor of LpPLA2(P=.007) and oxLDL(P=.004).

Conclusion: Highly inflamed adipose tissue, in the context of SAT loss and/or VAT accumulation, may be linked to arterial inflammation. Strategies to reduce lipodystrophy and restore normal adipose biology may have therapeutic benefit to dampen arterial inflammation in the HIV population among whom traditional risk factor modification does not completely mitigate CVD risk.

686 CARDIAC BNP DEFICIENCY RELATES TO EXCESS ADIPOSITY AND METABOLIC PERTURBATIONS IN HIV

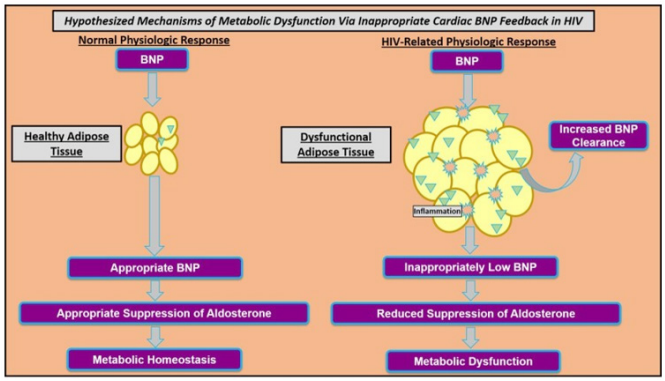
Kathleen V. Fitch[1], Meghan Feldpausch[1], Patrick Maehler[1], Martin Torriani[1], Gail K. Adler[2], Steven K. Grinspoon[1], **Suman Srinivasa**[1]
[1]Massachusetts General Hospital, Boston, MA, USA, [2]Brigham and Women's Hospital, Boston, MA, USA

Background: Well-treated persons living with HIV(PLWH) at risk for fat dysfunction demonstrate renin-angiotensin-aldosterone system(RAAS) dysregulation. Natriuretic peptides(NP) are key cardiac hormones which serve as negative regulators on the RAAS and play a role in preserving cardiac structure and metabolic homeostasis. In generalized obesity, relative NP deficiency contributes to advanced metabolic risk. We investigated BNP in relation to aldosterone and body composition for the first time in HIV.

Methods: Serum brain natriuretic peptide(BNP) was prospectively assessed during acute activation of the RAAS using a 7-day low sodium diet and controlled posture techniques among 20 PLWH and 10 persons living without HIV(PLWOH) well-phenotyped for body composition. Non-normally distributed variables were log transformed for the analyses(Pearson's correlation, Student's t-test, ANOVA); these data are shown as median[IQR] only for clinical interpretation.

Results: PLWH(mean age 49±2yrs, duration HIV 18±1yrs, duration ART 11±1yrs, CD4+ count 571±73cells/μL, log VL 1.77±0.19copies/mL) were of similar age, sex, and body composition vs. PLWOH. Log BNP was significantly and inversely related to body composition [waist circumference(r=-0.46,P=.04), BMI(r=-0.55,P=.01), body adiposity index (r=-0.49,P=.03)], metabolic indices [total cholesterol(r=-0.44,P=.05), HOMA-IR(r=-0.44,P=.05)], and aldosterone(r=-0.49,P=.03) among the HIV group. No significant correlations were demonstrated to BNP among PLWOH. BNP(60[44,152] vs. 196[91,251],P=.04) was significantly lower and aldosterone(13.8[9.7,30.9] vs. 9.2[7.6,13.6]ng/dL,P=.03) higher among PLWH vs. PLWOH. In a four-group comparison stratifying by HIV serostatus and above/below BMI 25(overweight category), BNP decreased significantly across groups, being highest in PLWOH with BMI<25 and lowest in PLWH with BMI≥25(238[77,935], 193[77,206], 125[49,157], 52[31,215]ng/dL in PLWOH/BMI<25, PLWOH/BMI≥25, PLWH/BMI<25, PLWH/BMI≥25, respectively (overall=.01)). Further stratification among the HIV group into 3 standardized BMI categories, under/normal weight(BMI<25), overweight(25≤BMI<30), and obese(BMI≥30), was also significant for a reduction in BNP across increasing BMI(P=.01).

Conclusion: Relative BNP deficiency among PLWH with excess adiposity may contribute to RAAS dysregulation and potentially drive metabolic disease, such as insulin resistance. Novel strategies which block aldosterone and augment BNP may be potentially useful to reduce cardiometabolic risk in HIV.



687 ASSOCIATION OF SUBCLINICAL CMV DNA AND IMMUNOLOGIC MARKERS OF CARDIOVASCULAR DISEASE

Ankita Garg, Sara Gianella, Masato Nakazawa, **Stephen A. Spector**
University of California San Diego, La Jolla, CA, USA

Background: HIV-CMV co-infected persons are at increased risk of cardiovascular disease (CVD) associated with persistent inflammation. Persons with high interferon (IFN)γ response to CMV have increased numbers of endothelium homing receptor (CX3CR1)- expressing cells that are associated with CVD. Here, we investigated the effect of subclinical CMV replication on these markers.

Methods: 80 paired PBMC samples were collected from 40 CMV-seropositive, early HIV-infected men starting ART within a median of 3 mo from estimated date of infection, and achieved suppressed HIV RNA within a median of 3 mo on ART. PBMC were obtained >12 mo apart (1st sample a median of 34 wks post-ART initiation). CMV IFNγ response was determined by ELISPOT using a CMVpp65 peptide pool; CMV specific memory T cells were identified by flow cytometry. CMV and EBV levels were measured by ddPCR. Data were analyzed using a mixed effects regression model to predict associations between CMV shedding, IFNγ production and CX3CR1-expressing CD4+ and CD8+ T cells over time. Bayesian hierarchical models were used to quantify differences in CMV and EBV replication over time. Participants were classified as low (LR)- or high-responders (HR) according to IFNγ production (100 SFU/10^6 cells).

Results: 26 (65%) participants were classified as HR and 14 (35%) as LR at the 1st time-point which did not change over time nor was influenced by CMV DNA levels (median SFU/10^6 cells at 1st/2nd time-point: HR: 383/308 vs LR: 21/41). Change in IFNγ levels over time was influenced by CMV levels ($p<0.01$), as individuals with a greater decline in IFNγ had increased levels of CMV DNA compared to those with low CMV. Higher CMV DNA was also associated with increased numbers of CD28+CD27-CD4+ T cells expressing CX3CR1 ($p<0.001$). Similarly, increased IFNγ production was associated with increased numbers of CMV-specific CX3CR1+CD28+CD27-CD4+ and CD8+ T cells ($P<0.001$). Using a similar interaction model, EBV was not associated with any of these findings.

Conclusion: These findings demonstrate in HIV-CMV co-infected persons on suppressive ART that higher CMV levels and IFNγ responses are associated with a subset of CMV-specific memory T cells expressing CX3CR1, and that high and low IFNγ responders maintain their response category over time. Thus, we have identified a subgroup of HIV-infected CMV IFNγ HR with increased numbers of circulating T cells expressing CX3CR1 who may be at increased risk of CVD and other inflammatory diseases.

688 CYSTATIN C AND ATHEROSCLEROSIS IMAGING MARKERS IN HIV INFECTED PATIENTS

Mitchell R. McClean[1], Petra Buzkova[2], Matthew Budoff[3], Michelle Estrella[4], Matthew Freiberg[5], Howard Hodis[6], Frank J. Palella[7], Wendy Post[8], Cecilia Shikuma[9], Samir K. Gupta[1]
[1]Indiana University, Indianapolis, IN, USA, [2]University of Washington, Seattle, WA, USA, [3]University of California Los Angeles, Los Angeles, CA, USA, [4]University of California San Francisco, San Francisco, CA, USA, [5]Vanderbilt University, Nashville, TN, USA, [6]University of Southern California, Los Angeles, CA, USA, [7]Northwestern University, Chicago, IL, USA, [8]Johns Hopkins Hospital, Baltimore, MD, USA, [9]University of Hawaii, Honolulu, HI, USA

Background: Reduced estimated glomerular filtration rate (eGFR) using serum creatinine (Cr) based estimates is associated with increased risk of cardiovascular disease (CVD) in HIV. Compared to eGFR using only Cr, serum Cystatin C (CC)-based eGFR is more predictive of CVD in the general population. However, it is unclear how CC-based eGFR compared to Cr-based eGFR in predicting subclinical CVD in HIV-infected persons.

Methods: We conducted a cross-sectional analysis of data pooled from three large cohorts of HIV+ patients (VACS, MACS, Hawaii Aging) comparing associations between three CKD-EPI eGFR equations (Cr, CC, and Cr-CC) with intima media thickness (CIMT) at the common carotid artery and coronary artery calcium (CAC) scores using multivariable regression analysis. CIMT, CAC, and CC were centrally measured. eGFR and CIMT were analyzed as continuous variables. CAC scores were analyzed as a binary variable (detectable vs non-detectable calcification) and as a $\log_{10}$ Agatston score in persons with detectable CAC. Statistical significance was defined as $P<0.05$.

Results: We included HIV+ patients (97% male; mean (SD) age 52.34 (6.98) years; 35% black) who had CIMT (n=562) or CAC (n=296) measured. Depending on the formula used, 6.1-6.9% had eGFR <60 mL/min/1.73m2, and 32.8-51.6% had eGFR <90 mL/min/1.73m2. Mean (SD) CIMT was 0.79 (0.15) mm. Of the 296 with CAC measures, 145 (49%) had CAC, with a mean (SD) $\log_{10}$Agatston score of 1.85 (0.79). After adjusting for traditional CVD risk factors, demographics, and HIV parameters, each 10 mL/min/1.73m2 lower eGFR by Cr-CC, by Cr, and by CC was associated, respectively, with an 8.3μm (95% CI, 0.6-16μm; P=0.035), a 7.6μm (95%CI, 0.0-1.51μm; P=0.052), and a 5.4μm (95% CI, -1.5-12.3μm; P=0.124) higher CIMT. Each 10 mL/min/1.73m2 lower CC-eGFR was associated with higher $\log_{10}$Agatston score of 0.0941 (95% CI 0.0151-0.173; P=0.022), but associations with other eGFR formulae did not reach significance. eGFR was not associated with detectable CAC.

Conclusion: In this group of HIV+ patients who were predominantly male and with eGFR ≥60mL/min/1.73m2, lower eGFR was significantly associated with higher CIMT when using the Cr-CC formula and with higher CAC scores using the CC formula. GFR estimating formulae incorporating cystatin C may identify HIV+ patients with subclinical CVD and for whom there is a greater need of aggressive CVD risk reduction.

689 EFFECTS OF PITAVASTATIN ON ATHEROSCLEROTIC-ASSOCIATED BIOMARKERS IN PEOPLE WITH HIV

Angsana Phuphuakrat, Artit Wongsa, Sirawat Srichatrapimuk, Boonrat Tassaneetrithep, Sasisopin Kiertiburanakul, Somnuek Sungkanuparph
Mahidol University, Bangkok, Thailand

Background: Despite undetectable plasma viral load, HIV-infected individuals receiving antiretroviral drug (ARV) have chronic immune activation and persistent low-grade inflammation. This has been associated with increased risk of cardiovascular diseases. Pitavastatin is a newer statin that has less drug-drug interactions with ARV compared with older statins. Thus, it is a preferred drug for the treatment of dyslipidemia in patients with HIV. Data regarding anti-inflammatory effect of pitavastatin in HIV-infected patients are limited. We studied the effects of pitavastatin on atherosclerotic-associated cellular inflammatory biomarkers in virologically-suppressed HIV-infected individuals.

Methods: This study was an exploratory analysis of atherosclerotic-associated inflammatory cellular biomarkers. The study was a substudy of a randomized, double-blind, crossover study that evaluated the effect of pitavastatin versus placebo in HIV-infected dyslipidemic patients, who received atazanavir/ritonavir-based antiretroviral agents (ClinicalTrials.gov NCT02442700). Patients were randomized to receive 12 weeks of pitavastatin 2 mg/day or placebo, followed by 2 weeks of washout period and 12 weeks of another treatment arm. Blood collected at 12 weeks of treatment were analyzed for atherosclerotic-associated cellular inflammatory biomarkers on a flow cytometer. Comparisons of the biomarkers between patients receiving pitavastatin and placebo treatment were performed by Wilcoxon signed ranks test.

Results: Twenty-four HIV-infected individuals were included. Median (interquartile range; IQR) age of the patients was 46 (41-56) years and 14 (58%) patients were men. Median (IQR) baseline CD4+ lymphocyte counts was 662 (561-836) cells/mm^3. As compared to placebo, treatment with pitavastatin resulted in significantly lower the proportions of patrolling (CD14DimCD16+) monocytes ($p=0.018$) and PD1+CD4+ T cells ($p=0.029$). However, no significant difference in the proportions of HLA-DR+CD38+ CD4+ T cells, HLA-DR+CD38+ CD8+ T cells, PD1+CD8+ T cells, and Treg was found.

Conclusion: This preliminary study shows that pitavastatin lowers the proportions of patrolling monocyte and PD1+CD4+ T cells in virologically-suppressed HIV-infected individuals. Further study on effects of pitavastatin to prevent cardiovascular diseases in HIV-infected individuals should be investigated.

690 STATIN COVERAGE IN AN HIV COHORT: COMPARISON OF ATP III, ACC/AHA, AND NLA GUIDELINES

Matthew E. Levy, Alan Greenberg, Manya Magnus, Naji Younes, Amanda D. Castel
The George Washington University, Washington, DC, USA

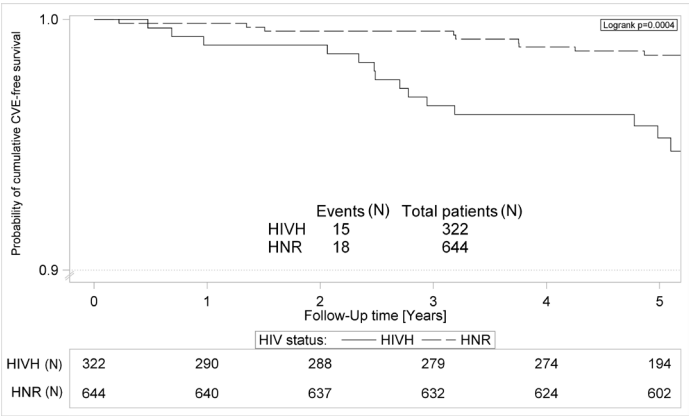
Background: Dyslipidemia is a major cardiovascular disease risk factor that is highly prevalent among HIV-infected populations. Statin coverage has been examined among HIV-infected patients using 2004 Adult Treatment Panel III (ATP III) and 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, yet the impact of 2014 National Lipid Association (NLA) guidelines has yet to be examined. We investigated statin eligibility, prescribing practices, and clinical responses using these three guidelines.

Methods: Demographic, clinical, and laboratory data were collected between 2011-2016 for HIV-infected patients enrolled in the DC Cohort Study, a multicenter prospective observational study of HIV-infected persons in care in Washington, DC. To determine whether participants ≥21 years old were eligible for statins, we applied ATP III, ACC/AHA, and NLA guidelines to data for participants receiving primary care at their HIV clinic site with ≥1 cholesterol result available. Demographic, behavioral, and clinical predictors of being prescribed statins and of achieving NLA non-high-density lipoprotein cholesterol (non-HDL-C) goals were assessed using multivariable Cox proportional hazards regression.
Results: Of 3,312 participants (median age 52; 78% male; 79% Black), 52% were eligible for statin therapy based on ≥1 guideline, including 30% (ATP III), 40% (ACC/AHA), and 45% (NLA). Using each guideline, 73% (ATP III), 56% (ACC/AHA), and 49% (NLA) of eligible participants were prescribed statins. Predictors of receiving prescriptions were older age (aHR=1.16 [1.07-1.25]/5 years), body mass index ≥30 (aHR=1.50 [1.07-2.11]), and diabetes (aHR=1.37 [1.04-1.82]). Hepatitis C coinfection was associated with a lower likelihood of prescription (aHR=0.66 [0.44-0.98]). Among 216 NLA-eligible participants with available cholesterol results pre-/post-prescription, 53% achieved their non-HDL-C goal within six months. Depression (aHR=0.61 [0.37-0.99]) and nadir CD4 cell count 200-500 (vs. >500) cells/μL (aHR=0.51 [0.27-0.99]) were associated with a lower likelihood of achieving the goal.
Conclusion: Approximately half of HIV-infected participants were eligible for statins based on current US guidelines, with the highest proportion eligible based on NLA guidelines, yet statin coverage was substantially lower as measured by prescriptions and achievement of treatment goals. Greater compliance with recommended statin prescribing practices may reduce cardiovascular risk among HIV-infected individuals.

691 HIV+ MEN MATCHED BY AGE AND FRS WITH CONTROLS HAVE MORE CARDIOVASCULAR EVENTS

Stefan Esser[1], Marina Arendt[1], Christina Schulze[1], Volker Holzendorf[2], Norbert H. Brockmeyer[3], Karl-Heinz Joeckel[1], Raimund Erbel[1], Nico Reinsch[4]
[1]University Hospital Essen, Essen, Germany, [2]University Leipzig, Leipzig, Germany, [3]Ruhr-University Bochum, Bochum, Germany, [4]Alfried Krupp Hospital, Essen, Germany

Background: Cardiovascular events (CVE) are more frequent in the HIV-positive patients (HIV+) than in the general population. HIV-infection may be causative for more CVE beside the traditional risk factors. Therefore, we investigated the incidence of CVE in HIV+ and HIV-negative controls leading to more insides of HIV-specific effects on CVE.
Methods: We compared CVE of HIV+ outpatients of the HIV HEART study (HIVH) with controls of the population-based Heinz Nixdorf Recall study (HNR) without any CVE at baseline. Both were recruited from the German Ruhr area since 2000. HIVH men with HNR controls were matched in a 1:2 ratio by age and Framingham risk score (FRS). For comparability we limited the follow-up time (FUP) of HNR to the maximum FUP of HIVH of 7.8 years. CVE are defined by myocardial infarction and sudden cardiac death. Hazard Ratios (HR) with corresponding 95%-confidence intervals (CI) were evaluated using Cox proportional Hazard regression with time to CVE and CVE as event. In Kaplan-Meier curves we show CVE-free survival stratified by HIV status. In HIV+ subgroup the CVE-free survival was compared in different ART groups, viral load and clinical HIV-stage.
Results: 322 HIVH males were matched with 644 HNR controls by age (54.7 ± 6.5 years) and FRS (14.7 ± 8.5). The mean follow-up time was 7.8 ± 0.8 years in HNR and 4.6 ± 1.7 years in HIVH. The HIV+ were diagnosed for 9.2 ± 6.5 years and 118 (37.0 %) already had AIDS as defined in the CDC classification. At baseline in 245 HIV+ (76.1 %) the viral load was below the level of detection and 302 (93.8 %) received antiretroviral treatment (ART). For HIV+ we achieved HR of 3.9 (CI: 1.7; 8.7) for CVE in comparison to HNR. A Kaplan-Meier curve of CVE-free survival between HIVH and HNR is shown in figure 1. In HIV+, CVE-free survival tended to be different in main ART regimens compared to ART-naïve HIV+ (HR of NNRTI or PI as third agent: 0.3 (CI: 0.03; 3.3) and 1.1 (CI: 0.1; 8.5)), was worse in those having AIDS (HR: 1.6 (0.6; 4.5)) and a viral load above the detection limit (1.2 (CI: 0.4; 3.7)).
Conclusion: HIV-infection was associated with a higher CVE incidence. We could show that ART, clinical HIV stage and viral load seem to an effect on CVE-free survival. Other not in the FRS requested CVE risk factors like effects of the HIV infection itself, drug use and vascular inflammation may have an impact on CVE in HIV+ and must be evaluated in further studies.



692 COMPARING STRATEGIES FOR REDUCING MYOCARDIAL INFARCTION RATES IN HIV PATIENTS

Priscilla Hsue[1], Grace A. McComsey[2], Calvin Cohen[3], Alejandro Sola[4], Anne C. Beaubrun[3]
[1]University of California San Francisco, San Francisco, CA, USA, [2]Case Western Reserve University, Cleveland, OH, USA, [3]Gilead Sciences, Inc, Foster City, CA, USA, [4]Datakhan Analytics Solutions, New York, NY, USA

Background: Studies show higher rates of myocardial infarctions (MI) with HIV and aging. Abacavir (ABC) has also been associated in some studies with an increased risk of cardiovascular (CV) events. To assess the relative impact of one intervention to reduce MI risk in HIV patients versus another, we modelled the impact of interventions that address traditional risk factors and replacing ABC on predicted MI rates. While other HIV antivirals have been associated with elevated MI risk, we used ABC as an example of the impact of changing HIV treatment in addition to a focus on traditional risk factors.
Methods: Strategies for reducing MI rates in HIV patients were compared over 10 years using a decision tree model. Assumptions about the effectiveness of smoking cessation counseling, substitution of ABC with an alternative regimen, anti-hypertensive and anti-hyperlipidemia medication use were based on publications from the HIV or general population. We adjusted for sex, age, and presence of the four MI risk factors. Interventions were compared based on published data on the probability of success of changing the risk factor and the impact of changing it when successful. For smoking cessation, the impact was based on published quit rates following counseling, 36.5% after one year and 10% annual relapse rate.
Results: In the base case of 50-year old HIV positive male smokers who only replaced ABC, there was a 46% reduction in the MI rate compared to those who continued ABC (0.31/ 100 vs. 0.58/ 100 PY). Men who are counseled and treated for smoking cessation which resulted in an 11% MI rate reduction versus those who did not attempt smoking cessation (0.52/ 100 vs. 0.58/ 100 PY). Over 10 years, compared to no MI intervention, ABC substitution prevented more MIs than counseling about smoking (2.64 vs 0.63 MIs per 100 persons). The impact of treating hypertension and hyperlipidemia was a 19% and 31% reduction in MI risk, respectively (see Table).
Conclusion: By incorporating the impact of CV risk factor modification based on real world data, this model suggests that replacing ABC, which can be accomplished in most patients, is potentially more impactful in reducing MI risk than interventions solely on traditional risk factors. While this model does not account for all tobacco risks, findings highlight the role that ABC substitution can have on MI risk over time compared to antismoking, hypertension and lipid lowering interventions. Interventions to address all CV risk factors are warranted.

Intervention type	HIV+ patient profile	MI rate without intervention (1/100 patient-years)	MI rate with intervention (1/100 patient-years)	% MI rate reduction of intervention
Abacavir substitution with an alternative antiviral without association to higher MI rate[1][2][3]	50 y/o, male, on abacavir	0.38	0.21	45%
Counseling including standard treatment for smoking cessation [4][5][6]	50 y/o, male, on abacavir, smoker	0.58	0.51	11%
Prescribing anti-hypertensive medication[4][7][8]	50 y/o, male, on abacavir, w/ hypertension	0.61	0.49	19%
Prescribing anti-hyperlipidemia medication [4][8]	50 y/o, male, on abacavir, w/ hyperlipidemia	0.61	0.42	31%

[1] Westring Worm S, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, De Wit S, Law M, D'Arminio Monforte A, Friis-Møller N, Kirk O, Fontas E, Weller I, Phillips A, Lundgren J. Risk of Myocardial Infarction in Patients with HIV Infection Exposed to Specific Individual Antiretroviral Drugs from the 3 Major Drug Classes: The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. The Journal of Infectious Diseases (2010) 201 (3): 318-330.
[2] Sabin C, Reiss P, Ryom L, Phillips A, Weber R, Law M, Fontas E, Mocroft A, de Wit S, Smith C, Dabis F, d'Arminio Monforte A, El-Sadr W, Lundgren J. Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration. BMC Medicine (2016) 14:61.
[3] Poorolajal J, Hooshmand E, Mahjub H, Esmailnasab N, Jenabi E. Survival rate of AIDS disease and mortality in HIV-infected patients: a meta-analysis. Public Health 139 (2016) 3-12.
[4] Gutiérrez J, Albuquerque AL, Falzon L. HIV infection as vascular risk: A systematic review of the literature and meta-analysis. PLoS One (2017) 12(5): e0176686.
[5] Christiansen B et al. Treating Tobacco Use and Dependence: 2008 Update. U.S. Department of Health and Human Services (2008).
[6] Hughes J, Peters E, Naud S. Relapse to Smoking After 1 Year of Abstinence: A Meta-analysis. Addictive Behavior (2008) December ; 33(12): 1516–1520.
[7] Taverny G, Mimouni Y, LeDigarcher A, Chevalier P, Thijs L, Wright JM, Gueyffier F. Antihypertensive pharmacotherapy for prevention of sudden cardiac death in hypertensive individuals. Cochrane Database of Systematic Reviews (2016) Issue 3. Art. No.: CD011745.
[8] Kirkendall W. Clinical Evaluation of Chlorothiazide. Circulation (1959) 19:933-941.
[9] Chou R, Dana T, Blazina I, Daeges M, Jeanne T. Evidence Summary: Statins for Prevention of Cardiovascular Disease in Adults. U.S. Preventive Services Task Force (2016).

693 ZINC TO REDUCE MORTALITY AND CVD RISK AND HIV DISEASE PROGRESSION IN RUSSIAN DRINKERS

Matthew Freiberg[1], Natalia Gnatienko[2], Debbie Cheng[3], E Blokhina[4], Sharon Coleman[3], Margaret F. Doyle[5], Carly Bridden[2], Kaku So-Armah[3], Sally Bendiks[2], Russell Tracy[5], Kendall J. Bryant[6], Evgeny Krupitsky[4], Jeffrey H. Samet[3]
[1]Vanderbilt University, Nashville, TN, USA, [2]Boston Medical Center, Boston, MA, USA, [3]Boston University, Boston, MA, USA, [4]First Pavlov State Medical University of St. Petersburg, St. Petersburg, Russian Federation, [5]University of Vermont, Colchester, VT, USA, [6]NIH, Bethesda, MD, USA

Background: Zinc deficiency is common among HIV+ heavy drinkers and linked to high mortality rates. In HIV negative people, zinc reduces levels of inflammatory biomarkers that are strongly linked to mortality and cardiovascular disease (CVD) risk. Given that alcohol use among HIV+ individuals is common, determining whether zinc supplementation reduces mortality risk, CVD risk, and HIV disease progression is of interest.

Methods: We conducted a double-blinded randomized placebo-controlled trial of zinc supplementation among HIV-infected, ART-naïve heavy drinkers recruited 2013-2015 in St. Petersburg, Russia. We randomly assigned 254 participants, in a 1:1 ratio, to receive either zinc (15 mg men; 12 mg women) or matching placebo, daily for 18 months. We assessed the following study outcomes at 18 months: 1) VACS index (a validated predictor of total mortality, primary); 2) CD4 count; and 3) Reynolds CVD Risk Score. We performed linear regression analyses controlling for gender and baseline past week heavy drinking using the intention-to-treat approach.

Results: Participants had the following baseline characteristics: 72% male; age 34 years; 86% regular smokers; 88% HCV antibody positive; CD4 cell count 521 cells/mm^3; and BMI 23 kg/m2. Randomization groups were balanced demographically and clinically. VACS index score increased between baseline and 18 months in both arms, the increase was smaller in the zinc group (0.49 point) than in the placebo group (5.5 point); adjusted mean difference in change between groups was -4.68 points (95% confidence interval [CI] -9.62, 0.25; p=0.06). Mean CD4 cell counts decreased between baseline and 18 months in both zinc (-128.8) and placebo (-176.2) groups; adjusted mean difference in change between groups was 41.8 (95% CI -20.3, 103.8; p=0.19). At 18 months there was no significant difference in mean log-transformed Reynolds risk score between the two groups (see Table, p=0.85).

Conclusion: While participants in the zinc group had a clinically significant smaller increase in VACS index scores and a smaller decline in CD4 counts compared to the placebo group, the differences were not statistically significant. We detected no differences in Reynolds CVD risk scores between the zinc and placebo groups at 18 months. Additional analyses examining factors such as the role of ART use during the follow-up period, measured zinc deficiency and study medication adherence are needed to further understand these preliminary findings.

Differences in Change in VACS Index, Change in CD4 cell count, and Reynolds Risk Score between ZINC and placebo groups after 18 months

Exposure	Mean Difference in Change in VACS Index (95%CI)	p-value	Mean Difference in Change in CD4 Cell Count (95%CI)	p-value	Mean Difference in Reynolds Risk Score*(95%CI)	p-value
Zinc vs. Placebo	-4.68 (-9.62, 0.25)	p=0.06	41.8 (-20.3, 103.8)	p=0.19	-0.014 (-0.167, 0.139)	p=0.85

Analyses controlled for gender, past 7-day alcohol use (randomization stratification factors). Reynolds Risk Score has additional adjustment for baseline value of Reynold's Risk Score.
*Log-transformed

694 MYOCARDIAL STEATOSIS IN RELATION TO CARDIAC DYSFUNCTION AMONG WOMEN LIVING WITH HIV

Mabel Toribio, Tomas G. Neilan, Lauren Stone, Adam Rokicki, Corinne Rivard, Jacob C. Calkins, Mary O'Hara, Magid Awadalla, Virginia Triant, Lidia S. Szczepaniak, Markella V. Zanni
Massachusetts General Hospital, Boston, MA, USA

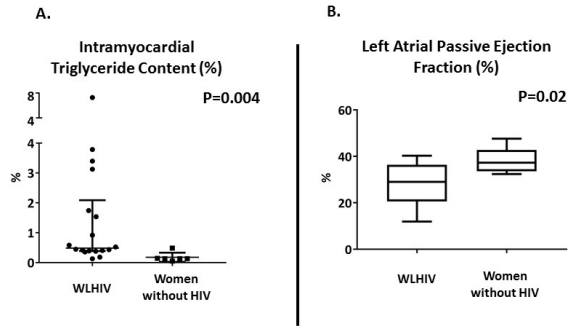
Background: Among women living with HIV (WLHIV) with access to ART, heart failure incidence is increased and outcomes are poor. Heart failure is typically preceded by an asymptomatic stage of diastolic dysfunction. Studies in diverse patient populations have suggested myocardial steatosis, or increased intramyocardial triglyceride content, predisposes to diastolic dysfunction. Among WLHIV, data on cardiac structure and function are scarce. We hypothesized asymptomatic WLHIV would demonstrate myocardial steatosis and diastolic dysfunction as compared with women without HIV.

Methods: In this prospectively recruited cross-sectional cohort study, 18 asymptomatic WLHIV on ART and 6 asymptomatic women without HIV completed cardiac magnetic resonance spectroscopy, cardiac magnetic resonance imaging, and metabolic phenotyping procedures. Women with heart failure, diabetes, and current use of lipid-lowering medications were excluded. Intramyocardial triglyceride content and left atrial passive ejection fraction (a measure of diastolic function) were compared between groups and intra-group correlations were assessed.

Results: WLHIV and women without HIV did not differ with respect to age (52.1 vs. 51.7 years, p=0.84), BMI (31.5 vs. 29.7 kg/m2, p=0.61), prevalence of hypertension (22 vs. 33%, p=0.62), HbA1c (5.6 vs. 5.5%, p=0.51), or LDL cholesterol (113 vs. 109 mg/dl, p=0.76). Circulating triglyceride levels were higher among WLHIV (107 vs. 69 mg/dl, p=0.01). Among WLHIV, duration of known HIV was 19±9 years, 100% were on ART, median VL was 19 copies/ml (IQR 19, 19), and median CD4 was 558 cells/mm^3 (IQR 450, 773). Notably, the intramyocardial triglyceride content was over three-times higher among WLHIV (0.49 [0.39, 2.09] vs. 0.13 [0.11, 0.23] %, p=0.004) (Figure, Panel A). Further, left atrial passive ejection fraction was reduced among WLHIV (28±9 vs. 38 ±6 %, p=0.02) (Figure, Panel B). Among WLHIV, intramyocardial triglyceride content was not related to BMI (p=0.92) or to circulating triglyceride levels (p=0.34), but was inversely related to left atrial passive ejection fraction (rho -0.51, p=0.03).

Conclusion: Asymptomatic WLHIV on ART evidence a more than three-fold increase in intramyocardial triglyceride content in relation to diastolic dysfunction, as compared with age- and BMI-matched women without HIV. Further studies are needed to determine whether strategies targeting myocardial steatosis also improve diastolic function and potentially prevent heart failure among WLHIV.

Figure: Intramyocardial Triglyceride Content (%) and Left Atrial Passive Ejection Fraction (%) Among Women With and Without HIV



695 SUB-CLINICAL CARDIAC SYSTOLIC DYSFUNCTION AMONG WOMEN LIVING WITH HIV

Magid Awadalla, Markella V. Zanni, Mabel Toribio, Lauren Stone, Adam Rokicki, Corinne Rivard, Virginia Triant, Tomas G. Neilan
Massachusetts General Hospital, Boston, MA, USA

Background: Among women living with HIV (WLWH), there is a markedly increased risk of incident heart failure and once clinical heart failure develops, outcomes are poor. Traditional non-invasive imaging measures such as ejection fraction are limited predictors of incident heart failure. In broad populations, abnormal cardiac strain has been shown to predict the development of heart failure. There are no data assessing cardiac strain specifically among WLWH. We hypothesized that cardiac strain would detect impaired cardiac systolic function among WLWH despite a normal ejection fraction.

Methods: We performed a prospective cross-sectional study using cardiac MRI and metabolic phenotyping. We compared measures of cardiac strain (global longitudinal strain (GLS), longitudinal strain rate (SR), global circumferential strain (GCS) and global radial strain (GRS)) between 19 WLWH without cardiovascular symptoms to 7 confirmed HIV-uninfected controls. Images were analyzed using Medis Q-strain software by two readers blinded to HIV status.

Results: The mean age of WLWH was 52±4 years with a median duration of HIV of 21 years (range 2.4 to 31) and all were on ART. The mean CD4 count was 828±354 cell/mm^3, and 13 (68.4%) had an undetectable viral load. Women with and without HIV were similar in respect to age, cardiovascular risk factors, body mass index, and blood pressure. On MRI, there was no difference in the left ventricular (LV) volumes (LV end diastolic volume, 134±24 vs. 139±32 mls, p=0.62), LV ejection fraction (58±4 vs. 59±4%, p=0.77), LV mass (88±26 vs. 86±21 grams, p=0.93), right ventricular (RV) volumes (RV end diastolic volume, 128±28 vs. 132±27 mls, p=0.67) or RV ejection fraction (52±6 vs. 54±5%, p=0.4) between the groups of women with and without HIV. However, we found that GLS (-19 ±3 vs -24±2%, p=0.004, Figure, Panel A), GCS (-27±4 vs -31±4%, p=0.03), GRS (47±9 vs 57±10% p=0.03) and SR (-0.7±0.2 vs. -1.0±0.2 s-1, p=0.009, Figure, Panel B) were reduced among WLWH as compared to women without HIV. Within the group of WLWH, there was no association between the reduction in GLS and duration of HIV or HIV control (CD4 count).

Conclusion: Women living with HIV without heart failure demonstrated impaired strain and strain rate despite having normal cardiac chamber size and ejection fraction. Future work will be needed to determine the factors associated with impaired cardiac strain and whether impaired cardiac strain predicts those women with HIV who go on to develop heart failure.

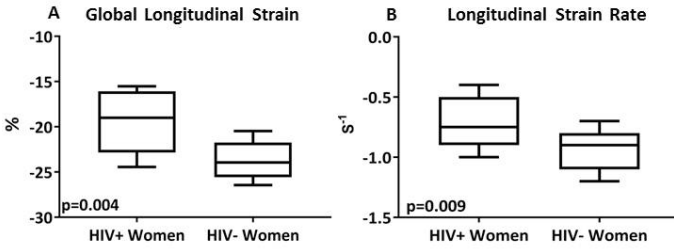


Figure: As compared to un-infected controls, global longitudinal strain (A) and longitudinal strain rate (B), sensitive measures of sub-clinical left ventricular systolic function were lower among women living with HIV. These women were free of known cardiac disease and were free of cardiovascular symptoms.

696 SYSTOLIC HEART FAILURE AND HEART FAILURE OUTCOMES AMONG PERSONS LIVING WITH HIV

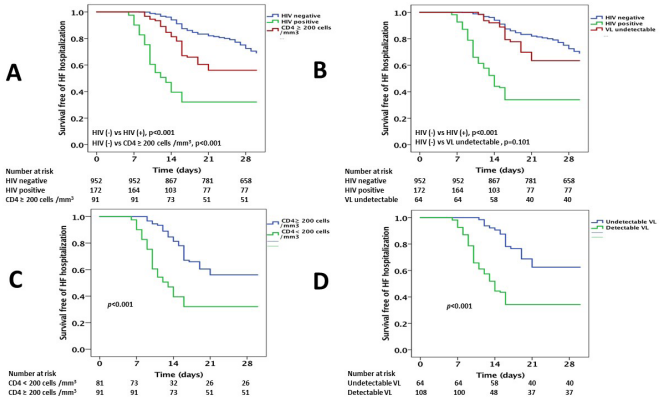
Raza M. Alvi[1], Maryam Afshar[2], Noor Tariq[3], Jaime Gerber[3], Virginia Triant[1], Markella V. Zanni[1], Tomas G. Neilan[1]
[1]*Massachusetts General Hospital, Boston, MA, USA,* [2]*Bronx–Lebanon Hospital Center, Bronx, NY, USA,* [3]*Yale University, New Haven, CT, USA*

Background: Persons living with HIV (PLHIV) have an increased risk of heart failure with a reduced ejection fraction (HFrEF). However, little is known about outcomes among PLHIV with HFrEF. We aimed to compare HF outcomes among PLHIV with HFrEF vs. individuals without known HIV with HFrEF.

Methods: Our cohort included 1,124 individuals admitted with decompensated HF and an LVEF of∠50%; of these, 15% (172/1,124) were PLHIV. We compared baseline characteristics, 30-day HF readmission rate (primary outcome), and cardiovascular (CV) and all-cause mortality (secondary outcomes). Within PLHIV, outcomes were stratified by CD4 count and viral load (VL) and the association between traditional and HIV-specific parameters with 30-day HF readmission were tested.

Results: There were no differences in age, sex, race, LVEF or traditional CV risk factors. Amongst PLHIV, pulmonary artery pressure and cocaine use were higher. In follow-up, PLHIV had a higher 30-day HF readmission rate (55 vs. 30%, p∠0.001), and increased CV (27 vs. 14%, p∠0.001) and all-cause mortality (41 vs. 26%, p∠0.001). Among PLHIV hospitalized with HFrEF, those with a lower CD4 count had a higher 30-day HF readmission rate (68% vs. 44%, p∠0.001), and higher rates of CV (36% vs. 19%, p∠0.001) and all-cause (54% vs. 29%, p∠0.001) mortality. PLHIV with a detectable VL had a higher 30-day HF readmission rate (65 vs. 37%, p∠0.001), and higher rates of CV (34% vs. 14%, p∠0.001) and all-cause mortality (53% vs. 20%, p∠0.001). Finally, among PLHIV, traditional (e.g. CAD, HF medications), non-traditional (cocaine use), and HIV-specific risk parameters (CD4 count, viral load) were predictors of 30-day HF readmission.

Conclusion: PLHIV hospitalized with HFrEF have increased 30-day HF readmission rates and CV and all-cause mortality as compared with uninfected individuals hospitalized with HFrEF. These outcomes were more common among those with lower CD4 count and higher VL.



697 SLEEP APNEA AND HEART FAILURE WITH REDUCED EJECTION FRACTION AMONG HIV PATIENTS

Raza M. Alvi[1], Magid Awadalla[1], Atul Malhotra[2], Noor Tariq[3], Adam Rokicki[1], Virginia Triant[1], Markella V. Zanni[1], Tomas G. Neilan[1]
[1]*Massachusetts General Hospital, Boston, MA, USA,* [2]*University of California San Diego, La Jolla, CA, USA,* [3]*Yale University, New Haven, CT, USA*

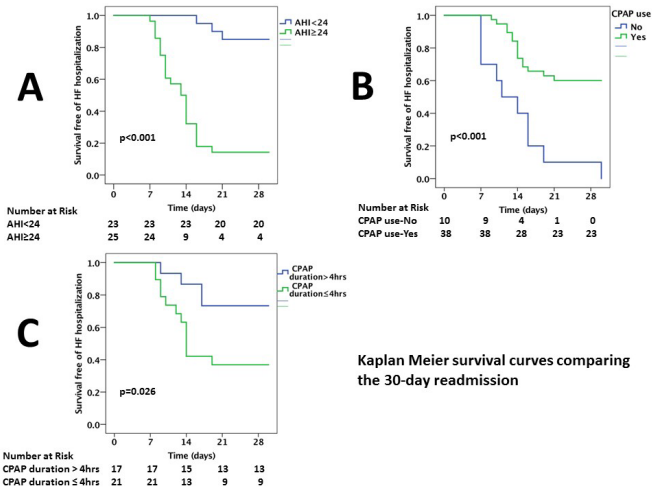
Background: Among patients with heart failure with a reduced ejection fraction (HFrEF), sleep apnea (SA) is common and associated with worse outcomes. People living with HIV (PLHIV) exhibit increased rates of both HFrEF and SA; however, there are no data characterizing SA among PLHIV with HFrEF. The aim of this study was to characterize the presence, associations and prognostic significance of SA among PLHIV with HFrEF.

Methods: We conducted a single center study of PLHIV admitted with HFrEF (LVEF of∠50%) and analyzed the relationship between SA (and traditional and HIV-specific risk factors) with 30-day HF hospital readmission rate (primary outcome), as well as cardiovascular (CV) and all-cause mortality (secondary outcomes). Among PLHIV with SA, we also assessed whether SA disease severity (apnea hypopnea index (AHI)), CPAP use and duration influenced HF outcomes.

Results: Our cohort included 1,124 individuals admitted to a US tertiary care hospital with HFrEF; 15% (172/1,124) were PLHIV. Sleep apnea was noted in 28% of PLHIV (48/172) and 26% (248/952) of uninfected controls. Patients with HFrEF with SA were compared according to HIV status; those with HIV had a lower BMI (32.1±5.4 vs. 39.2±4.6 kg/m2, p∠0.001), lower LVEF (37±8 vs. 41±6%, p∠0.001), a higher pulmonary artery systolic pressure (PASP, 50±9.5 vs. 40±9.0 mmHg, p∠0.001), were more likely to have obstructive rather than central SA (66 vs 45%, p=0.33), higher rates of CPAP use (79 vs. 64%, p=0.03) and for a longer duration (6 vs. 4 hours/night, p=0.001). In a multivariable model among PLHIV with HFrEF, traditional HF risk factors (CAD, PASP), non-traditional HF risk factors (cocaine use), HIV-specific parameters (low CD4 count, high viral load) and SA parameters (AHI, CPAP use and duration) were predictors of 30-day HF

hospital readmission rate. Each 1 hour increase in CPAP use was associated with a 14% decreased risk of 30-day HF hospital readmission.

Conclusion: As compared to uninfected controls with HFrEF and SA, PLHIV were more likely to have obstructive SA rather than central SA and were more likely to use CPAP and for a longer duration. Apnea severity was positively associated with 30-day HF hospital readmission rate whereas CPAP use and increased duration of CPAP use conferred protection.



Kaplan Meier survival curves comparing the 30-day readmission

698 CARDIAC VENTRICULAR DISFUNCTION IN YOUNG VERTICALLY INFECTED HIV PATIENTS

Lidia Capotosto, **Eugenio Nelson Cavallari**, Giuseppina Cusano, Ivano Mezzaroma, Giancarlo Ceccarelli, Luigi Celani, Camilla Ajassa, Gabriella d'Ettorre, Vincenzo Vullo, Antonio Vitarelli
Sapienza University of Rome, Rome, Italy

Background: Ventricular disease is common among HIV infected subjects. Vertically infected patients offer the possibility to study young individuals with a long history of infection and antiretroviral treatment. The evaluation of left ventricular (LV) and right ventricular (RV) function trough standard echocardiographic measures commonly provides normal evidences during early stages of ventricular disease. Clinical implementation of 3D Speckle-Tracking Echocardiography (3DSTE) represents a novel opportunity for an accurate evaluation of ventricular function.

Methods: 16 HIV infected subjects and 16 age and gender matched controls were enrolled in this study. Pulmonary hypertension (>35 mmHg), abnormal findings at standard echocardiography, history of cardiac disease, chronic systemic disease other than HIV infection and detectable plasma HIV RNA represented exclusion criteria from the study. LV and RV function, as well as Tricuspid annular systolic plane excursion (TAPSE), were assessed trough standard echocardiography in all participants. LV global longitudinal, circumferential and radial strains were calculated and 3DSTE was applied to measure global area strain (percentage variation in surface area defined by the longitudinal and circumferential strain vectors) and RV 3D global and free-wall longitudinal strains.

Results: Main characteristics of the HIV infected population are shown in Table1. Reduced values of LV global longitudinal strain and global area strain were observed among HIV infected subjects compared to controls (-15.9% vs. -19.1%, p=0.013 and -33.9% vs. -38.7%, p=0.004), while no differences were observed in LV ejection fraction between the two groups. We also observed a significant reduction of RV free-wall longitudinal strain among HIV positive participants (-19.8% vs. -23.7%, p=0.025). A trend toward a lower TAPSE was noted in the HIV positive group (20.2±2.3mm vs. 23.4±2.6mm, p=0.08). Between the evaluated echocardiographic parameters, LV mass index resulted correlated with age (r=0.395, p=0.036) and CD4 count (r=0.331, p=0.048) of HIV infected participants and LV longitudinal strain was correlated with age (r=0.453, p=0.032), CD4 count (r=0.312, p=0.041) and DAD risk score (r=0.342, p=0.047) of the same group.

Conclusion: With 3DSTE we found early bi-ventricular disfunction, in the absence of pulmonary hypertension, among HIV infected participants to our study. This novel technique could help recognize HIV infected individuals with high cardiac risk.

	Median	Interquartile range
Age (years)	23.5	17.5 – 29.7
Age at diagnosis (months)	28	9 – 84
CD4 nadir (cell/μL)	387	267 – 439
Actual CD4 count (cell/μL)	833	699 – 920
Years on HAART	19.5	16 – 24
DAD risk score	2.61	0.80 – 4.66

Table 1. Main characteristics of HIV infected participants.

699 ACUTE HIV INFECTION RESULTS IN SUBCLINICAL AND REVERSIBLE INFLAMMATORY CARDIOMYOPATHY

Christopher Schuster, Florian Mayer, Corinna Wohlfahrt, Rodrig Marculescu, Michael Skoll, Robert Strassl, Maximilian Aichelburg, Noemi Pavo, Theresia Popow-Kraup, Martin Hülsmann, Armin Rieger, Georg Goliasch
Medical University of Vienna, Vienna, Austria

Background: Acute HIV infection (AHI) is characterized by high plasma levels of plasma HIV-1 RNA in the absence of HIV-1 antibodies accompanied by symptoms of acute infection in around 70% of patients. It has recently been shown that viral replication is associated with subclinical cardiac dysfunction in chronic HIV infection. However, the impact of excess viral RNA on myocardial function and morphology in the setting of acute HIV infection remains unknown. The objective of this study is to assess the impact of AHI on the heart using functional (i.e. NT-proBNP) and morphological (i.e. troponin T) cardiac markers and to determine whether a correlation to inflammatory parameters (CRP, leukocyte numbers, platelet count, HLA-DR$^+$CD3$^+$ T cells, Il-6, serum amyloid A) exists.

Methods: A total of 49 patients with AHI showing a normal cardiac and renal status were enrolled in this retrospective study. Laboratory measurements were performed at the time of diagnosis and at the first follow-up demonstrating suppression of viremia below the limit of quantification (BLQ, after a median of 22 months (12-42).

Results: During AHI, median level of NT-proBNP was 79 pg/ml (31-179) compared to 28 pg/ml (10-39) after suppression of viremia BLQ (P<0.001; Fig. 1). NT-proBNP showed a significant correlation with absolute CD4 count (r=0.29; p=0.044) and viral load (r=0.48; P=0.002). Concomitantly, the median level of the cardiac cell injury marker troponin T was 4.9 ng/ml (2.9-12.8) during AHI and 1.5 (1.5-3.9) after attainment of plasma HIV-1 RNA BLQ (P<0.001). Similar to NT-proBNP, Troponin T also showed a significant correlation with viral load (r=0.44; P=0.001). In a multivariate linear regression model, levels of NT-proBNP were determined by the humoral and cellular inflammatory activation reflected by CRP, Il-6, serum amyloid A, leukocyte numbers, platelet count, HLA-DR+CD3+ T cells, resulting in a R2 of 0.71 [F(9,39)=10.36; p=0.001] at the time of AHI diagnosis. Upon suppression of viremia BLQ this association vanished (R2=0.24; F(10,36)=1.15; p=0.357).

Conclusion: We observed a significant functional as well as morphologic myocardial impairment during AHI fueled by both humoral and cellular inflammatory activation resulting in a subclinical inflammatory cardiomyopathy, which appears to be fully reversible owing to treatment effects or the abatement of AHI after some weeks.

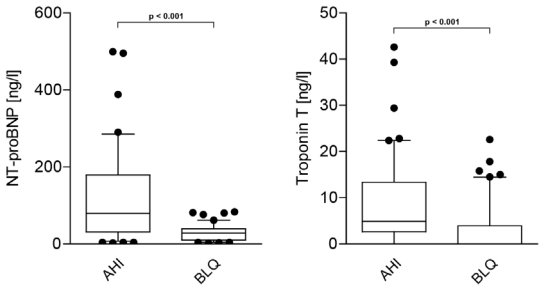


Fig. 1: Box plots with medians, interquartile ranges, 10–90 range and outliers for NT-proBNP and troponin T at the time of diagnosis (AHI) and after attainment of viremic control (i.e. below level of quantification (BLQ) <50 copies/ml)

700 CORONARY WALL THICKENING AND ASSOCIATION WITH MYOCARDIAL DIASTOLIC FUNCTION IN HIV

Julia Purdy[1], Khaled Z. Abd-Elmoniem[1], Hwaida Hannoush[1], Vandana Sachdev[1], Colleen Hadigan[2], Ahmed M. Gharib[1]
[1]NIH, Bethesda, MD, USA, [2]NIAID, Bethesda, MD, USA

Background: Cardiovascular disease (CVD) is a rising cause of morbidly and mortality in human immune deficiency virus (HIV) infected patients. Coronary vessel wall (VW) thickening as measured by MRI in young HIV patients has demonstrated early coronary artery pathology. Further, early diastolic dysfunction and myocardial strain abnormalities were detected in HIV patients despite a preserved global myocardial function. The goal of this study is to assess both coronary vascular disease burden and its relation to myocardial function in adults with and controls.

Methods: In this prospective, cross-sectional study, a total of 100 HIV+ adults without known CVD and 30 matched healthy controls underwent time resolved phase-sensitive dual inversion recovery black-blood vessel wall magnetic resonance imaging (TRAPD) at 3T to measure proximal right coronary artery (RCA) wall thickness, and echocardiography to assess left ventricular function. Coronary Computer Tomography Angiography (CCTA) was also obtained to measure coronary calcification and overall coronary plaque burden. The presence of coronary calcification and Agatston score were recorded. Addition other non-calcified plaque was accounted for in segment involvement (SIS) and segment severity scores (SSS).

Results: There was no difference in age (HIV+48.6 ± 10.1 vs. controls = 46.3 ± 7.8 years), sex, body mass index and Framingham risk score between groups. VW measurements by MRI were successful obtained in 74 HIV-infected patients and 25 controls. HIV+ patients demonstrated a significantly thicker ($p<0.05$) coronary VW (1.5 ± 0.22mm) compared to controls (1.3 ± 0.18mm). Echocardiography measured ejection fraction (EF) and early (E) to late (A) ventricular filling velocities ratio (E/A) and all CCTA-based coronary plaque burden were not different between the two groups. However, in a regression analysis of HIV+ subjects, there was significant negative correlation between VW thickness and E/A ratio ($p<0.05$).

Conclusion: Subclinical coronary artery disease (CAD) is present in HIV-infected patients without a known history of CVD as shown by increased coronary VW thickness compared to controls. Furthermore, coronary VW thickness measured by MRI was associated with a detrimental effect on the myocardial function as demonstrated by the significant negative relationship between early mild diastolic dysfunction (impaired relaxation) depicted by decrease in E/A ratio on echocardiography.

701 CONTRIBUTION OF HIV, HCV, AND VASCULAR RISK FACTORS TO PERIPHERAL ARTERIAL DISEASE

Emily Cedarbaum[1], Yifei Ma[1], Rebecca Scherzer[1], Jennifer Price[1], Michael Plankey[2], Margaret Fischl[3], Eric C. Seaberg[4], Mardge H. Cohen[5], Marcas Bamman[6], Jason Lazar[7], Adaora Adimora[8], Michael T. Yin[9], Phyllis Tien[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]Georgetown University, Washington, DC, USA, [3]University of Miami, Miami, FL, USA, [4]Johns Hopkins University, Baltimore, MD, USA, [5]Cook County Health & Hospitals System, Chicago, IL, USA, [6]University of Alabama at Birmingham, Birmingham, AL, USA, [7]SUNY Downstate Medical Center, Brooklyn, NY, USA, [8]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [9]Columbia University, New York, NY, USA

Background: Peripheral artery disease (PAD) increases cardiovascular disease (CVD) risk by 3-6 fold and is associated with physical function decline and increased mortality. Studies of PAD in HIV have been mostly small in sample size and lacked a comparison seronegative group. None have studied the impact of HCV coinfection. We examine the association of HIV, HCV, and traditional CVD risk factors with PAD in the Women's Interagency HIV Study (WIHS), a multicenter US cohort of women with and at risk for HIV.

Methods: Ankle-brachial index (ABI) was calculated using Doppler ultrasound with manual sphygmomanometer measurement of ankle and brachial pressures in 1865 participants (1064 HIV+/HCV-;94 HIV-/HCV+;283 HIV+/HCV+;424 HIV-/HCV-) age >40. Multivariable logistic regression was used to determine the association of HIV and HCV with PAD (defined as ABI≤0.9 or >1.3) after controlling for demographics, behavioral and vascular risk factors.

Results: HIV+/HCV+ and HIV-/HCV+ women were older than HIV+/HCV- and HIV-/HCV- women (median age:54-55 vs 49-50) and more likely to be a current smoker (>50% of HIV+/HCV+ and HIV-/HCV+ vs 35% of HIV+/HCV-;47% of HIV-/HCV-). Over 67% of the cohort was Black. PAD prevalence was high but showed little difference by HIV and HCV status (29% in HIV+/HCV+;28% in HIV-/HCV+;27% in HIV+/HCV-;29% in HIV-/HCV-). In adjusted models, women with HIV and HCV infection did not have greater odds of PAD compared to uninfected women (Table). Rather, greater odds of PAD were associated with Black race (OR:1.98(95% Confidence Interval[CI]:1.33,2.95), longer pack-year smoking history (OR:1.02 per year increase; 95%CI:1.01,1.03), and greater waist circumference (OR:1.04 per 5cm increase;95%CI:1.00,1.08) and pulse pressure (OR:1.01 per 1mm Hg;95%CI:1.00,1.02). Higher HDL (OR:0.93 per 10% increase;95%CI:0.87,0.99) and DM (OR:0.77;95%CI:0.61,0.98) were associated with lower PAD risk. CVD risk factors showed similar associations with PAD in each infection group. In the HIV+ women, there was little association of CD4 count, HIV RNA, or HIV duration with PAD.

Conclusion: HIV and HCV infections are not associated with greater PAD risk in WIHS. However, the high PAD prevalence in our cohort is striking; general population studies show a >25% prevalence at ages >20 years older. Our findings suggest that smoking cessation, weight loss, and blood pressure control are important to target early in women with and at risk for HIV. Investigation of factors associated with PAD progression is underway.

702 CARDIAC ABNORMALITIES IN PERINATALLY INFECTED HIV+ SOUTH AFRICAN ADOLESCENTS ON ART

Sana Mahtab, John Lawrenson, Norme J. Luff, Nana Akua Asafu-Agyei, Liesl Zülke, **Landon Myer**, Heather Zar
University of Cape Town, Cape Town, South Africa

Background: Little is known about the cardiac health of perinatally HIV-infected adolescents (PHIV+) in African settings. We studied cardiac structure and function in PHIV+ on antiretroviral (ART) compared to age matched HIV- controls.

Methods: Echocardiograms were performed on PHIV+ and controls enrolled in the Cape Town Adolescent Antiretroviral cohort(CTAAC).Participants were eligible if they were aged 9-14 years and had been on ART for at least 6 months. Lipid profile was measured on fasting serum samples.Echo parameters were adjusted by using z-scores according to body surface area.Logistic regression were used to examine the adjusted association between echo measures and HIV-related and traditional cardiovascular risk factors

Results: Overall 474 PHIV+ (median age,12 years; 51% male; mean age at ART initiation 5 years,SD ±3.5) and 109 controls (median age,11.8 years; 45% male) were included. Mean duration on ART was 7 years (SD±3.0) with 36.5% initiating <2 years of age. Median total cholesterol (4.1 vs 3.8 mmol/L,$p<0.01$), low-density lipoprotein (2.2 vs 2.0 mmol/L,$p=0.01$) and triglyceride (0.9 vs 0.7 mmol/L,$p<0.01$) were higher in PHIV+. PHIV+ had lower mean z-scores for left ventricular (LV) internal dimension at the end of diastole (-0.16 vs -0.49,p=<0.01), LV posterior wall thickness at the end of systole (-0.45 vs -0.65,$p=0.01$) and right ventricular (RV) internal dimension at end diastole (0.24 vs 0.43,$p=0.01$) and higher for thickness of inter-ventricular septum at the end of systole (0.7 vs 0.6,$p=0.04$) vs controls. Only 2 PHIV+ had mild pulmonary hypertension.There was no difference in ejection fraction or simple diastolic function assessment between groups. Later initiation of ART between age 6-14 years was associated with increased risk of LV hypertrophy (LVH) (>88/102 g/m^2-female/male) (OR 2.9,$p=0.01$) compared to those who started ART earlier (before age of 6 years).PHIV+ with WHO HIV stage IV at diagnosis were at increased risk (OR 2.14,$p=0.05$) of having LV diastolic dysfunction (LVDD)(abnormal mitral E/A ratio for age) compared to those with less advanced clinical disease.

Conclusion: ART is cardioprotective in our participants despite delayed onset of therapy, with no difference in systolic or diastolic function between groups. However, starting ART at an older age was a significant risk factor for LVH while more advanced clinical disease was associated with LVDD. Surprisingly PHIV+ had less dilated left and right ventricles than controls;the clinical significance of this is uncertain.

Logistic regression models for key predictors of left ventricular hypertrophy and left ventricular diastolic dysfunction amongst PHIV+ in CTAAC

Models	Multivariate Analysis*			
	Left ventricular hypertrophy		Left ventricular diastolic dysfunction	
	OR (95% CI)	p	OR (95% CI)	p
Blood Pressure (mmHg)				
Systolic§	0.99 (0.44-5.71)	0.64	0.99 (0.95-1.02)	0.36
Diastolic§	0.97 (0.93-1.01)	0.19	0.98 (0.95-1.02)	0.43
Viral load (copies/ml)				
≤1,000	Ref		Ref	
>1,000	1.45 (0.50-4.22)	0.50	2.08 (0.82-5.32)	0.13
CD4 count (cells/uL)				
≤499	Ref		Ref	
≥500	1.89 (0.54-6.65)	0.32	0.56 (0.23-1.34)	0.19
WHO HIV staging				
Less than stage IV	Ref		Ref	
Stage IV	1.20 (0.48-2.98)	0.70	2.14 (0.99-4.60)	0.05
Age at initiation of ART				
0-5 years	Ref		Ref	
6-14 years	2.89 (1.26-6.63)	0.01	0.87 (0.39-1.94)	0.74
Current ART regimen				
2 X NRTI + NNRTI	Ref		Ref	
2 X NRTI + PI	1.35 (0.60-3.06)	0.47	1.14 (0.53-2.43)	0.74

*Adjusted for age, gender, lipid profile and BMI
§Continuous variables

703 THE MEDITERRANEAN PORTFOLIO DIET IN HIV DYSLIPIDAEMIA: A RANDOMIZED CONTROLLED TRIAL

Clare Stradling[1], G N. Thomas[2], Karla Hemming[2], Shahrad Taheri[3], Stephen Taylor[1], Jonathan Ross[4], Satyajit Das[5]
[1]Heart of England NHS Foundation Trust, Birmingham, UK, [2]University of Birmingham, Birmingham, UK, [3]Weill Cornell Medicine College in Qatar, Doha, Qatar, [4]University Hospitals Birmingham, Birmingham, UK, [5]Coventry & Warwickshire Partnership NHS Trust, Coventry, UK

Background: The risk of cardiovascular disease is increased in the HIV population, potentially due to the additional burdens of infection, inflammation and antiretroviral treatment (ART). This trial aims to examine the effect of dietary intervention on cardiovascular risk (CVR) in HIV dyslipidaemia.
Methods: This pilot, parallel, randomized controlled trial (ISRCTN32090191) recruited adults with stable HIV infection on ART and LDL-cholesterol >3mmol/l from 3 UK centres. Randomization (1:1) compared the effect of dietary advice to reduce saturated fat (Diet1) versus MedDiet with additional cholesterol lowering foods e.g. plant stanols, soya, oats (Diet2). Measurements of CV risk factors, fasting blood lipids, food intake, body composition, and arterial stiffness were conducted at baseline, month 6 and month 12. Between-group changes of CVR factors were assessed using ANCOVA, with adjustments for baseline values of the dependent variables. Analysis was by intention to treat (ITT) and Complier Average Causal Effect.
Results: 60 eligible adults were randomized with mean age 42±7years, LDL-cholesterol 3.9±0.6mmol/l, 50% female, 65% non-smokers, 50% black African, 40% white European. Baseline characteristics were comparable between groups. At 6 months, Diet2 participants (n=29) showed a significantly greater reduction in LDL-cholesterol, total to HDL-cholesterol ratio, systolic blood pressure (BP) and increase in Mediterranean Diet Score, than those in Diet1 (n=31), see table. Intake of Mediterranean (olive oil, fish, legumes) and Portfolio foods (nuts, stanols) increased significantly in the Diet2 group (p<0.01). Individual adherence varied from 11 to 100% (mean 59±21%). Body composition, arterial stiffness, gut function, and levels of physical activity were not significantly different between the groups. As expected, the estimated treatment effect among compliers to MedDiet (LDL-cholesterol -0.87mmol/l, 95%CI -1.79 to 0.05) and Portfolio foods (-0.76mmol/l, 95%CI -1.54 to 0.01) appears larger than that for ITT analysis (-0.38mmol/l, 95%CI -0.68 to -0.09).
Conclusion: Dietetic advice to follow a Mediterranean diet containing nuts, plant stanols, soya protein, beans and oats produced a greater improvement in diet quality, blood pressure, and a 10% greater reduction in LDL-cholesterol than standard guidelines to reduce saturated fat intake. Analysis assuming full compliance and preserving randomisation suggests a possible doubling of this estimated treatment effect.

Table: Mean difference between low saturated fat (Diet1) and Mediterranean Portfolio (Diet2) groups at month 6

Endpoint	Time	Diet1 low saturated fat group Mean ±SD (n = 29)	Diet2 Med Portfolio group mean ±SD (n = 31)	Mean difference (MD), adjusted for baseline value (95% CI)	P value	MD, adjusted for baseline value, smoking, gender, socioeconomic status, baseline MDS (95% CI)	P value
LDL-cholesterol (mmol/l)	Baseline	3.9±0.5	3.9±0.6				
	Month 6	3.9±0.7	3.5±0.6	-0.4 (-0.7 to -0.1)	0.01	-0.5 (-0.8 to -0.2)	0.002
Total cholesterol to HDL ratio	Baseline	4.3±0.9	4.4±1.4				
	Month 6	4.3±1.0	4.1±1.2	-0.3 (-0.6 to -0.1)	0.01	-0.4 (-0.6 to -0.1)	0.004
Systolic BP (mm Hg)	Baseline	123±15	125±14				
	Month 6	127±17	121±10	-7 (-2 to -12)	0.008	-8 (-13 to -2)	0.005
Diastolic BP (mm Hg)	Baseline	78±12	78±9				
	Month 6	80±10	78±8	-2 (-6 to 2)	0.3	-2 (-6 to 2)	0.2
Mediterranean Diet Score (14-item)	Baseline	6.8±2.4	6.0±2.3				
	Month 6	6.6±2.9	9.5±2.2	3.3 (2.0 to 4.7)	<0.001	3.1 (1.6 to 4.5)	<0.001
Saturated fat (g/day)	Baseline	24.5±13.5	25.0±16.5				
	Month 6	23.6 ±12.4	20.2±10.1	-3.5 (-10.4 to 3.5)	0.3	-2.7 (-11.1 to 5.6)	0.5

Key: SD standard deviation; CI confidence interval; MD mean difference; LDL Low-density lipoprotein; BP blood pressure

704 BIOMARKERS AND GENETICS OF CELL CHOLESTEROL DYSREGULATION IN HIV NONPROGRESSORS

Giovanna Rappocciolo, Diana Campbell DeLucia, Jeremy J. Martinson, Stacy Wendell, Charles Rinaldo
University of Pittsburgh, Pittsburgh, PA, USA

Background: Professional antigen-presenting cells (APC) from HIV nonprogressors (NP) are inefficient mediators of HIV-1 trans infection of CD4+ T cells due to altered cell cholesterol metabolism (Rappocciolo, et al., mBio 2014), potentially reducing spread of virus and controlling disease progression. Here, we show the role of host genetic variation and signaling metabolites in control of cell cholesterol homeostasis in NP.
Methods: We tested 29 NP (9 elite controllers, 10 long term NP, 10 viremic controllers), 13 HIV progressors (PR) and 10 seronegatives (SN) in the MACS. Plasma-mediated cholesterol efflux (CE) was measured by fluorometry (Biovision). To measure CE from participants APC, B cells and DC were loaded with BODIPY-labelled cholesterol and incubated with apolipoprotein A-1 (APOA1) as a cholesterol acceptor. Levels of apolipoprotein A-II (APOAII) in sera were measured by ELISA. Targeted lipidomics analysis was done by LC-MS on lipid fractions of sera. SNP analysis was performed using TaqMan assays.
Results: Plasma from NP and SN showed higher induction of CE than PR (p< 0.008). Similarly, B cells and DC from NP had higher CE to APOA1 than APC from PR (p<0.05). CE from CD4+ T cells was similar among PR, NP and SN. Targeted lipidomic analysis revealed significantly higher levels of 5-oxo-eicosatetraenoic acid (5-oxo-ETE) and PGE2, metabolites of arachidonic acid, in sera from NP compared to PR (p<0.05). Finally, the SNP rs5082 (APOAII c.-265 T>C, located in the APOAII gene) was associated with the NP phenotype (p=0.0003 for a dominant role for the minor allele).
Conclusion: NP have a unique combination of metabolic and genetic factors that impact altered cholesterol homeostasis, conferring on their APC the inability to transfer HIV to CD4+ T cells, thus controlling HIV dissemination. In NP we detected higher levels of 5-oxo-ETE, a metabolite produced by B cells and DC. This is a signaling agent that acts in both an autocrine and paracrine fashion and binds PPARγ nuclear receptor, increasing transcription of ABCA1 thus elevating cell CE. We hypothesize that such autocrine signaling could be a mechanism by which APC from NP escape downregulation of CE induced by HIV. The presence of a SNP in the APOAII gene could contribute to higher cholesterol efflux by modifying HDL composition. These data suggest that HIV eradication interventions need to incorporate strategies to shape cell cholesterol content

705 STATIN USE AND CARDIOVASCULAR DISEASE MITIGATION AMONG PERSONS LIVING WITH HIV

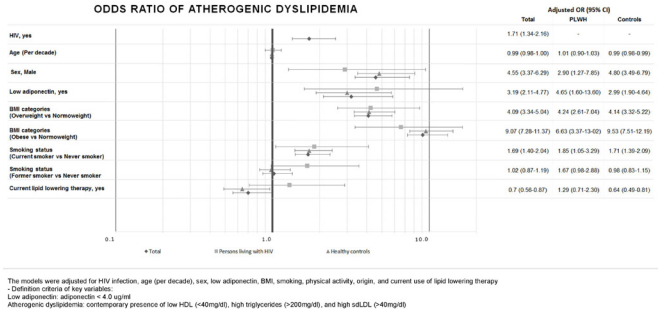
Derek T. Larson[1], Seung Hyun Won[2], Anuradha Ganesan[3], Ryan Maves[1], Jason Okulicz[4], Karl Kronmann[5], Xiuping Chu[2], Christina Schofield[6], Thomas O'Bryan[2], Brian K. Agan[2], Robert Deiss[1]
[1]Naval Medical Center San Diego, San Diego, CA, USA, [2]Uniformed Services University of the Health Sciences, Bethesda, MD, USA, [3]Walter Reed National Military Medical Center, Bethesda, MD, USA, [4]Brooke Army Medical Center, San Antonio, TX, USA, [5]Naval Medical Center Portsmouth, Portsmouth, VA, USA, [6]Madigan Army Medical Center, Takoma, WA, USA

Background: Chronic inflammation associated with HIV infection can result in increased risk for cardiovascular disease, and the baseline risk of cardiovascular-related mortality is up to 50% higher for HIV+ compared with HIV- persons. Indications for statin therapy are similar among HIV infected and uninfected individuals. Adherence to guideline-based care is critical and has been found deficient across multiple cohorts.
Methods: The U.S. Military HIV Natural History Study (NHS, RV168 database) is an ongoing cohort comprised of Department of Defense beneficiaries. We conducted a retrospective cross-sectional analysis of adherence to guidelines for statin therapy, including subjects aged 21-75 whose most recent study visit was between October 2015-September 2016. To determine statin eligibility, we used the American College of Cardiology/American Heart Association 2013 atherosclerotic cardiovascular disease (ASCVD) management guidelines and included subjects who had all necessary data elements for analysis.
Results: Selected baseline demographics of the cohort (n=1,066) included median age 47 (Interquartile Range [IQR] 34-55), male (95%), white race (40%), African-American race (45%), smokers (16%) and diabetic (12%). Statin eligibility was noted by having a previous cardiovascular event in 91 (8.5%) subjects, low-density lipoprotein (LDL) levels greater than 190 in 6 (0.6%), qualifying diabetics in 84 (7.9%), and ASCVD 10 year risk >7.5% in 303 (28.4%). In total, 342 (32%) patients met at least 1 criterion for therapy, and of those, 188 (55% of those eligible) were currently prescribed a statin. Among diabetics, 58% of eligible subjects were receiving statin therapy. Individuals receiving statin therapy tended to be older (median age 56 vs 42, p <0.001), white (52% vs 35%, p <0.001), and more likely to currently be on a protease inhibitor (57% vs 32%, p <0.001).
Conclusion: We found significant discrepancies between ASCVD guidelines and primary care management of HIV+ persons in the military health system, and racial disparities persisted even in this single-payer network. Despite wide acceptance, poor adherence to the 2013 guidelines remains common in the management of HIV+ persons. This persists despite easy determination of statin eligibility through use of the ASCVD risk calculators. Improved adherence to ASCVD guidelines will be critical to minimize risk of cardiovascular disease in the aging HIV population.

706 INCREASED RISK OF LOW ADIPONECTIN AND ATHEROGENIC DYSLIPIDEMIA IN HIV INFECTION

Marco Gelpi[1], Shoaib Afzal[2], Ashley Roen[3], Amanda Mocroft[3], Anne-Mette Lebech[1], Birgitte Lindegaard[1], Klaus F. Kofoed[1], Børge Nordestgaard[2], Jens D. Lundgren[1], Susanne D. Nielsen[1]
[1]Rigshospitalet, Copenhagen, Denmark, [2]Copenhagen University Hospital, Copenhagen, Denmark, [3]University College London, London, UK

Background: People living with HIV (PLWH) have increased risk of cardiovascular disease (CVD). Low levels of adiponectin have been linked to atherosclerosis, lipoprotein metabolism disorders, and unfavorable changes in LDL particle size in HIV-negative individuals. High levels of small dense LDL (sdLDL) together with high triglycerides (Tgl) and low HDL define the "atherogenic dyslipidemia" (AD) phenotype, which is a better predictor of CVD events than LDL alone. In this study we aimed to assess possible associations between HIV infection and adiponectin and AD.
Methods: 1,099 PLWH from the Copenhagen Co-morbidity in HIV infection (COCOMO) study and 12,161 controls from the Copenhagen General Population Study were recruited. Associations between HIV infection and adiponectin, and AD were explored by uni- and multivariable logistic regression analyses. The model used to assess predictors of low adiponectin was adjusted for HIV infection, age, sex, smoking, BMI, lipid lowering therapy, and physical activity (Model 1). When assessing predictors of AD, low adiponectin was added to Model 1. When assessing HIV-specific predictors of low adiponectin and AD, CD4 nadir, current CD4 count and viral load, duration of HIV infection and cART, and hepatitis C coinfection were added to the models. Key variables are defined in Fig 1.
Results: PLWH were younger (50.1 vs 52.2, p <.001), with a higher proportion of males (85.3% vs 81.4%, p .001) compared to uninfected controls. Furthermore, use of lipid lowering therapy was higher in PLWH (14.0% vs 10.6%, p .001). PLWH had lower levels of adiponectin (11.6 vs 12.2 ug/ml, p .014) and higher prevalence of both low adiponectin (2.0% vs 1.1%, p .019) and AD (13.4% vs 8.7%, p <.001) compared to uninfected controls. HIV infection was associated with higher odds of low adiponectin and AD (univariable models: OR 1.81, CI 1.05-2.92 and OR 1.61, CI 1.33-1.95, respectively; adjusted models: OR 2.08, CI 1.16-3.51 and OR 1.67, CI 1.31 -2.12, respectively). Predictors of AD are depicted in Fig. 1. In PLWH, longer cART duration was associated with low adiponectin and presence of AD (OR per year 1.31, CI 1.10-1.56 and OR 1.09, CI 1.01-1.71, respectively, in adjusted models).
Conclusion: HIV infection was associated with higher risk of low adiponectin and AD. Low adiponectin and longer duration of ART were strongly associated with the presence of AD in PLWH. These findings suggest perturbed adiponectin metabolism in PLWH, which is linked with higher risk of AD.



The models were adjusted for HIV infection, age (per decade), sex, low adiponectin, BMI, smoking, physical activity, origin, and current use of lipid lowering therapy
- Definition criteria of key variables:
Low adiponectin: adiponectin < 4.0 ug/ml
Atherogenic dyslipidemia: contemporary presence of low HDL (<40mg/dl), high triglycerides (>200mg/dl), and high sdLDL (>40mg/dl)

707 NON-CLASSICAL MONOCYTE AND CD4/CD8 RATIO PREDICTS ANKLE BRACHIAL INDEX IN TREATED HIV

Dominic Chow, Nattawat Klomjit, Louie M. Gangcuangco, Scott A. Souza, Sean Terada, Lindsay Kohorn, Lishomwa C. Ndhlovu, Cecilia Shikuma
University of Hawaii at Manoa, Honolulu, HI, USA

Background: HIV-infected individuals on stable antiretroviral therapy are at a heighted risk of peripheral vascular disease (PVD). Chronic inflammation, monocyte (MO) subset and T cell activation have been associated with PVD in the general population. We investigated the relationship between MO, T cell activation, and measures of PVD using ankle-brachial index (ABI).
Methods: Cross-sectional analysis of entry data from a cohort study of cardiovascular risk in HIV-infected subjects age > 40 years on stable antiretroviral therapy (ART) > 3 months. ABI was measured following the American Heart Association guidelines and was classified into 3 categories: low (ABI ≤0.90), borderline (ABI 0.91-0.99), normal (ABI 1.00-1.40). Banked PBMCs were phenotyped for MO subsets [classical MO (CD14++CD16-), intermediate (CD14++CD16+), non-classical (CD14low/+CD16++)] and for T cell activation (CD38+HLA-DR+CD8+) using multiparametric flow cytometry. CD4/CD8 ratio was calculated. Linear regression was performed between MO subsets, T cell activation, CD4/CD8 ratio and ABI. Multinomial logistic regression was conducted to determine predictors of ABI categories.
Results: Among 160 subjects, median age was 51.0 years and 86% were virally suppressed. There were 5.6%, 22.5% and 71.96% of individuals who had low, borderline and normal ABI, respectively. CD4/CD8 ratio predicted ABI independent of age, gender, hypertension, diabetes, LDL cholesterol and current smoking (β=0.06, p=0.05). Multinomial logistic regression showed that increases in non-classical MO led to an increase in the odds (OR 1.05) of being in the low ABI group compared to the normal group (p = 0.02) and remained statistically significant after adjusting for age, hypertension, diabetes, current smoking, LDL, and CD4 Nadir (p=0.04). Similarly, an increase in non-classical MO led to 3.55 times the odds of being in the borderline ABI group compared to the normal group. No correlation was noted between CD8 T-cell activation and ABI.
Conclusion: Higher numbers of non-classical monocytes was associated with low ABI category, while CD4/CD8 ratio predicted ABI. This suggests a potential role of non-classical monocytes and CD4/CD8 ratio in worsening the progression of PVD in HIV patients.

708 MICROBIAL-RELATED METABOLITE TMAO AND CAROTID ARTERY ATHEROSCLEROSIS IN HIV INFECTION

Zhilei Shan[1], David B. Hanna[2], Clary Clish[3], Justin M. Scott[3], Robert Burk[2], Sabina Haberlen[4], Sanjiv J. Shah[5], Joseph B. Margolick[4], Wendy Post[4], Howard Hodis[6], Alan Landay[7], Kathryn Anastos[2], Robert C. Kaplan[2], Qibin Qi[2]
[1]Harvard University, Cambridge, MA, USA, [2]Albert Einstein College of Medicine, Bronx, NY, USA, [3]Broad Institute of MIT and Harvard, Cambridge, MA, USA, [4]The Johns Hopkins University, Baltimore, MD, USA, [5]Northwestern University, Chicago, IL, USA, [6]University of Southern California, Los Angeles, CA, USA, [7]Rush University Medical Center, Chicago, IL, USA

Background: Trimethylamine-N-oxide (TMAO) is a choline metabolite generated from TMA which is produced by gut microbiota. TMAO may promote atherosclerosis and cardiovascular disease (CVD). Yet, the relationships of plasma TMAO and other choline metabolites with progression of atherosclerosis in HIV-infected (HIV+) individuals remain unclear.
Methods: Plasma TMAO, choline, betaine, dimethylglycine, and sarcosine were measured among 520 HIV+ and 217 HIV-uninfected (HIV-)participants from WIHS (398 women) and MACS (339 men). Progression of carotid atherosclerosis was assessed by repeated B-mode carotid artery ultrasound imaging from2004–2013.Poisson regression models were used to examine associations of choline metaboliteswith incident carotid artery plaque (focal intima-media thickness >1.5 mm) over 7 years (all participants without carotid plaque at baseline).
Results: Median ages were similar between HIV+ and HIV- groups (42 years in women and 46 years in men); In the HIV+ group, 74% of women and 83% of men used potent ART, and 46% of women and 66% of men had undetectable HIV-1 viral load(≤80 copies/mL).Over 7 years, 112 individuals (90 HIV+ and 22 HIV-) developed incident carotid artery plaque (focal intima-media thickness >1.5 mm).There was no significant difference in plasma TMAO or other choline metabolite levels between HIV+ andHIV- groups. After multivariate adjustment, higher plasma TMAO was significantly associated with increased risk of incident carotid artery plaque in HIV+individuals(risk ratio=1.22 [95% CI, 1.03-1.46] per standard deviation increment; P=0.02), but not in HIV- individuals (Table). However, there was no significant effect modification by HIV infection. The results were consistent between HIV+ women and men, and across subgroups stratified by HIV related parameters (e.g., viral suppression status). No significant associations between other choline metabolites and incident carotid artery plaque were observed.Plasma TMAO was positively correlated with serumsCD14 and sCD163, biomarkers of monocyte and macrophageactivation and inflammation, but had little correlation withIL-6, CRP or CVD risk factors (blood pressures, lipids, body mass index).
Conclusion: Among HIV+ individuals, plasma TMAO, rather than other choline metabolites, is associated with greater progression of carotid artery atherosclerosis. The association between TMAO and monocyte and macrophage activation markers suggests foam cell formation as a potential link of TMAO with atherosclerosis.

Table Associations between plasma choline metabolites and risk of incident carotid artery plaque in HIV-infected and HIV-uninfected individuals

	HIV-infected		HIV-uninfected	
	RR (95% CI)	*P*	RR (95% CI)	*P*
N (cases/total)	90/520		22/217	
TMAO				
Model 1	1.21 (1.01, 1.45)	0.04	1.04 (0.64, 1.69)	0.87
Model 2	1.22 (1.03, 1.46)	0.02	0.93 (0.58, 1.49)	0.93
Choline				
Model 1	1.32 (0.98, 1.78)	0.08	0.91 (0.57, 1.45)	0.69
Model 2	1.31 (0.97, 1.76)	0.11	0.90 (0.58, 1.39)	0.74
Betaine				
Model 1	1.03 (0.82, 1.30)	0.80	1.31 (0.74, 2.34)	0.35
Model 2	1.02 (0.80, 1.30)	0.71	1.36 (0.82, 2.27)	0.29
Dimethylglycine				
Model 1	1.11 (0.93, 1.32)	0.28	1.31 (0.88, 1.95)	0.18
Model 2	1.13 (0.94, 1.36)	0.20	1.38 (0.89, 2.14)	0.17
Sarcosine				
Model 1	1.19 (0.92, 1.55)	0.20	1.24 (0.81, 1.90)	0.33
Model 2	1.15 (0.88, 1.51)	0.27	1.22 (0.82, 1.82)	0.39

Data are risk ratios (RRs) and 95% confidence intervals (CIs) on incident carotid artery plaque per standard deviation incrementof metabolites, adjusted for age, sex, race/ethnicity, education, study site, current smoking, and history of HCV (Model 1); and further adjusted for HIV serostatus, HIV treatment, baseline viral load, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, lipid lowering medication use, and body mass index (Model 2).

709 IL-32 ISOFORMS AS NOVEL BIOMARKERS FOR CVD IN HIV-INFECTED INDIVIDUALS

Mohamed El-Far[1], Sarah M. Zaidan[1], Carl Chartrand-Lefebvre[1], Petronela Ancuta[1], Nicolas Chomont[1], Etienne Larouche-Anctil[1], Jean-Pierre Routy[2], Benoit Trottier[3], Jean-Guy Baril[1], Paul MacPherson[4], Sylvie Trottier[5], Robert C. Kaplan[6], Alan Landay[7], Madeleine Durand[1], Cécile Tremblay[1]
[1]Centre de Research du Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada, [2]McGill University Health Centre Research Institute, Montreal, QC, Canada, [3]Clinique Médicale l'Actuel, Montreal, QC, Canada, [4]Ottawa General Research Institute, Ottawa, ON, Canada, [5]Centre Hospitalier de l'Université Laval, Quebec, QC, Canada, [6]Albert Einstein College of Medicine, Bronx, NY, USA, [7]Rush University Medical Center, Chicago, IL, USA

Background: Human il32 gene encodes for multiple IL-32 isoforms known to exhibit distinct immune-regulatory potential: proinflammatory (α and γ), anti-inflammatory (β), and regulatory (δ). The contribution of these isoforms to infectious and inflammatory diseases is poorly understood. We have recently reported that overexpression of total IL-32 in HIV infection correlates with persistent inflammation and disease progression. As chronic inflammation is associated with high prevalence of cardiovascular diseases (CVDs) in HIV-infected individuals, we investigated the potential use of specific IL-32 isoforms as biomarkers for CVD.
Methods: Blood was collected from 800 participants living with HIV and 200 control subjects from the Canadian HIV and Aging Cohort Study. Overt CVD and complete medical history is recorded prospectively. A subgroup of participants without overt CVD (n=200) undergoes cardiac computed tomography with injection of contrast media and measurement of total atherosclerotic coronary plaque volume. Baseline plasma levels of total IL-32 (pool of all IL-32 isoforms) were measured by ELISA in all participants. To distinguish between different IL-32 isoforms, we developed a quantitative isoform-specific SYBR Green RT-PCR to quantify single isoforms in peripheral blood mononuclear cells (PBMCs).
Results: Total plasmatic IL-32 protein was significantly higher in HIV+ ART-treated individuals compared to HIV- participants (median 384 pg/ml vs 287, respectively, p=0.0001). Interestingly, sex and age were associated with differential levels of IL-32; women under the age of 50 had significantly higher levels of IL-32 compared to their counterparts over 50 (p=0.016), whereas the opposite was observed in men. At the transcriptional level, all IL-32 isoforms were highly expressed in PBMCs from HIV+ individuals compared to non-infected controls (p=0.005). In individuals with cardiovascular imaging, the ratio between the delta and beta isoforms (δ/β ratio), positively and significantly correlated with the total atherosclerotic plaque volume (n=60 subjects with coronary atherosclerosis and n=26 subjects without, p=0.02, Spearman r=0.36). Of note, IL-32δ is known to bind to IL-32β and inhibits its anti-inflammatory functions.
Conclusion: Our data suggest a protective role for IL-32β in CVD but a deleterious role for IL-32δ. Furthermore, our study shows for the first time that the ratio IL-32δ/IL-32β may be used as a predictive biomarker for coronary plaque formation and CVD in HIV+ individuals on ART.

710 INTEGRATED VS REFERRED MANAGEMENT OF CVD RISK FACTORS FOR HIV+ PATIENTS IN SWAZILAND

Miriam Rabkin[1], Anton M. Palma[1], Margaret McNairy[2], Samkelo Simelane[3], Averie B. Gachuhi[1], Raymond A. Bitchong[4], Harriet Nuwagaba-Biribonwoha[3], Pido Bongomin[3], Velephi Okello[5], Wafaa M. El-Sadr[1]
[1]ICAP at Columbia University, New York, NY, USA, [2]Weill Cornell Medicine, New York, NY, USA, [3]ICAP at Columbia University–Swaziland, Mbabane, Swaziland, [4]Raleigh Fitkin Memorial Hospital, Manzini, Swaziland, [5]Ministry of Health, Mbabane, Swaziland

Background: Cardiovascular disease risk factors (CVDRF) are prevalent in HIV-positive (HIV+) persons, but the optimal model for managing patients with both HIV and CVDRF in low-resource settings is unknown. We compared integrated vs. referred CVDRF management for adults on antiretroviral therapy (ART) in Swaziland.
Methods: HIV+ persons ≥40 years on ART were screened for hypertension (HTN), diabetes (DM), hyperlipidemia (HL) and tobacco use. Those with HTN and/or >10% ten-year CVD risk (by WHO/ISH risk stratification) were randomized 1:1 to receive CVDRF care at HIV clinic (INT) or at outpatient clinic (REF). Primary outcomes were linkage to CVDRF care within 1 month and retention in both CVDRF and HIV care at 6 months. Other outcomes were: number of visits, adherence with assigned study arm, medication initiation, systolic blood pressure (SBP), HbA1c, and total cholesterol (TC).
Results: 240 participants (pts) were enrolled (Table). Median age was 51 years, 66% were female, 97% had HTN, 17% had DM and 14% had HL; baseline characteristics were similar in both arms. Linkage to CVDRF care within 1 month was achieved by 85% and 84% of pts in the INT and REF arms, respectively. Pts in both arms attended 2.8 CVDRF visits on average; those in the INT arm were more likely to adhere to their assigned study arm (86% *vs*. 68%, risk ratio [RR]: 1.28). At 6 months, retention in HIV care was high (98%) but retention in CVDRF care was low (21%) with no differences between arms. Despite limited retention in CVDRF care, 122/193 (63%) of pts with HTN initiated anti-hypertensive medicines; this was more likely in the INT arm (72% *vs*. 53%, RR: 1.35). Reductions in SBP and HbA1c occurred equally in both arms. Compared to baseline, mean ΔSBP was -15.0 mmHg (confidence interval [CI] -18.0, -11.8) in the INT arm and -15.9 mmHg (CI -19.0, -12.8) in the REF arm; mean ΔHbA1c was -0.68% (CI -1.26, -0.10) and -1.37% (CI -2.51, -0.24) in the INT and REF arms, respectively. Pts with HL in the REF arm also achieved significant reduction in TC (-0.91 mmol/L, CI -1.76, -0.65); there was no significant ΔTC in the INT arm.

Conclusion: Among HIV+ persons with both HIV and CVDRF, linkage and retention rates were similar for the integrated and referred CVDRF care models. Despite suboptimal retention in CVDRF management, pts in both arms showed improvement in CVDRF control. Integrated HIV and CVDRF services are more convenient for pts; additional provider training may further improve outcomes.

Table. Outcomes among n=240 ART patients randomized to integrated (HIV clinic) vs. referred (OPD) CVDRF management for 6 months

		Study arms		Integrated *vs.* referred arms	
Domain	Variable	Integrated (n=123)	Referred (n=117)	Parameter	Estimate (95% CI)[1]
Intervention fidelity	CVDRF management visits attended, mean (SD)	2.8 (2.0)	2.8 (2.1)	Difference	-0.0 (-0.5, 0.5)
	100% compliance with assigned study arm, n (%)	106 (86%)	79 (68%)	Risk ratio	**1.28 (1.10, 1.47)**
Clinical outcomes	Primary outcome (combined), n (%)	25 (20%)	23 (20%)	Risk ratio	1.03 (0.62, 1.72)
	Linked to CVDRF management within 1 month, n (%)	105 (85%)	98 (84%)	Risk ratio	1.02 (0.91, 1.14)
	Retained in CVDRF management at 6 months, n (%)	25 (20%)	25 (21%)	Risk ratio	0.95 (0.58, 1.56)
	Retained in HIV care at 6 months, n (%)	121 (98%)	115 (98%)	Risk ratio	1.00 (0.97, 1.03)
	Initiated anti-hypertensive medication use within 6 months, n (%)	74/103 (72%)	48/90 (53%)	Risk ratio	**1.35 (1.07, 1.69)**
	Δ in Systolic BP (mmHg), mean (95% CI)[3]	**-15.0 (-18.0, -11.8)**	**-15.9 (-19.0, -12.8)**	Difference	0.9 (-3.4, 5.3)
	Δ in HbA1c (%), mean (95% CI)[3]	**-0.68 (-1.26, -0.10)**	**-1.37 (-2.51, -0.24)**	Difference	0.69 (-0.44, 1.82)
	Δ in Total cholesterol (mmol/L), mean (95% CI)[3]	-0.39 (-0.90, 0.12)	**-0.91 (-1.76, -0.05)**	Difference	0.51 (-0.34, 1.37)

[1] Differences by study arm were estimated using linear regression, and risk ratios were estimated using poisson regression models with robust SEs.
[2] Initiation of anti-hypertensive medication use was calculated only among patients who had hypertension and were not on medication at baseline (n=193).
[3] Mean Δ in CVDRF biomarkers (from baseline to 6 months) were calculated only for patients with CVDRF at baseline. Systolic BP for hypertensives (n=224), HbA1c for diabetics (n=41) and total cholesterol for hyperlipidemics (n=33). 95% CIs excluding 0 indicate statistically significant change from baseline, using t-tests.

711 HIGH PREVALENCE OF HYPERTENSION IN HIV-INFECTED AND HIV-UNINFECTED ADULTS IN BOTSWANA

Mosepele Mosepele[1], Kara Bennett[2], Tendani Gaolathe[3], Joseph Makhema[4], Mompati O. Mmalane[3], Molly Pretorius Holme[5], Refeletswe Lebelonyane[6], Kathleen M. Powis[7], Jean Leidner[8], Joseph N. Jarvis[4], Neo Tapela[6], Tiny Masupe[1], Lucky Mokgatlhe[1], Kathleen Wirth[5], Shahin Lockman[5]
[1]University of Botswana, Gaborone, Botswana, [2]Bennett Statistical Consulting, Inc, New York, NY, USA, [3]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [4]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [5]Harvard University, Cambridge, MA, USA, [6]Botswana Ministry of Health, Gaborone, Botswana, [7]Massachusetts General Hospital, Boston, MA, USA, [8]Goodtables Data Consulting, Norman, OK, USA

Background: Hypertension is a major risk factor for cardiovascular disease, and treated HIV infection has been associated with hypertension in some but not all studies. The prevalence of hypertension among HIV-infected and –uninfected individuals at a population level in high HIV-prevalence settings in Africa is not well described.
Methods: We are following a random sample of ~20% of adults in 30 rural communities in Botswana as part of a community-randomized HIV prevention trial. During the final household survey, we conducted a one-time hypertension assessment, including blood pressure measurement, in 8 communities from February to August 2017. Hypertension was defined as any combination of the following: self-reported prior diagnosis of hypertension, use of any anti-hypertensive medications (prior or current), or either mean systolic blood pressure >140mmHg or mean diastolic blood pressure >90mmHg. We examined differences in hypertension diagnosis and use of anti-hypertensive medications by current HIV-status as crude and adjusted prevalence ratios.
Results: Among 2,441 participants assessed (709 [29%] HIV-infected, 1,652 [68%] female, median age 37.4 years [range 18-67]), 732 (30%, 95% CI 27-34%) were hypertensive. HIV-infected individuals were less likely to meet the definition of hypertension than HIV-uninfected (adjusted prevalence ratio [aPR]: 0.7; 95%CI: 0.66-0.8). Of the 732 participants with hypertension, 358 (49%) had a pre-existing diagnosis of hypertension; 90% of these participants were currently taking anti-hypertensive medication, and there was no difference in use of anti-hypertensive medications by HIV status, among those previously diagnosed with hypertension (aPR: 0.99; 95%CI: 0.96-1.03). Fifteen percent of those assessed were found to have elevated BP in the absence of a prior hypertension diagnosis. Undiagnosed hypertension was significantly less common among HIV-infected persons (aPR: 0.7; 95%CI: 0.6-0.9).
Conclusion: Nearly one in three adults in rural Botswana had hypertension (previously diagnosed or current). While the vast majority of previously-diagnosed individuals were receiving antihypertensive medications, one-half of those with hypertension had not previously been diagnosed. Consideration should be given to leveraging HIV healthcare infrastructure for diagnosing hypertension among HIV-uninfected individuals in this setting.

712 HYPERTENSION AND DIABETES CONTROL ALONG THE HIV CARE CASCADE IN SOUTH AFRICA

Jennifer Manne-Goehler[1], Mark J. Siedner[2], Livia Montana[3], Guy Harling[4], Pascal Geldsetzer[3], Julia K. Rohr[3], Xavier Gomez-Olive[5], Alisha Wade[5], Thomas Gaziano[6], Kathleen Kahn[5], Stephen Tollman[5], Till Bärnighausen[7]
[1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]Harvard University, Cambridge, MA, USA, [4]University College London, London, UK, [5]University of the Witwatersrand, Johannesburg, South Africa, [6]Brigham and Women's Hospital, Boston, MA, USA, [7]Heidelberg University, Heidelberg, Germany

Background: ART programs may promote greater utilization of healthcare services for co-morbid diabetes and hypertension, but the implications of this relationship for blood pressure (BP) and glycemic control remain unclear. In this study, we sought to assess whether the "ART advantage" extends to improved blood pressure and glucose measures among participants with these conditions.
Methods: This study was conducted using baseline data from Health and Aging in Africa: a Longitudinal Study of an INDEPTH Community in South Africa (HAALSI). HAALSI is a cohort of 5,059 adults aged 40+ in rural South Africa. Participants in HAALSI were randomly sampled and surveyed between November 2014 and November 2015. Height, weight, BP, blood glucose and HIV infection parameters, including viral load (VL) and ART drug levels, were collected on all consenting participants. Healthcare utilization was self-reported. We first fit log binomial regression models to examine the association between stage in the HIV care cascade ([1] HIV-, [2] HIV+/No ART, [3] ART/Detectable VL, and [4] ART/Suppressed VL) and diagnosis, treatment and control of hypertension or diabetes. We then used linear regression models to estimate differences in systolic BP and blood glucose among those with diagnosed hypertension or diabetes. In all regression models, we controlled for age, sex, BMI, education and wealth; the model for blood glucose was additionally adjusted for fasting status.
Results: In this cohort, ART/Suppressed VL was associated with greater awareness of hypertension diagnosis [adjusted risk ratio (aRR) 1.21, 95% CI: 1.10 – 1.32] and treatment of hypertension [aRR 1.25, 95% CI: 1.09 – 1.44] among those who met criteria for a diagnosis of hypertension, compared to being HIV-. There were no significant relationships between stage in the HIV care cascade and awareness of diagnosis or treatment of diabetes. Among those with diagnosed hypertension or diabetes, ART/Suppressed VL was associated with lower mean systolic BP [-5.94 mm Hg, 95% CI: -9.68 – -2.20] and lower mean glucose [-3.74 mmol/L, 95% CI: -5.95 – -0.58], compared to being HIV-.
Conclusion: Progression in the HIV care cascade was associated with improved clinical hypertension and diabetes control. HIV treatment programs may provide a platform for health systems strengthening for cardiometabolic disease. Future studies are needed to assess the causality and mechanisms that underlie ART program use and control of cardiometabolic conditions.

713 PREVALENCE OF NON-COMMUNICABLE DISEASES IN LONG-TERM AIDS SURVIVORS IN HAITI

Samuel Pierre[1], Vanessa Rivera[2], Grace Seo[2], Benedict Charles[1], Gaetane Julmiste[1], Alexandra Apollon[1], Emelyne Dumont[1], Molene Cadet[1], Myung Hee Lee[2], Katey Walsh[2], Adias Marcelin[1], Patrice Severe[1], Daniel Fitzgerald[2], Jean W. Pape[1], Margaret McNairy[2]
[1]GHESKIO, Port-au-Prince, Haiti, [2]Weill Cornell Medicine, New York, NY, USA

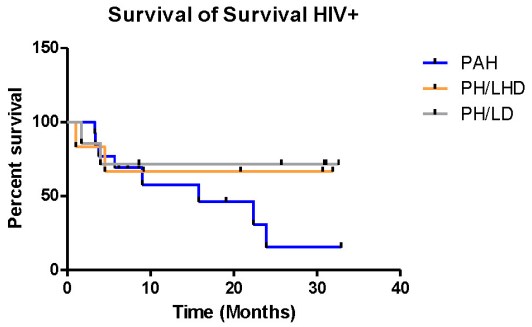
Background: Little is known about the prevalence of NCDs among long-term AIDS survivors in resource-poor settings, which is especially important as life expectancies for many patients who are on antiretroviral therapy (ART) are over 10 years. We describe the prevalence of CVD risk factors (CVDRF) and predictors among a cohort of 10-year AIDS survivors in care at the GHESKIO clinic in Port-au-Prince, Haiti.
Methods: As part of GHESKIO's expansion of HIV services to include CVDRF assessment among long-term AIDS survivors, GHESKIO staff were trained in screening for hypertension (HTN), diabetes (DM), obesity, smoking and cholesterol. Using routinely collected clinical data, we conducted a cross-sectional study among a cohort of patients who initiated ART from March 2003-April 2004 and remained in care at GHESKIO between October 2014-December 2016. CVDRF assessment for long-term AIDS survivors included: HTN defined as 2 measurements of systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg and/or pharmacy pick-up of HTN medication; DM as HbA1c >6.5% and/or pick up of DM medication; obesity as BMI >30 kg/m2; and hypercholesterolemia (HC) as total cholesterol >200mg/dL. Viral suppression was defined as HIV-1 RNA <1,000 copies/mL. Factors from ART initiation and CVDRF assessment were evaluated for association with HTN using logistic regression. Variables in this model were chosen by backward selection (exit criteria of p>0.05).
Results: 397 patients were alive and remained in care at time of CVDRF evaluation. At ART initiation, 59% were female, median age was 38 years (IQR 33-44), and median CD4 count was 117 cells/mm^3 (IQR 34-201). At time of CVDRF assessment, median FU time from ART initiation was 12.1 years (IQR 11.7-12.7), median CD4 count was 574 cells/mm^3 (IQR 378-771), and 77% (282/366) were virally suppressed. At CVDRF assessment, 58% (224/385) had HTN with 24% (91/385) stage II (SBP>160 or DBP>100), 8% (24/297) had DM, 43% (119/275)

had HC, 8% (20/248) were smokers, and 10% (25/245) were obese. 80% of patients with HTN were not on HTN medication. Age (decade increment, adjusted OR (aOR) =1.73, p<0.001) and weight at CVDRF assessment (10lb increment, aOR=1.09, p=0.019) were significantly associated with HTN.
Conclusion: Long-term AIDS survivors have a high prevalence of CVDRFs, primarily HTN and HC. Improved screening and management of NCDs are needed into routine HIV care in order to maximize health outcomes among aging HIV patients in resource-limited settings

714 PAN AFRICAN PULMONARY HYPERTENSION COHORT COMPARING RISK AND SURVIVAL OF HIV+/HIV-

Friedrich Thienemann, Vitaris Kodogo, Feriel Azibani, Karen Sliwa
University of Cape Town, Cape Town, South Africa

Background: The incidence of pulmonary hypertension (PH) in human immunodeficiency virus (HIV) infected persons is much higher than in the general population. Further, PH is more prevalent in Africa due to the high prevalence of risk factors in the region. Data characterizing risk and survival of HIV infected adults presenting with PH in Africa is lacking.
Methods: The Pan African Pulmonary Hypertension Cohort (PAPUCO), a prospective, multinational registry of 254 consecutive patients (97% of African descent) from 9 specialist centers in 4 African countries was implemented. The antecedents, characteristics and management of newly diagnosed PH plus 3 year survival were studied in patients that underwent HIV testing. We compared data of HIV+ to HIV- patients presenting with PH.
Results: There were 134 cases of PH (median age 39 years, range 19 to 91 years), 47 (35%) HIV+ (median age 36 years) and 87 (65%) HIV- (mean age 44 years, p=0.0004). 40% HIV+ were living in temporary shelters, compared to 18% HIV- (p=0.0215). Cardiovascular risk factors and co-morbidities were similar except for previous history of TB (HIV+ 62% vs. HIV- 18%, p<0.0001). Six-minute walk test (6MWT) distance less than 300 meters was a common finding in HIV- (36%), but rare in HIV+ (1%, p=0.0030). In contrast, HIV+ were tachycardic (p=0.0160) and tachypnoeic (p=0.0374) at presentation. PAH was more common in HIV+ (36% HIV+ vs. 15% HIV-, p=0.0084), whereas PH due to left heart disease (PH/LHD) was more common in HIV- (72% HIV- vs. 36% HIV+, p=0.0009). PH due to lung diseases and hypoxia (PH/LD) was more common in HIV+, but did not reach statistical significance (HIV+ 19% vs. HIV- 9%, p=0.1102) and was attributed to previous TB in HIV+ (100%) and HIV- (67%). There was a clear trend of poorer survival in patients with HIV PAH, compared to HIV+ diagnosed with PH/LHD or PH/LD (Figure 1, p=0.14).
Conclusion: HIV+ patients diagnosed with PH, where younger, poorer, previously co-infected with TB compared to HIV- patients. HIV+ patients appear to be better off at presentation (6MWT) despite raised vital parameters suggestive for early heart failure, but have excess mortality. HIV was a common cause PAH and TB a contributing factor to the overall burden of PH in HIV. Carefully clinical evaluation is warranted and early echocardiography assessment recommended, especially in those with previous TB. Access to specific PH treatment in Africa needs to be established.



715 INTEGRATING HYPERTENSION SCREENING AT VOLUNTARY HIV TESTING IN SOUTH AFRICA

Paul K. Drain[1], Ting Hong[1], Hilary Thulare[2], Mahomed-Yunus Moosa[3], Connie L. Celum[1]
[1]University of Washington, Seattle, WA, USA, [2]AIDS Healthcare Foundation, Durban, South Africa, [3]University of KwaZulu-Natal, Durban, South Africa

Background: Guidelines recommend integrating hypertension screening for untreated HIV-infected. We sought to understand the association between HIV infection and hypertension among South African adults accessing HIV testing services in a poor urban township. Since hypertension screening routinely occurs after HIV testing, the goal of this study was to determine if blood pressure measurements and hypertension screening are dynamic around the time of HIV testing in South Africa.
Methods: We measured a seated resting blood pressure in adults (≥18 years) prior to HIV testing, and again after receiving HIV test results, in an ambulatory HIV clinic in KwaZulu-Natal, South Africa. We assessed sociodemographics, smoking, body mass index, diabetes, substance abuse, and anxiety/depression. We used blood pressure categories defined by the Seventh Joint National Committee (JNC 7) classifications, which includes normal, pre-hypertension, stage 1 hypertension, and stage 2 hypertension.
Results: Among 5,428 adults, mean age was 31 years, 51% were male, and 35% tested HIV-positive. 47% (2,634) had a normal blood pressure, 40% (2,225) had prehypertension, and 10% (569) had stage 1 or 2 hypertension. HIV-infected adults had significantly lower blood pressure measurements and less hypertension, as compared to HIV-negative adults; while also having significantly elevated blood pressures after HIV testing. In separate multivariable models, HIV-infected adults had a 26% lower odds of hypertension, compared to HIV-uninfected adults (aOR=0.74, 95% CI: 0.60-0.90), and HIV-infected adults with a CD4 ≤200 cells/mm^3 had a 42% lower odds of hypertension (aOR=0.58, 95% CI: 0.38-0.89). The mean arterial blood pressure was 6.8 mmHg higher among HIV-infected adults after HIV testing (p <0.001).
Conclusion: Untreated HIV-infected adults, and particularly immunocompromised adults, had lower baseline rates of hypertension compared to HIV-negative adults, and that blood pressure transiently increased after receiving a positive HIV test result. Since hypertension screening may be dynamic around the time of HIV testing, hypertension screening should ideally occur before HIV testing, be repeated again after ART initiation and viral load suppression, and be continued at regular intervals. As ART delivery increase the life expectancy of those with HIV, providing appropriate diagnosis and management of hypertension will become increasingly important.

Table. Mean blood pressure and prevalence of hypertension by HIV status.

	Total (n=5,428)	HIV- (n=3,523)	HIV+ (n=1,905)	p-value	HIV+ CD4 >200 (n=1,102)	HIV+ CD4 ≤200 (n=500)	p-value
	Mean ±SD or N (%)	Mean ±SD or N (%)	Mean ±SD or N (%)			Mean ±SD or N (%)	
Blood Pressure (mmHg)							
Systolic blood pressure	118 ±15	118 ±15	116 ±16	**<0.0001**	118 ± 15	115 ± 17	**0.003**
Diastolic blood pressure	72 ±16	73 ±15	71 ±18	**<0.0001**	71 ± 18	70 ± 18	0.463
Mean arterial blood pressure	87 ±14	88 ±13	86 ±14	**<0.0001**	87 ± 15	85 ± 15	0.087
Hypertension							
Normal blood pressure	2,634 (48.5%)	1,650 (45.3%)	984 (49.7%)	**0.013**	185 (44.5%)	244 (49.0%)	0.113
Prehypertension	2,225 (40.0%)	1,489 (40.9%)	736 (37.2%)		164 (39.4%)	198 (39.8%)	
Stage 1 Hypertension	419 (7.7%)	289 (7.9%)	130 (6.6%)		34 (8.2%)	23 (4.6%)	
Stage 2 Hypertension	150 (2.8%)	95 (2.6%)	55 (2.8%)		12 (2.9%)	14 (2.8%)	

SD=standard deviation

716 SIGNS OF CARDIOVASCULAR DISEASE IN A RURAL AFRICAN POPULATION; DOES HIV PLAY A ROLE?

Alinda Vos[1], Kerstin Klipstein-Grobusch[1], Hugo Tempelman[2], Diederick Grobbee[1], Roel Coutinho[1], Walter Devillé[2], Roos Barth[1]
[1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Ndlovu Care Group, Groblersdal, South Africa

Background: HIV is associated with an increased risk of cardiovascular disease (CVD) in high income countries, but not necessarily in low- and middle income countries. As 70% of people living with HIV reside in sub-Saharan Africa, a good insight into the effects of HIV on the cardiovascular system is mandatory to pursue healthy aging. Increased arterial stiffness, measured with carotid-femoral pulse wave velocity (cfPWV), is regarded as a marker of organ damage and is a strong predictor for CVD. This study investigates the prevalence of abnormal arterial stiffness and whether HIV is associated with arterial stiffness in a rural African setting.
Methods: Data were collected as part of the Ndlovu Cohort study. This is a prospective, ongoing study in a rural area in South Africa including HIV-positive and HIV-negative adults without known CVD. Data collection includes assessment of hypertension, body mass index (BMI), dyslipidemia, diabetes mellitus (DM), and cfPWV measurement (SphigmoCor). Abnormal arterial stiffness was defined as a cfPWV of more than 8 m/s as previously suggested to

be appropriate for a young African population. Logistic regression analysis was used to investigate if HIV was associated with abnormal arterial stiffness.
Results: cfPWV was available in 853 participants, of whom 365 (42.8%) were HIV-positive. HIV-positive participants were older, mainly women and had fewer cardiovascular risk factors than HIV-negative participants. Median CD4 count was 491 (IQR 335-680), and 77.7% were on antiretroviral treatment. The prevalence of abnormal arterial stiffness was 32.3% in the HIV-positive group, in contrast to 24.6% in the HIV-negative group, and this was significantly different after adjustment for gender and age (p = 0.02). HIV was independently associated with abnormal stiffness following regression analysis adjusted for age, gender, hypertension, BMI, DM and dyslipidemia (OR 1.64, 95% CI 1.13-2.39).
Conclusion: Abnormal arterial stiffness is more common in HIV-positive individuals than in HIV-negative individuals despite a lower burden of cardiovascular risk factors in the HIV-positive group. HIV is independently related to abnormal arterial stiffness. More research is needed to identify HIV-related factors that contribute to arterial stiffness in order to develop targeted prevention and treatment strategies. Awaiting these results we emphasize the need for screening and treatment of well-known cardiovascular risk factors.

Table 1: **Baseline characteristics**

	All	HIV-	HIV+
	N=853	*N=488*	*N=365*
Age	38.6 (12.6)	36.3 (13.5)	41.8 (10.5)*
Men	412 (48.3%)	298 (61.1%)	114 (31.2%)*
Smoking	247 (28.6%)	174 (35.7%)	73 (20.0%)[1]
Hypertension (*n = 850*)	277 (32.6%)	173 (35.5%)	104 (28.5%)[1]*
Diabetes Mellitus (*n=850*)	40 (4.7%)	26 (5.3%)	14 (3.9%)[1]*
Dyslipidemia (*n=842*)	324 (38.5%)	186 (38.9%)	138 (37.9%)[1]*
BMI >25 kg/m^2 (*n=850*)	291 (34.2%)	165 (33.9%)	126 (34.7%)[1]*[#]
cfPWV >8 m/s	238 (27.9%)	120 (24.6%)	118 (32.3%)[1]*

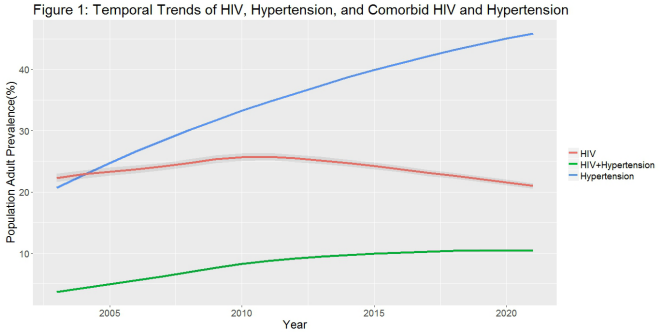
BMI, body mass index. Data in n (%) or mean (SD). [1]Comparisons were adjusted for gender and age. *p<0.05. [#] HIV-infected participants have a lower BMI after adjusting for gender and age.

717 HYPERTENSION AND HIV AS COMORBIDITES IN SOUTH AFRICA: MODELING THE DUAL BURDEN

Brianna Osetinsky[1], Omar Galarraga[1], Mark Lurie[1], Stephen McGarvey[1], Till Bärnighausen[2], Sake de Vlas[3], Jan A. Hontelez[3]
[1]Brown University, Providence, RI, USA, [2]Heidelberg University, Heidelberg, Germany, [3]Erasmus University Medical Center, Rotterdam, Netherlands

Background: Non-communicable diseases (NCDs) are a significant and growing source of morbidity and mortality among HIV positive people in sub-Saharan Africa. Calls for greater research in healthcare priorities and direct investments in the treatment of the co-epidemics of NCDs and HIV are stymied by the lack of viable population level estimates of hypertension and the co-burden of disease. In this study we demonstrated that we can effectively model the prevalence and incidence of hypertension, as well as HIV and hypertension comorbidity among the adult population of KwaZulu-Natal (KZN), South Africa.
Methods: We incorporated microsimulation of hypertension to the established agent-based Sexually Transmitted Diseases Simulation Model (STDSIM). Hypertension was modeled as a stochastic distribution calibrated to fit age- and sex-specific prevalence using Africa Health Research Institute's HIV and hypertension surveillance data of adults over 18 years in KZN from 2003 and 2010, with 6,751 and 15,343 respondents respectively. It was parameterized as the initial development of hypertension along the life course of an individual as drawn from a convex combination of densities for the baseline, calibrated to the 2003 prevalence, and a growth factor calibrated from the 2010 data. Hypertension was added to the STDSIM model calibrated for HIV prevalence and incidence in KZN, and we conducted a sensitivity analysis of the fit for HIV and hypertension as comorbidities.
Results: The model recreates the adult population increase of hypertension from 21% in 2003 to 33% in 2010. We predict a 2017 prevalence of 42%, with 595 new cases per 10,000 people. The prevalence of HIV and hypertension as comorbidities from the surveillance estimates is replicated with an increase from 3.5% in 2003 to 8% in 2010. The predicted 2017 prevalence of both as comorbidities is 10%, with 150 new cases per 10,000 people. There are substantial temporal increases in these conditions from the 2003 baseline to 2020 (Figure1). Among people living with HIV, the predicted 2017 prevalence of hypertension is 46%. In the total 2017 adult population, a projected 52% has either hypertension, HIV, or both.
Conclusion: The model projects a continued increase of a substantial dual burden of HIV and hypertension both at the population and individual level. In the absence of more recent data on the co-burden of disease, these estimates of prevalent and incident cases approximate the dynamics of both conditions and may be used to address the gap in data.

Figure 1: Temporal Trends of HIV, Hypertension, and Comorbid HIV and Hypertension



718 CORONARY ARTERY CALCIFICATION IN VIROLOGICALLY SUPPRESSED AGING HIV-INFECTED THAIS

Pairoj Chattranukulchai[1], Monravee Tumkosit[1], Sarawut Siwamogsatham[1], Tanakorn Apornpong[2], Sivaporn Gatechompol[2], Akarin Hiransuthikul[2], Win M. Han[2], Stephen J. Kerr[2], Opass Putcharoen[1], Smonporn Boonyaratavej[1], Kiat Ruxrungtham[1], Praphan Phanuphak[2], **Anchalee Avihingsanon**[2]
[1]Chulalongkorn University, Bangkok, Thailand, [2]HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand

Background: Coronary artery calcification (CAC) is a known surrogate marker for coronary atherosclerosis, and is significantly related to future major cardiovascular events (MACE) and mortality. HIV-infected patients are at risk of cardiovascular disease (CVDs) but there is scarce data in Asian adults. We determined the prevalence and factors associated with subclinical atherosclerosis by CAC among HIV-infected adults from Thailand.
Methods: HIV infected subjects aged >50 years who received HIV care in a prospective long term cohort at HIV-NAT, Thailand were enrolled. Subjects with a history of MACE were excluded. CAC was measured by cardiac multidetector row computed tomography (MDCT). All MDCT scans were read by an experienced radiologist blinded from patient care. Subclinical atherosclerosis was defined as CAC >0. Liver fibrosis was assessed by fibroscan.
Results: 316 subjects (60.8% male, median age 54 years, 13.3% /21.5% current/former smokers, 97% virally suppressed) were enrolled. The median duration of ART was 16 years and 38% were on boosted PIs. Median overall CAC was 35.4 (IQR 6.9-130.1) and 46.8% had CAC>0. The CAC score category frequencies were 1-10 (minimal CAD:13.6%), 11-99(mild: 19.3%), 100-399(moderate: 8.5%) and >400 (severe: 5.4%). Compared to CAC=0, CAC score >0 group had significantly higher traditional risk factors (older, male sex, higher ASCVD risk score (9.0% vs 4.1%), diabetes (25.7% vs 8.6%), hypertension (52.7 % vs 28.6%), BMI>25 kg/m2, waist/hip ratio, fasting glucose, fasting glucose >100 mg/dl, low HDL, blood pressure > 130/85 mmHg), NNRTI use and higher liver fibrosis scores. In a multivariate regression model, older age (aOR 1.07, 95%CI 1.01-1.14, p=0.02), male sex (aOR 4.03, 95%CI 1.88-8.64, p<0.001), hypertension (aOR 1.79, 95%CI 1.01-3.18, p=0.046), and fibroscan >7.2 KPa (aOR 2.15,95% CI 1.14-4.05), p=0.02) were independently associated with the CAC score >0 after adjusting for smoking history, diabetes, current ART regimen, statin use and BMI. Other HIV related factors such as CD4 count and ART duration, were not associated with CAC score>0.
Conclusion: Despite low prevalence of current/former smokers, subclinical atherosclerosis among well suppressed HIV-infected Aging Thais was relatively high (46.8%). In addition to traditional CVD risk factors, liver fibrosis was significantly associated with subclinical atherosclerosis. Strategies to prevent future MACE such as statins, are warranted.

719 ARV-NAIVE HIV-INFECTED ADULTS HAD LOWER BONE FORMATION MARKERS THAN HIV-UNINFECTED

Lalita Wattanachanya[1], Jureeporn Jantarapakde[2], **Anchalee Avihingsanon**[3], Reshmie Ramautarsing[2], Stephen J. Kerr[3], Deondara Trachunthong[2], Thanaporn Mansawat[3], Kanitta Pussadee[3], Nipat Teeratakulpisarn[2], Tanate Jadwattanakul[4], Tawatchai Chaiwatanarat[1], Nittaya Phanuphak[2], Sarat Sunthornyothin[1], Praphan Phanuphak[2]

[1]Chulalongkorn University, Bangkok, Thailand, [2]Thai Red Cross AIDS Research Center, Bangkok, Thailand, [3]HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [4]Queen Savang Vadhana Memorial Hospital, Chonburi, Thailand

Background: There are limited studies regarding bone health among HIV-infected patients from Asia, especially in females. We determined bone mineral density (BMD), bone markers and vitamin D status in HIV-infected Thais who had not started ART.

Methods: The TNT-HIV 003 cohort was established in 2012 to evaluate morbidity and mortality among HIV-infected patients from 3 sites in Thailand. Healthy subjects (free of diabetes, hypertension, fracture, active OI) aged ≥30 years, with and without HIV infection were enrolled. BMD at the lumbar spine, femoral neck, and total hip were measured using Hologic DXA. BMD, serum 25-hydroxyvitamin D levels, and bone turnover markers (serum procollagen type 1 N-terminal propeptide(P1NP), osteocalcin(OC) and C-terminal cross-linking telopeptide of type I collagen(CTX) at the patients' baseline visit were analysed.

Results: BMD from 302 HIV positive (56.2% male) and 269 HIV negative (47.2% male) were analyzed. HIV-positive patients were 1.5 years younger (men:39.7±6 vs. 41.3±6yr; women:39.5±4 vs.41.2±5 yr) and had lower BMI (men:22.5±3vs 24.1±3yr; woman:22.7±4 vs 23.3±4yr). Compared to HIV-negative control, HIV-positive had higher mean serum 25-hydroxyvitamin D level(32.2±10 vs. 26.1±10 ng/ml; women:29.9±9 ±6 vs. 20.7±6ng/ml) but this was not correlated with BMD. There were no differences in the lumbar spine, total femur or femoral neck BMD between subjects with and without HIV. Only few participants were classified as having low BMD. In 296 patients who participated in a bone marker turnover sub-study, the markers for bone formation, serum P1NP and osteocalcin were significantly lower in HIV-infected patients, particularly those with CD4 count<350cells/mm^3.

Conclusion: Middle-aged Thai patients with HIV infection, who were not yet on ART, did not have lower BMD or lower vitamin D levels compared to HIV-uninfected control. However, they had lower bone formation markers, particularly those with low CD4 count < 350 cells/mm^3. This finding supports the early initiation of ART.

Table. Laboratory findings of the BMD substudy

Laboratory results	Male				Female			
	HIV- (n=60)	HIV + CD4≥350 (n=38)	HIV + CD4<350(n=52)	P-value	HIV-(n=67)	HIV + CD4≥350 (n=29)	HIV + CD4<350(n=50)	P-value
Calcium (mg/dL)	9.76(0.3)	9.57(0.42)	9.48(0.48)	0.02	9.4(0.27)	9.4(0.39)	9.35(0.41)	0.60
iPTH (pg/mL)	50.4(21.3)	31.1(12.0)	36.4(14.4)	<0.001	41.9(17.5)	38.9(22.2)	33.9(16.0)	0.17
25(OH)D (ng/mL)	26.1(9.8)	32.1(12.8)	32.2(8.3)	0.003	20.7(6.2)	27.2(9.9)	31.9 (8.2)	<0.001
< 20, n (%)	14(23.3)	4(10.5)	2(3.85)	<0.001	34(50.8)	7(24.1)	2(4.0)	<0.001
20-30, n (%)	32(53.3)	13(34.2)	18(34.62)		26(38.8)	12(41.4)	18(36.0)	
>30, n (%)	14(23.3)	19(50)	27(51.92)		6(9.0)	10(34.5)	24(48.0)	
P1NP (ng/mL)	51.3(14.5)	48.2(16.2)	43.1(16.9)	<0.001	43.1(14.7)	36.0(11.0)	29.1(11.4)	<0.001
OC (pg/mL)	18.8(5.5)	15.5(5.7)	14.7(5.6)	<0.001	15.5(5.1)	12.4(3.6)	10.3(4.2)	<0.001
CTX (ng/mL)	0.38(0.14)	0.37(0.2)	0.31(0.13)	0.049	0.23(0.1)	0.24(0.11)	0.19(0.1)	0.09
Free androgen index (%)	61(18)	57(21)	57(18)	0.52	-	-	-	-

Data are reported as mean (SD) or number (percentage). Difference between the HIV-uninfected and the HIV-infected population was compared using ANOVA, Mann-Whitney two-sample statistic, as appropriate, iPTH, intact parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; P1NP, procollagen type 1 N-terminal propeptide ; OC, Osteocalcin; CTX, C-terminal cross-linking telopeptide of type I collagen

720 TDF PROPHYLAXIS FOR PMTCT OF HBV: EFFECT ON MATERNAL AND INFANT BONE MINERAL DENSITY

Nicolas Salvadori[1], Bo Fan[2], Waralee Teeyasoontranon[1], Nicole Ngo-Giang-Huong[3], Siriluk Phanomcheong[4], Anita Luvira[4], Achara Puangsombat[4], Arunrat Suwannarat[4], Ussanee Srirompotong[4], Chaiwat Putiyanun[4], Athena Kourtis[5], Marc Bulterys[6], George K. Siberry[7], **Gonzague Jourdain**[3]

[1]Chiang Mai University, Chiang Mai, Thailand, [2]University of California San Francisco, San Francisco, CA, USA, [3]IRD, Chiang Mai, Thailand, [4]Ministry of Pubic Health, Nonthaburi, Thailand, [5]CDC, Atlanta, GA, USA, [6]WHO, Geneva, Switzerland, [7]NIH, Bethesda, MD, USA

Background: Tenofovir disoproxil fumarate (TDF) is increasingly used for hepatitis B virus (HBV) mono-infected pregnant women with high HBV DNA levels to prevent mother-to-child transmission (PMTCT) of HBV. In HIV infected women, TDF may adversely affect maternal and infant bone mineral density (BMD). In a sub-study of a randomized controlled trial of TDF for PMTCT of HBV, we assessed the effect of TDF on maternal and infant BMD one year after delivery/birth.

Methods: HBV chronically infected mothers were randomized to receive TDF or a matching placebo from 28 weeks gestational age (GA) to 2 months postpartum, in the iTAP study (NCT01745822) in Thailand. Breastfeeding was encouraged. Maternal hip and lumbar spine BMD and infant lumbar spine BMD were measured at 12 months after delivery/birth using dual-energy X-ray absorptiometry (DXA) at three participating sites (phantoms were circulated for cross calibration). All investigators and operators were blinded to the treatment arm. The analysis was based on DXA scans performed at sites and centrally reviewed by two experts (BF, WT) for accuracy. A sample of at least 45 mother-infant pairs per arm provided over 80% power to detect a 13.5% mean reduction in infant lumbar spine BMD in the TDF arm compared to the placebo arm (two-sided Student's t-test, significance level 0.05).

Results: A total of 135 mother-infant pairs (69 TDF, 66 placebo) plus 5 singleton mothers (2 TDF, 3 placebo) who did not come with their infants and 2 singleton infants (1 mother unavailable, on TDF; 1 mother pregnant, not eligible, on placebo) were included. Median (interquartile range) maternal body mass index before pregnancy was 21.1 kg/m2 (19.1 to 23.9), weight at enrollment 62 kg (56 to 71), age at enrollment 26.7 years (23.3 to 29.2) and GA at delivery 39.1 weeks (38.3 to 40.1). Of the 140 mothers, 135 breastfed for a median 6.1 months (3.8 to 12.0) and 5 did not breastfeed. BMD was assessed at a median 12.2 months (11.9 to 12.5) after delivery/birth. Infant median weight was 8.9 kg (8.2 to 9.8) and length 74 cm (72 to 76). Maternal and infant characteristics were balanced between arms. Results of maternal hip and lumbar spine BMD and infant lumbar spine BMD measurements are provided in the table.

Conclusion: One year after delivery/birth, there were no significant differences in maternal hip or lumbar spine BMD or infant lumbar spine BMD between arms. In the hypothesis that BMD was affected by TDF exposure, this did not persist 10 months after treatment discontinuation.

Table: Maternal hip and lumbar spine, and infant lumbar spine BMD valid measurements by treatment arm (invalid measurements were caused by movement or improper positioning during DXA assessment)

	TDF (N=72)		Placebo (N=70)		Mean difference	
BMD (g/cm^2)	n	Mean (SD)	n	Mean (SD)	percentage (95% CI)	P-value
Maternal hip	64	0.893 (0.096)	65	0.885 (0.109)	+0.9% (-3.2% to +5.0%)	0.67
Maternal lumbar spine	71	0.964 (0.100)	67	0.944 (0.136)	+2.0% (-2.2% to +6.3%)	0.34
Infant lumbar spine	62	0.324 (0.036)	52	0.330 (0.036)	-1.8% (-5.8% to +2.3%)	0.39

721 OPTION B-PLUS ART, PREGNANCY, LACTATION AND BONE HEALTH IN UGANDAN WOMEN

Florence Nabwire[1], Ann Prentice[1], Matthew M. Hamill[1], Mary G. Fowler[2], Josaphat Byagumisha[3], Adeodata Kekitiinwa[4], Gail R. Goldberg[1]

[1]MRC Elsie Widdowson Laboratory, Cambridge, UK, [2]Johns Hopkins University, Baltimore, MD, USA, [3]Makerere University, Kampala, Uganda, [4]Baylor College of Medicine Children's Foundation, Kampala, Uganda

Background: Pregnancy and lactation are associated with physiological changes in bone mineral (BM), but most evidence shows that this is recovered after weaning. ART may disrupt the normal process of BM mobilisation in the mother, leading to bone loss that is not recovered. However, data are limited on whether HIV-infected (HIV+) women on option B+ ART experience greater reductions in BM during lactation compared to HIV-uninfected (HIV-). The object

of this research was to investigate the effect of ART on maternal BM in the context of pregnancy and lactation.

Methods: Two groups of pregnant women, 95 HIV+ (on TDF-3TC-EFV, previously ART naïve) and 96 HIV- were recruited in Kampala, Uganda and followed prospectively. Data were collected at 36 wks gestation (PG36), 2 (PP2) and 14 wks postpartum (PP14). Whole body (WB), lumbar spine (LS) and total hip (TH) BM density (BMD) was measured by DXA. Bone turnover markers (BTM), PTH and 25(OH)D were measured. The primary outcome was the difference between the groups in % change (± SE) in maternal LS BMD between PP2 and PP14.

Results: Median age was 24.5 (IQR 21.1, 26.9) yrs. Body weight was 4-5% lower in HIV+ women. By PP14, mean duration on ART was 29.3±5.1 wks, adherence was >95% and median CD4 count was 403 (IQR 290-528). All women were breastfeeding (BF) at PP2 and PP14. More HIV+ women reported exclusive BF (PP2 82.9% v 58.7%; PP14 86.7% v 66.2%, both p<0.05). BMD decreased between PP2 and PP14 at all skeletal sites in HIV+ (WB -1.2±0.2%; LS 1.8±0.4%; TH 4.0±0.4%; all p<0.05) and HIV- women (WB -0.6±0.2%; LS 2.5±0.4%; TH 2.7±0.4%; all p<0.05). Reductions in LS BMD were not different between groups (p=0.3). However, HIV+ women had a greater reduction in TH BM which remained after size-adjustment (TH -3.7±0.3% v -2.7±0.3%, p=0.04). BTM increased in both groups between PG36 and PP14. HIV+ women had greater increases (CTX 74.6±5.9% v 56.2±5.9%; P1NP 100.3±5.0% v 72.6±5.0%; BAP 67.2±3.6% v 57.1±3.6%; all p<0.05). Changes in PTH and 25(OH)D were not different between groups (PTH +60.0±6.4% v +57.6±6.4%; 25(OH)D -13.9±4.1% v -11.1±3.1%; both p<0.05). HIV+ women had 33-35% higher PTH at PG36 and PP14 (p≤0.0001).

Conclusion: These data show a significantly greater reduction in TH BMD in Ugandan HIV+ mothers on option-B+ ART compared to HIV- mothers in the first 3 mo of lactation, consistent with changes in BTM. It is important to determine if these are temporary or have long-term consequences for bone health.

722 RATES OF BONE LOSS SLOW AFTER THE FIRST YEAR OF ART: START BMD SUBSTUDY FINAL RESULTS

Andrew Carr[1], Birgit Grund[2], Ann V. Schwartz[3], Anchalee Avihingsanon[4], Sharlaa Badal-Faesen[5], Jose I. Bernadino[6], Patrick W. Mallon[7], Vicente Estrada[8], Alberto M. La Rosa[9], Sanjay Pujari[10], David White[11], Nicole Wyman Engen[2], Kristine E. Ensrud[2], Jennifer Hoy[12]

[1]St. Vincent's Hosp, Sydney, NSW, Australia, [2]University of Minnesota, Minneapolis, MN, USA, [3]University of California San Francisco, San Francisco, CA, USA, [4]Chulalongkorn University, Bangkok, Thailand, [5]University of the Witwatersrand, Johannesburg, South Africa, [6]Hospital La Paz Institute for Health Research, Madrid, Spain, [7]University College Dublin, Dublin, Ireland, [8]University Hospital Clinic of San Carlos, Madrid, Spain, [9]Asociacion Civil Impacta Salud y Educacion, Lima, Peru, [10]Institute of Infectious Diseases, Pune, India, [11]Heart of England NHS Foundation Trust, Birmingham, UK, [12]Monash University, Melbourne, VIC, Australia

Background: Initial antiretroviral therapy (ART) in adults with normal CD4 counts accelerates loss of bone mineral density (BMD) over the first 1-2 years. Whether this loss continues with longer therapy is unclear.

Methods: We compared the effects of immediate and deferred ART on BMD change in adults in the BMD substudy of START, which randomized ART-naïve adults with CD4>500 cells/μL to immediate or deferred (CD4<350) ART. Deferred group offered ART after May 2015. BMD was measured annually for up to 5 years at the total hip and lumbar spine (L1-L4) by dual-energy X-ray absorptiometry. Mean percent changes in BMD from baseline and annual percent changes were estimated and compared between treatment groups using longitudinal mixed models, by intention to treat (ITT) and by ART use (Immediate vs. no ART [Deferred group censored at ART start]). We also assessed predictors of BMD change within group.

Results: 411 participants were included (Immediate=201; Deferred=210). Median baseline age was 32 years, with 80% non-white, 24% women and median CD4 count 643 cells/μL. Groups were well balanced at baseline. The most common initial drugs in the Immediate group were tenofovir disoproxil fumarate (TDF; 83%) and efavirenz (79%); a protease inhibitor was used by 13%. Mean follow-up was 4.5 years. In the Immediate group, 96%-97% of participants used ART throughout Years 1-5. In the Deferred group, 16%, 28%, 58%, and 85% used ART at the Year 1, 2, 3, and 4 visits, respectively. BMD changes by ITT and by ART use are shown in the Table. Averaged through follow-up, BMD decreased more in the Immediate versus the Deferred group (Table, first 2 rows), but groups converged by Year 3 at the spine (diff=-0.5, p=0.26) and Year 4 at the hip (diff=-0.2, p=0.68) as most Deferred group participants started ART. In the Immediate group, BMD declined by 2.1% at the spine and 2.0% at the hip during Year 1; afterwards, BMD was stable at the spine and continued to decline at the hip by 0.5% per year. The annual rates of BMD change after Year 1 were similar in the Immediate group and those who remained ART-naïve in the Deferred group. No clinical, HIV-related or ART characteristic consistently predicted greater BMD loss with immediate ART (including use of TDF), or while ART-naïve in the Deferred group.

Conclusion: BMD declined at both hip and spine after ART initiation. After Year 1, BMD change was comparable between the Immediate group and those who remained ART-naive, suggesting that bone loss slows after the first year of ART.

Table. Mean changes in BMD from baseline

Change in BMD	Comparison	Region	Immediate ART group		Deferred ART group		Diff. (95% CI)	P
			n*	Change (%)	n*	Change (%)		
Overall	ITT	Spine	201	-1.8	210	-0.9	-1.0 (-1.6, -0.3)	0.004
		Hip	200	-2.8	210	-1.7	-1.1 (-1.6, -0.3)	<0.001
	ART vs no ART	Spine	196	-1.8	176	0.2	-2.0 (-2.7, -1.3)	<0.001
		Hip	195	-2.9	176	-0.5	-2.1 (-2.9, -1.4)	<0.001
Baseline to Year 1	ITT	Spine	194	-2.1	197	-0.3	-1.7 (-2.3, -1.2)	<0.001
		Hip	193	-2.0	197	-0.5	-1.6 (-2.2, -0.9)	<0.001
	ART vs no ART	Spine	189	-2.1	171	0.0	-2.0 (-2.6, -1.4)	<0.001
		Hip	188	-2.2	171	-0.2	-2.0 (-2.6, -1.3)	<0.001
Annual rate of change after Year 1	ITT	Spine	197	0.1	204	-0.5	0.5 (0.3, 0.8)	<0.001
		Hip	196	-0.5	204	-0.9	0.4 (0.0, 0.7)	0.04
	ART vs no ART	Spine	192	0.1	140	0.2	0.0 (-0.4, 0.4)	0.88
		Hip	191	-0.4	139	-0.3	-0.2 (-0.7, 0.3)	0.37

* Number of participants with available data; in the ART vs no ART comparison, number of participants who initiated ART in the immediate group and did not yet initiate ART in the deferred group.

723 GREATER BONE TURNOVER MARKER DECLINE WITH ZOLEDRONIC ACID THAN WITH TDF-SWITCHING

Andrew Carr[1], Robyn Richardson[1], Stephen J. Kerr[2], Peter R. Ebeling[3], Nicholas Pocock[1], Jhon Rojas[4], Esteban Martinez[4], Jennifer Hoy[3]

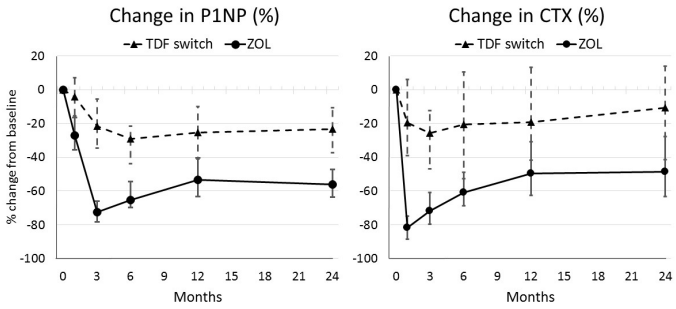
[1]St. Vincent's Hosp, Sydney, NSW, Australia, [2]HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [3]Monash University, Melbourne, VIC, Australia, [4]Hospital Clinic of Barcelona, Barcelona, Spain

Background: Zoledronic acid (ZOL) 5mg annually was more effective than switching tenofovir disoproxil fumarate (TDF) at increasing bone mineral density (BMD) over 24 months in HIV-infected, osteopenic adults. The relative effects of ZOL vs. TDF-switching on plasma bone turnover markers (BTMs) are unknown. Further, it is not clear if TDF causes bone loss by reducing bone formation or increasing bone resorption.

Methods: We measured plasma levels of C-terminal telopeptide of type 1 collagen (CTX; a marker of bone resorption) and procollagen type 1 N propeptide (P1NP; a marker of bone formation) in participants in the randomised trial comparing annual ZOL 5mg with TDF switching over 24 months. Percent changes in CTX and P1NP were compared in the per-protocol population at Months 1, 3, 6, 12 and 24 with a Wilcoxon test and over all follow-up with Generalised Estimating Equations (GEE). We also determined whether BTM changes at Month 3 predicted hip and spine BMD changes (Pearson's correlation coefficient).

Results: Plasma samples were available for 42 of 44 participants (95%) in the TDF switch group and 41 of 42 participants (98%) in the ZOL group. Median percent decreases in both BTMs were significantly greater with ZOL than with TDF-switching through Month 24 by GEE and at each time point (all p<0.001; see Figure 1). For example, at Month 12 the median (IQR) changes for ZOL vs. TDF-switch groups for P1NP were -53.5% (IQR -40.5%, -63.3%) and -25.4% (-9.8%, -41.0%), respectively, and for CTX were -49.7% (-30.7%, -62.7%) and -19.1% (+13.4%, -41.6%), respectively. Combining both groups, decreases in P1NP at M3 were more strongly correlated with decreases in BMD at M24 at the spine (r2=-0.44; p<0.001) and hip (r2=-0.45; p<0.001) than were the respective decreases in CTX (spine r2=-0.36; p=0.001, and hip r2=-0.23; p=0.051). In patients who switched TDF, the decrease at Month 1 in CTX was -19.7% (IQR -39.2%, +6.1%) whereas the change for P1NP was only -4.0% (–15.4%, +7.1%).

Conclusion: ZOL resulted in larger decreases in bone turnover than did TDF-switching. The decrease in bone turnover in the TDF-switch group suggests that TDF reduces BMD by increasing bone turnover. Early changes in P1NP predicted BMD changes at 24 months with both ZOL and TDF-switching.



724 COMBINED EFFECTS OF BISPHOSPHONATES & TDF→ TAF SWITCH IN HIV+ ADULTS WITH LOW BMD

Todd T. Brown[1], Michael T. Yin[2], Samir K. Gupta[3], William R. Short[4], Melanie Thompson[5], Daniel Podzamczer[6], Giovanni Di Perri[7], Cheryl McDonald[8], Matthias Cavassini[9], Pablo Tebas[4], Ya-Pei Liu[10], Scott McCallister[10], Andrew Cheng[10], Moupali Das[10]

[1]Johns Hopkins University, Baltimore, MD, USA, [2]Columbia University Medical Center, New York, NY, USA, [3]Indiana University, Indianapolis, IN, USA, [4]University of Pennsylvania, Philadelphia, PA, USA, [5]AIDS Research Consortium of Atlanta, Atlanta, GA, USA, [6]Hospital Universitario de Bellvitge, Barcelona, Spain, [7]Amedeo di Savoia Hospital, Torino, Italy, [8]Tarrant County Infectious Disease Associates, Fort Worth, TX, USA, [9]Lausanne University Hospital, Lausanne, Switzerland, [10]Gilead Sciences, Inc, Foster City, CA, USA

Background: Bone mineral density (BMD) improves by 2-3% in HIV+ adults who switch from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF). The extent to which these increases can be augmented with concomitant bisphosphonate (BP) use is unknown.

Methods: We pooled data from two prospective 144-week, Phase 3 studies of HIV-infected adults virologically suppressed on TDF-based regimens who switched to elvitegravir, cobicistat, and emtricitabine (E/C/F) co-formulated with TAF. In adults with clinically significant low BMD by dual energy x-ray absorptiometry (T-score ≤-2.0 at lumbar spine, femoral neck, or total hip) at baseline (BL), we compared the percentage change in BMD and change in T-score at the lumbar spine and total hip in BP users v. non-users over 144 weeks. We estimated the effect of BP use on bone outcomes independent of age, race, sex, BMI, current smoking status, and BL BMD with linear regression.

Results: Of 1117 adults enrolled who switched from TDF to TAF, 214 (19%) had clinically significant low BL BMD, of whom 43% (93/214) had osteoporosis. Over 144 weeks, 30/214 (14%) reported using BPs with median (Q1, Q3) use of 754 (425, 1032) days. At BL, BP users were more likely to be women (33% vs 12%), to be current smokers (40% vs 23%), and to have lower spine and hip BMD. At 144 weeks, spine BMD increased by the mean (Q1, Q3) of 5.1% (4.0, 8.3) (p<0.001) in the BP users and 2.6% (-0.5, 5.4) (p<0.001) in the non-BP users (between group p=0.002). In the hip, median (Q1, Q3) BMD increased in BP users [4.0% (1.2, 6.7)] (p<0.001) and non-users [2.3% (0.9, 4.4)] (p<0.001) with no difference between the groups (p=0.29). In multivariable models, compared to non-users, BP users tended to have greater increase in lumbar spine BMD [2.6% (95% CI: -0.3, 5.4); p=0.08], corresponding to a 0.21 (95% CI:-0.01, 0.42; p=0.06) T-score increase. At the hip, the magnitude of the increase in BMD and T-score was similar in BP vs non-users (p>0.80).

Conclusion: Switching from TDF to TAF improved BMD over 144 weeks in HIV+ adults with low BMD. In this cohort, concomitant BP use augmented these gains at the spine but not the hip. Future controlled studies are required to confirm these findings and examine whether a sequential strategy of TDF switching followed by BP use would result in improved BMD gains compared to a combined strategy of concomitant TDF switching plus BP use.

725 BONE, RENAL, AND INFLAMMATION MARKERS IN THE DOLUTEGRAVIR MONOTHERAPY (DOMONO) STUDY

Ingeborg Wijting[1], Casper Rokx[1], Sandra A. Smits[1], M. C. Zillikens[1], Theodora de Vries-Sluijs[1], Karin Schurink[1], Hannelore Bax[1], Maarten Derksen[1], Elrozy Andrinopoulou[1], Ineke van der Ende[1], Eric van Gorp[1], Jan Nouwen[1], Annelies Verbon[1], Wouter Bierman[2], Bart Rijnders[1]

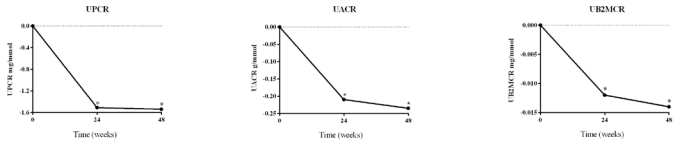
[1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]University Medical Center Groningen, Groningen, Netherlands

Background: Tenofovir disoproxil fumarate (TDF) containing combination antiretroviral therapy (cART) can result in unfavorable metabolic changes. These may recover after TDF discontinuation. We measured renal, bone, lipid and inflammatory markers before and after a switch from TDF-containing cART to dolutegravir (DTG) monotherapy in the DOlutegravir maintenance MONOtherapy for HIV (DOMONO) study (NCT02401828).

Methods: In DOMONO patients were switched from cART to DTG maintenance monotherapy. Eligible patients had been on cART with HIV-RNA < 50 c/ml for >6 months and with a CD4-nadir and HIV-RNA-zenith ≥200 cells/mm^3 and >100.000 c/ml respectively. The study was discontinued prematurely due to an unforeseen number of virological failures with acquired resistance in integrase in 3 patients (CROI 2017, abstract 451LB). In the entire subgroup of patients on a TDF-containing cART ('TDF') before DTG monotherapy initiation, the following makers were measured at week 0, 24 and 48; (1) Bone Mineral Density (BMD) and Trabecular Bone Score (TBS), (2) estimated glomerular filtration rate (eGFR), urine protein:creatinine-ratio (UPCR), urine albumin:creatinine-ratio (UACR) and urine beta-2 microglobulin:creatinine-ratio (UB2MGCR), (3) lipids and (4) C-reactive protein and CD4:8 T-cell-ratio as markers of inflammation and immune activation. Paired T-tests and Wilcoxon Rank Sum tests were used to compare week 0 with week 48 and standard deviations and interquartile ranges are given when appropriate.

Results: 85 patients on TDF were included and were mostly male with a mean age of 47 years. Mean baseline eGFR was 90 ml/min and mean (SD) lumbar and hip BMD at baseline were 1.174 (0.161) and 1.009 (0.156) g/cm3 and TBS of 1.313 (0.119). Lumbar and total hip BMD improved at week 48: +1.8% and +1.5% respectively (p<0.01 for all). Mean TBS improved as well by week 48: +0.012, p<0.01. As expected, the start of DTG led to a decrease in the creatinine-based eGFR measurement of -6.7 (9.2) ml/min at week 48. However, other renal markers improved significantly (p<0.01 for all) (figure 1). Lipids did not change significantly (LDL +0.14, TC/HDL +0.1 p>0.1 for all), and neither did CRP (+0.00, p>0.1) and CD4:8-ratio (+0.00, p>0.1).

Conclusion: In those patients without virological failure at week 48, a switch from TDF-containing cART to DTG monotherapy improved bone and renal markers and had a neutral effect on lipids and inflammatory and immune activation parameters.



726 OMEGA-3 FATTY ACID SUPPLEMENTATION IN HIV PATIENTS: A RANDOMIZED CLINICAL TRIAL

Juan M. Tiraboschi, Antonio Navarro-Alcaraz, Elena Ferrer, Carmen Gomez-Vaquero, Dolors Giralt, Arkaitz Imaz, Maria Saumoy, Daniel Podzamczer

Bellvitge University Hospital, Barcelona, Spain

Background: Osteopenia and osteoporosis are common comorbidities in HIV-infected patients and low level residual systemic inflammation is thought to be a contributor to these disorders. Omega-3 fatty acids (O3FAs) have beneficial effects on triglycerides and systemic inflammation. The anti-inflammatory effects of O3FAs are well-known and they are mediated through multiple mechanisms. We performed a randomized clinical trial in HIV-infected patients with hypertriglyceridemia, to compare the effects of O3FAs vs Fenofibrate in bone mineral density (BMD) and markers of bone turnover.

Methods: HIV-infected subjects on stable ART were randomized to receive either Omega-3-acid (O3) 2000mg/day or micronized fenofibrate 145 mg/day for 24 months. The primary outcomes were changes on BMD measured by hip and lumbar bone densitometry (DEXA Hologic QDR 4500)), The secondary outcomes were changes bone turnover markers such as PTH, calcitonin, CTX, BGLAP and 1,25-(OH)2D3 and serum triglycerides (TG). All markers were compared between the groups at pre-specified time points during the trial, as were changes in these parameters from baseline.

Results: Fifty eight virologically suppressed patients (13% female) were allocated to fenofibrate (n=30) or O3 (n=28), 12 pts (40%) in the fenofibrate group were over 50 years old and 15 (53%) in the O3 group (p:0.3). Mean CD4 count was 739 cells/ml (SD 251) and 650 cells/ml (SD 263) respectively. 63 % of pts in the fenofibrate group and 42% in the O3 group received ARV regimens

including protease inhibitor (p: 0.1). 22 pts in the Fenofibrate group and 23 in the O3 group completed follow up at week 96. Changes from baseline to week 96 in bone mineral density (BMD), bone turnover markers and TG are presented in table 1.

Conclusion: Twenty four month Omega-3 fatty acid supplementation resulted in no beneficial changes in BMD and bone turnover markers. Moreover, we observed a marked reduction in BMD in proximal femur in both groups, mainly in the O3 group associated with a significant decrease in 1,25-(OH)2D3. Larger studies are required to confirm these findings and investigate their clinical significance.

Table 1. Changes from baseline to week 96

Changes from baseline to week 96	Fenofibrate		Omega-3		P-value
	N	Mean (SD)	N	Mean (SD)	
Lumbar Spine BMD (g/cm2)	22	-0.04 (0.19)	24	0.02 (0.07)	0.090[2]
Lumbar Spine BMD (%)	22	-3.07 (16.85)	24	2.94 (6.63)	0.079[2]
Proximal Femur BMD (g/cm2)	22	-0.08 (0.07)	23	-0.12 (0.08)	0.046[1]
Proximal Femur DMO (%)	22	-8.18 (7.72)	23	-12.51 (7.89)	0.070[1]
1,25-(OH)2D3	20	-6.22 (44.52)	22	-34.16 (41.53)	0.042[1]
Calcitonin	12	-2.71 (10.39)	14	0.07 (1.17)	0.795[2]
CTX	20	0,006 (0,32)	22	-0,031 (0,45)	0,97
PTH	19	-1,41 (2,78)	22	0,23 (4,32)	0,229
BGLAP	20	-2,98 (8,8)	22	-7,29 (16,56)	0,457
Serum TG	20	-1.16 (1.21)	23	-0.76 (2.72)	0,706

BMD: Bone Mineral Desity, CTX: C-terminal telopeptide; PTH: Parathyroid hormone; BGLAP: osteocalcin; TG: Triglycerides.
1: T-test paired samples; 2: Wilcoxon

727 HYPERKYPHOSIS AND AGING IN THE WOMEN'S INTERAGENCY HIV STUDY

Anne M. Ritchie[1], Wendy B. Katzman[1], Yifei Ma[1], Rebecca Scherzer[1], Mardge H. Cohen[2], Michael T. Yin[3], Phyllis Tien[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]Cook County Health & Hospitals System, Chicago, IL, USA, [3]Columbia University Medical Center, New York, NY, USA

Background: HIV+ women have lower bone mineral density (BMD) and a higher rate of fracture than HIV- women, but the contribution of HIV infection to hyperkyphosis is not known. Hyperkyphosis is a geriatric syndrome of multifactorial etiology including decreased BMD, vertebral fracture, and muscle weakness, and is associated with decreased physical function and increased all-cause mortality. We examined whether HIV infection is associated with hyperkyphosis.

Methods: Cobb Angle, a radiographic measure of thoracic kyphosis was determined using dual energy Vertebral Fracture Assessment software in a cross-sectional sample of 130 HIV+ and 70 HIV- early post-menopausal women enrolled in the Musculoskeletal Substudy of the Women's Interagency HIV Study. We performed logistic regression to estimate odds of hyperkyphosis (defined as Cobb Angle≥40°) associated with HIV infection, and to identify factors associated with hyperkyphosis. Candidate covariates included demographic, lifestyle, body composition, and HIV-related factors.

Results: Over half of women were African-American; majority was overweight or obese [median BMI:29kg/m2 (interquartile range[IQR]:25,34) in HIV+;30kg/m2(IQR:27,34) in HIV-] and median age was 50(IQR:48,54) in HIV+ and 49 years (IQR:44,53) in HIV-. HIV+ women had lower lumbar spine(LS), femoral neck(FN), and total hip(TH) BMD than HIV- women [1.19(IQR:1.08,1.31) vs 1.30(IQR:1.15,1.41);0.97(IQR:0.89,1.09) vs 1.03(IQR:0.93,1.11)]; and 1.02(IQR:0.91,1.11) vs 1.07(IQR:0.98,1.17), respectively]. There was little difference in median Cobb angle [29°(IQR:23°,35°) in HIV+ vs. 30°(IQR: 23°,36°) in HIV-;p=0.86]; 10% of each group had hyperkyphosis. In age-adjusted analysis, HIV infection was not associated with hyperkyphosis (Odds Ratio [OR]:0.94;95% Confidence Interval [CI]:0.35,2.5) when compared to those without HIV infection. Factors associated with hyperkyphosis in age-adjusted analyses included LS BMD and CD4 count. Greater LS BMD was associated with lower odds of hyperkyphosis (OR:0.75 per 10% increase;95%CI: 0.57,0.99), while in HIV+ women, higher CD4 count was associated with non-significantly higher odds of hyperkyphosis (OR 2.47 per doubling;95%CI: 0.88,6.90).

Conclusion: In our study of early-postmenopausal women, contrary to our hypothesis, we did not find that HIV+ women had greater hyperkyphosis than HIV- women. As expected, lower lumbar spine BMD was associated with hyperkyphosis. Further study is needed in a larger cohort of aging post-menopausal women with HIV.

728 PEOPLE LIVING WITH HIV IN FRANCE HAVE DELAYED ACCESS TO KIDNEY TRANSPLANTATION

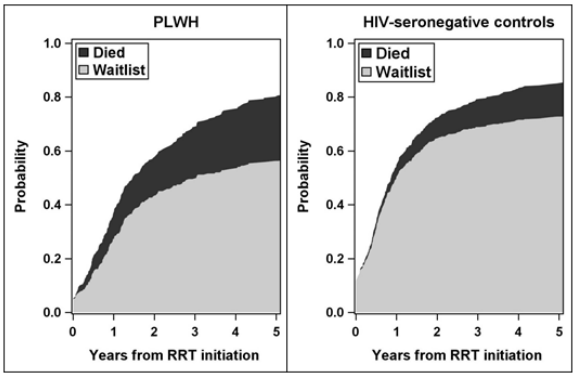
Jérome Tourret[1], **Sophie Abgrall**[1], Mathilde Lassalle[1], Sophie Grabar[1], Corinne Isnard-Bagnis[1], Gilbert Deray[1], Benoit Barrou[1], Dominique Costagliola[2], Cecile Couchoud[1], Marguerite Guiguet[2], Sophie Tezenas du Moncel[1]
[1]AP–HP, Paris, France, [2]INSERM, Paris, France

Background: Kidney transplantation (KT) is the best renal replacement therapy (RRT) for people living with HIV (PLWH) with end-stage renal disease (ESRD). We analyzed the access to KT waiting list (WL) and to KT after enrolment on WL of PLWH and compared them with those of uninfected patients.

Methods: Using REIN, the national end stage renal disease registry, we included all adult PLWH who initiated RRT in France between 2006 and 2010 and selected up to 2 HIV seronegative controls matched on age, sex, year of RRT initiation, existence of a diabetic nephropathy. Patients were prospectively followed until 12/31/2015. HIV-related data were extracted from the French Hospital Database on HIV (FHDH ANRS CO4). A competing-risk approach was used to assess the cumulative incidence of enrollment on a WL and of KT while listed with death as competing event. Adjusted sub-distribution hazard ratios (AsdHR) are given with 95% confidence intervals.

Results: 255 PLWH and 476 matched controls were included: median age 47yrs, 69% males, median follow-up 5.6 and 6.3 yrs since RRT initiation, respectively. PLWH were more often infected with HCV and presented more comorbidities. Two years after RRT initiation, the cumulative probability of enrollment on a KT WL was 46% for PLWH and 64% for controls, and the cumulative probability of death without enrollment was 14% for PLWH and 8% for controls (figure). WL enrollment was delayed for PLWH compared to controls despite an improvement over time (for pts initiating RRT in 2006-2008 : AsdHR 0.43 [0.33 to 0.56] and for those initiating in2009-2010 : AsdHR=0.66 [0.47 to 0.93]; p=0.04 for the test of interaction). After adjustment for blood group and the rate of incompatible transplant, KT was also delayed and less frequent for PLWH (AsdHR=0.68 [0.53 to 0.89]). Access to KT was not different between the periods of RRT initiation (p=0.37 for the test the interaction test). Transient inactivity on the WL was more frequent for PLWH (79%) than for controls (50%; p<0.0001). HIV infection data were available for 180 (71%) of the PLWH of whom 98% received ART. Results were similar when analyses were restricted to PLWH either on ART and having immunologic and virologic response (CD4>200/mm^3 and VL<500 copies/ml).

Conclusion: Despite a slight amelioration with time, PLWH access to WL and KT remains arduous and delayed compared to HIV seronegative controls of the same age.



729 CHRONIC KIDNEY DISEASE RISK FACTORS AND URINE KIDNEY INJURY MARKERS IN HIV+ PERSONS

Anthony Muiru[1], Michael Shlipak[2], Rebecca Scherzer[2], William Zhang[1], Simon Ascher[3], Chirag Parikh[4], Carl Grunfeld[2], Frank J. Palella[5], Ruibin Wang[6], Phyllis Tien[2], Qibin Qi[7], Michelle Estrella[2]

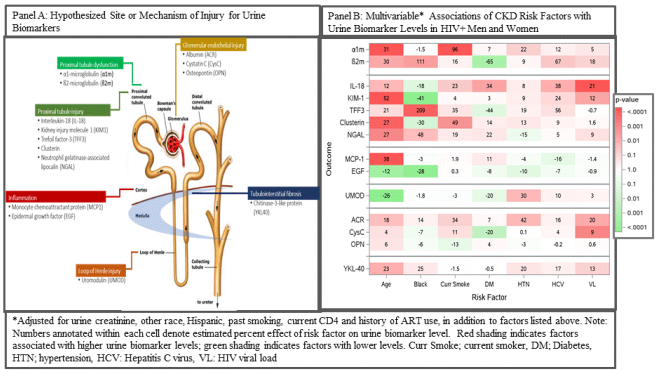
[1]University of California San Francisco, San Francisco, CA, USA, [2]San Francisco VA Medical Center, San Francisco, CA, USA, [3]University of California Los Angeles, Los Angeles, CA, USA, [4]Yale University, New Haven, CT, USA, [5]Northwestern University, Chicago, IL, USA, [6]Johns Hopkins University, Baltimore, MD, USA, [7]Albert Einstein College of Medicine, Bronx, NY, USA

Background: HIV+ persons bear an excess burden of chronic kidney disease (CKD), yet conventional methods to assess kidney health are insensitive and non-specific. We hypothesized that CKD risk factors would be differentially associated with unique patterns of urine kidney injury markers.

Methods: Cross-sectional study of HIV+ persons studied prior to TDF-based ART initiation in the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study between 2009 and 2015. By multiplex assays, we measured levels of 14 biomarkers, capturing multiple dimensions of kidney injury (Figure 1, Panel A). We evaluated associations of known CKD risk factors with urine biomarkers using separate multivariable adjusted models for each biomarker.

Results: We included 198 HIV+ persons. Median age was 48 years, 64% were black, and 56% were women. Median CD4 count was 483 cells/mm^3, 33% were on ART, 48% were hypertensive, 17% had diabetes, and 17% were HCV-infected. Median eGFRSCR by CKD-EPI equation was 103 mL/min|1.73 m2 (IQR 88-116). Each CKD risk factor was associated with a distinct pattern of urine biomarkers; the magnitudes of association between each CKD risk factor and biomarker varied (Figure 1, Panel B). For example, older age was associated with nearly all measures of kidney injury. Advancing age per decade was strongly associated with: 1) increases in biomarker levels of proximal tubular dysfunction/injury (52% KIM1, p<0.0001; 31% α1m, p<0.0001; 30% β2m, p=0.009; 27% clusterin, p=0.0002; 27% NGAL, p=0.002; 12% higher IL-18, p=0.021); 2) changes in biomarker levels of inflammation (38% higher MCP1, p<0.0001; 12% lower protective marker, EGF, p<0.0001; 3) 26% lower UMOD levels (p<0.0001) indicative of Loop of Henle injury; and 4) to a lesser degree, glomerular injury (18% higher ACR, p=0.03). In contrast, HIV viral load (per 10-fold increase) was most associated with 2 dimensions of injury: Glomerular (20% higher ACR, p=0.01; 9% higher CysC level, p=0.001) and proximal tubular (12% higher KIM1, p=0.008; 21% higher IL-18, p<0.0001). The latter marker though, may also reflect inflammation.

Conclusion: Among HIV+ persons, known CKD risk factors are associated with unique patterns of changes in urine biomarkers. To establish the clinical value of biomarker level measurement, future work is needed to confirm our findings in larger, diverse populations and to develop algorithms that discern the site of kidney injury and identify the related associated risk factors for individual patients.



*Adjusted for urine creatinine, other race, Hispanic, past smoking, current CD4 and history of ART use, in addition to factors listed above. Note: Numbers annotated within each cell denote estimated percent effect of risk factor on urine biomarker level. Red shading indicates factors associated with higher urine biomarker levels; green shading indicates factors with lower levels. Curr Smoke; current smoker, DM; Diabetes, HTN; hypertension, HCV: Hepatitis C virus, VL: HIV viral load

730 VALIDATION OF A CHRONIC KIDNEY DISEASE RISK SCORE IN HIV+ PATIENTS IN THE US

Anthony Mills[1], Kathy L. Schulman[2], Jennifer Fusco[2], Ricky Hsu[3], Andrew Beyer[4], Girish Prajapati[4], Karam Mounzer[5], Gregory Fusco[2]

[1]Southern California Men's Medical Group, Los Angeles, CA, USA, [2]Epividian, Durham, NC, USA, [3]AIDS Healthcare Foundation, Los Angeles, CA, USA, [4]Merck & Co, Inc, Kenilworth, NJ, USA, [5]Philadelphia FIGHT, Philadephia, PA, USA

Background: The risk of chronic kidney disease (CKD) increases with both HIV infection and aging, substantially complicating clinical decision-making. Our objective was to assess the validity, in an exclusively U.S. based cohort, of an easy-to-calculate CKD risk score, developed using data from the Data collection on Adverse events of Anti-HIV Drugs (D:A:D), a prospective, international, multi-site study.

Methods: HIV+ patients with no previous exposure to potentially nephrotoxic antiretroviral agents and ≥3 estimated glomerular filtration rate (eGFR) test results were identified in the OPERA® Observational Database, an aggregation of prospectively collected electronic medical records from HIV caregivers in 79 clinics across 15 states. Patients were followed from the first observed eGFR >60 ml/min/1.73 m2 (2002-2015) until last eGFR test result, the occurrence of the study outcome, lost to follow-up, or study end (31JUL2017). The study outcome was defined as a confirmed (≥2 consecutive results, >90 days apart) decrease in eGFR to < 60 ml/min/1.73m2. Three cohorts were drawn independently using Cockcroft-Gault (CG), MDRD and CKD-EPI eGFR estimation methods. Both full and short D:A:D risk scores were applied. Poisson models estimated incidence as a function of D:A:D risk score. Kaplan Meier survival curves estimated progression at five years. Incidence rate ratio's (IRR), adjusted IRR (aIRR), and Harrell's discrimination statistic were used to assess validity.

Results: After applying study eligibility criteria, there were 19444, 22727 and 22748 patients in the CG, CKD-EPI and MDRD samples, respectively. Median short and full risk scores were -3 in all three OPERA cohorts with very similar IQR. CKD incidence (95% CI) ranged from a low of 7.3 per 1000 person years (6.8, 7.9) in OPERA CG to a high of 11.0 (10.4, 11.6) in OPERA MDRD. While overall incidence was higher than observed in the D:A:D derivation cohort at 6.2 (5.7 - 6.7), IRR's by risk group were similar. Using the full risk score, the aIRR was 1.3 in all three OPERA cohorts, regardless of eGFR method, equivalent to the D:A:D derivation cohort. Harrell's c-statistic ranged from 0.87 to 0.92 in the three OPERA cohorts, comparable to that reported by D:A:D (0.92). Similar findings were observed after applying the D:A:D short risk score [Table].

Conclusion: This study supports the validity of the D:A:D short and full risk scoring method for assessing the probability of CKD in an exclusively U.S. based cohort regardless of eGFR method.

Table: CKD Incidence, 5-Year Progression, IRR, aIRR, and Discrimination of the D:A:D Full and Short Scores in the OPERA Database using Various eGFR Methods

	D:A:D Full Score Evaluation				D:A:D Short Score Evaluation			
	DAD Derivation Cockcroft-Gault N=17954	OPERA Cockcroft-Gault N=19444	OPERA CKD-EPI N=22727	OPERA MDRD_186.3 N=22748	DAD Derivation Cockcroft-Gault N=17954	OPERA Cockcroft-Gault N=19444	OPERA CKD-EPI N=22727	OPERA MDRD_186.3 N=22748
Incidence of CKD/1000 PY (95% CI)	6.2 (5.7 - 6.7)	7.3 (6.8, 7.9)	10.8 (10.2,11.4)	11.0 (10.4, 11.6)	6.2 (5.7 - 6.7)	7.3 (6.8, 7.9)	10.8 (10.2,11.4)	11.0 (10.4, 11.6)
Low (risk score <0)	0.51 (0.34-0.69)	1.4 (1.1,1.7)	2.7 (2.3,3.1)	2.6 (2.2, 3.0)	0.56 (0.38-0.75)	1.5 (1.2,1.8)	2.9 (2.5,3.3)	2.8 (2.4, 3.2)
Medium (risk score 0-4)	4.27 (3.45-5.10)	10.2 (8.7,12.0)	13.8 (12.3,15.4)	13.0 (11.6, 14.5)	4.67 (3.80-5.53)	11.6 (9.9,13.5)	14.7 (13.1,16.4)	13.7 (12.3, 15.2)
High (risk score > 5)	34.75 (31.72-37.78)	65.5 (59.3,72.3)	63.7 (58.9,68.7)	54.1 (50.1, 58.3)	36.05 (32.86-39.23)	69.8 (63.0,77.2)	66.3 (61.3,71.7)	56.3 (52.0, 60.8)
KM % progressed @ 5 y (95% CI)								
Low (risk score <0)	0.18 (0.09-0.26)	0.3 (0.2 - 0.4)	0.5 (0.4 - 0.7)	0.5 (0.4-0.6)	0.19 (0.10-0.27)	0.3 (0.2 - 0.4)	0.6 (0.5 - 0.7)	0.6 (0.5-0.7)
Medium (risk score 0-4)	1.50 (1.09-1.91)	2.9 (2.3 - 3.4)	3.8 (3.2-4.3)	3.7 (3.2-4.2)	1.62 (1.19-2.05)	3.2 (2.6 - 3.8)	4.1 (3.5-4.6)	4.0 (3.4-4.5)
High (risk score > 5)	14.68 (13.24-16.12)	18.8 (17.0 - 20.7)	20.8 (19.2-22.4)	18.4 (17.0-19.7)	15.33 (13.82-16.84)	19.8 (17.9 - 21.8)	21.6 (19.9-23.2)	19.1 (17.6-20.6)
Incidence rate ratio (95% CI)								
Low (risk score <0)	0.12 (0.081-0.18)	0.14 (0.11 - 0.18)	0.20 (0.16 - 0.23)	0.20 (0.17 - 0.24)	0.12 (0.08-0.18)	0.13 (0.10 - 0.16)	0.20 (0.17 - 0.23)	0.20 (0.17 - 0.24)
Medium (risk score 0-4)	1	1	1	1	1	1	1	1
High (risk score > 5)	8.13 (6.58-10.05)	6.4 (5.3 - 7.7)	4.6 (4.0 - 5.3)	4.2 (3.6 - 4.7)	7.73 (6.29-9.49)	6.0 (5.0 - 7.2)	4.5 (3.9 - 5.2)	4.1 (3.6 - 4.7)
aIRR (95% CI) per unit inc in score	1.32 (1.30-1.34)	1.29 (1.28-1.31)	1.25 (1.24-1.27)	1.25 (1.24-1.26)	1.33 (1.31-1.34)	1.30 (1.29-1.32)	1.26 (1.25-1.27)	1.25 (1.24-1.27)
Harrell's C-Statistic	0.92	0.92	0.88	0.87	0.91	0.9142	0.88	0.87

731 CHRONIC KIDNEY DISEASE IN HIV POPULATIONS OF AFRICAN DESCENT IN THE UK

Sophie Jose[1], **Lisa Hamzah**[2], Rachael Jones[3], Deborah Williams[4], Alan Winston[5], Fiona Burns[6], Caroline Sabin[1], Frank Post[2]

[1]University College London, London, UK, [2]King's College Hospital NHS Foundation Trust, London, UK, [3]Chelsea and Westminster NHS Foundation Trust, London, UK, [4]Brighton & Sussex University Hospitals NHS Trust, Brighton, UK, [5]Imperial College Healthcare NHS Trust, London, UK, [6]University College London Hospitals NHS Trust, London, UK

Background: Black ethnicity is a major risk factor for HIV-associated nephropathy (HIVAN) and hypertensive kidney disease through carriage of apolipoprotein L1 (*APOL1*) risk alleles. The prevalence of these alleles is highest in West Africans, intermediate in those from Southern Africa, and lowest in East Africans, while little is known about *APOL1* in Caribbeans (predominantly of West African ancestry). As HIVAN is an important cause of chronic kidney disease (CKD) in these populations, we hypothesized that rates of CKD vary in people from East, Southern and West Africa and the Caribbean.

Methods: Black participants in the UK CHIC cohort with at least 2 serum creatinine measurements were stratified by region of origin and followed from first creatinine measure to December 2014, their last visit or death. eGFR was estimated using the CKD-EPI formula adjusted for ethnicity and expressed in mL/min/1.73m^2. Poisson regression assessed the association between region of birth and CKD ≥3, ≥4 and 5 (eGFR <60,<30, and <15 for >3 months respectively), with adjustment for baseline (age, sex) and significant time-

updated (ART experience, CD4, viral load, AIDS, protease inhibitor (PI)/tenofovir (TDF) exposure) factors.

Results: The mean age at baseline of the 8334 participants was 36 years; most were female with median CD4 count 320 cells/mm^3 (Table). Median eGFR was 113 mL/min/1.73m^2; eGFR <60 was present in 1.2%, 2.4%, 2.9% and 4.7% of those from East Africa, Southern Africa, the Caribbean and West Africa, respectively (p <0.001). During >68000 person-years, 258, 97 and 71 persons, respectively, developed CKD stage ≥3, ≥4 and 5, with the highest incidence observed in West Africans (Table). Using East Africans as the reference group, the adjusted incidence rate ratio of CKD 5 was 5.38 (2.26, 12.82) among those from West Africa, 3.05 (1.31, 7.08) for those from Southern Africa, and 2.64 (0.98, 7.07) among Caribbeans. Participants from West Africa were also at significantly higher risk of CKD ≥3 (2.71 [1.82, 4.03]) and CKD ≥4 (2.83 [1.41, 5.67]).

Conclusion: The risk of CKD and kidney disease progression varied significantly among HIV positive black populations, with the highest rates observed in West Africans, suggesting that *APOL1* risk alleles is likely an important determinant of CKD in this population.

Table: Baseline characteristics and incidence of CKD stage ≥3, ≥4 and 5

	East Africa (N=2138)	Southern Africa (N=3492)	West Africa (N=1508)	Caribbean (N=1196)	P-value
Mean (SD) age (years)	36 (8.9)	36 (9.1)	36 (9.6)	37 (11.6)	0.035
Female sex	1386 (64.8)	2381 (68.2)	887 (58.9)	393 (32.9)	<0.001
Heterosexual	1929 (90.2)	3150 (90.2)	1339 (88.8)	634 (53.0)	<0.001
Hepatitis B virus	47 (2.2)	109 (3.1)	93 (6.2)	25 (2.1)	<0.001
Hepatitis C virus	14(0.7)	27 (0.8)	8 (0.5)	14 (1.2)	<0.001
Antiretroviral-therapy experienced	1096 (51.3)	1786 (51.2)	562 (37.3)	373 (31.2)	<0.001
Median (IQR) CD4 count [cells/mm^3]	300 (160, 474)	320 (170, 490)	296 (148, 460)	370 (206, 553)	0.401
Median (IQR) viral load [log_{10}copies/ml]	3.0 (1.7, 4.5)	2.9 (1.7, 4.4)	3.8 (1.8, 4.8)	3.9 (2.2, 4.7)	<0.001
eGFR [ml/min/1.73m^2]					
Median (IQR)	119 (100, 134)	113 (96, 129)	112 (94, 130)	108 (92, 125)	<0.001
≥90	1821 (85.2)	2867 (82.1)	1196 (79.3)	936 (78.3)	<0.001
75-89	220 (10.3)	416 (11.9)	178 (11.8)	165 (13.8)	
60-74	71 (3.3)	125 (3.6)	63 (4.2)	60 (5.0)	
<60	26 (1.2)	84 (2.4)	71 (4.7)	35 (2.9)	
CKD incidence per 1,000 PYFU (95% CI)					
CKD ≥3 (eGFR <60)	2.3 (1.6, 2.9)	3.3 (2.6, 4.0)	7.1 (5.4, 8.7)	5.0 (3.6, 6.4)	<0.001
CKD ≥4 (eGFR <30)	0.8 (0.4, 1.2)	1.3 (0.9, 1.8)	2.7 (1.7, 3.8)	1.5 (0.8, 2.3)	0.002
CKD ≥5 (eGFR <15)	0.4 (0.2, 0.7)	0.9 (0.6, 1.3)	2.3 (1.4, 3.3)	1.2 (0.6, 1.9)	<0.001

732 SAFETY AND EFFICACY OF E/C/F/TAF IN HIV-INFECTED ADULTS ON CHRONIC HEMODIALYSIS

Joseph J. Eron[1], Jean-Daniel Lelievre[2], Robert Kalayjian[3], Jihad Slim[4], Anson K. Wurapa[5], Jeffrey L. Stephens[6], Cheryl McDonald[7], Eric Cua[8], Aimee Wilkin[9], Brigitte Schmied[10], Mehri McKellar[11], Joseph M. Custodio[12], Shuping Jiang[12], Devi SenGupta[12], Moupali Das[12]

[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]Hôpital Henri Mondor, Créteil, France, [3]MetroHealth Medical Center, Cleveland, OH, USA, [4]Saint Michael's Medical Center, Newark, NJ, USA, [5]Infectious Disease Specialists of Atlanta, Atlanta, GA, USA, [6]Mercer University, Macon, GA, USA, [7]Tarrant County Infectious Disease Associates, Fort Worth, TX, USA, [8]Nice University Hospital, Nice, France, [9]Wake Forest University, Winston-Salem, NC, USA, [10]Otto-Wagner Hospital, Vienna, Austria, [11]Duke University, Durham, NC, USA, [12]Gilead Sciences, Inc, Foster City, CA, USA

Background: Elvitegravir (EVG)/cobicistat (COBI)/emtricitabine (FTC)/tenofovir alafenamide (E/C/F/TAF) is approved for use in HIV-1 infected individuals with mild to moderate chronic kidney disease (estimated glomerular filtration [eGFR] 30-69 mL/min). Current HIV treatment for individuals with renal failure on hemodialysis (HD) requires complex regimens with multiple pills. This is the first study to evaluate safety, efficacy, and pharmacokinetics (PK) of a daily single-tablet regimen (STR) in HIV-infected adults with end stage renal disease (ESRD) on chronic HD.

Methods: HIV1 infected, virologically suppressed adults with ESRD (eGFR <15mL/min) on chronic HD for ≥6 months were switched to open-label E/C/F/TAF 150/150/200/10 mg once daily for 48 weeks (W). Efficacy was assessed as the proportion of participants with HIV1 RNA <50 copies (c)/mL (Snapshot algorithm). Maintenance of virologic suppression (<50 c/mL), safety, and patient satisfaction (Treatment Satisfaction Questionnaire) were assessed throughout the study. A PK substudy was done at or between W2 and 4. W24 data are presented here and W48 data will be available for the conference.

Results: We enrolled 55 participants; median age 51yrs (range 23-64), 24% female, 82% Black, median time on HD 6yrs (range 1-17), median CD4 count 515 cells/mL (IQR 387, 672), and 22% Hepatitis C Ab positive, and 27% history of diabetes. At W24, 87% (48/55) had HIV-1 RNA <50 c/mL. The other 7 participants discontinued due to lack of efficacy (n=1), AE (n=2), or other reasons not related to efficacy (n=4). EVG, COBI, and TAF PK were consistent with exposures in normal renal function. As expected, exposures of FTC and TFV (metabolite of TAF), which are renally eliminated, were higher v. historical data in normal renal function (Table). 16 (29%) participants had Grade (G) 3 or 4 AEs unrelated to study drug; 6 (11%) participants experienced study drug related AEs (all were G1-2, including nausea in 4). Two participants discontinued E/C/F/TAF due to AEs (allergic pruritis, related; staphylococcal endocarditis, unrelated). The participant with endocarditis died from heart failure after entering hospice. 24 (44%) participants had G3-4 laboratory abnormalities, all of which were present at baseline. 79% of participants felt "much more satisfied" with the STR convenience compared to baseline.

Conclusion: Switching to E/C/F/TAF STR maintained virologic suppression at W24, was well tolerated, and more convenient for adults with ESRD on HD.

Table. Plasma exposure (AUC) after E/C/F/TAF administration in adults with ESRD on chronic HD

	Adults with ESRD on chronic HD (n=12) Mean (%CV) AUC, ng*h/mL
EVG	14300 (55)
COBI	10200 (59)
FTC	62900 (48)
TAF	232 (53)
TFV	8720 (39)

AUC_{tau} is presented for EVG, COBI, FTC, and TFV; AUC_{last} is presented for TAF.

733 CHANGE IN FAT/LEAN MASS IN HIV-POSITIVE AND -NEGATIVE SUBJECTS; DATA FROM HIV UPBEAT

Aoife G. Cotter[1], Alan Macken[1], **Willard Tinago**[1], Eoin Kavanagh[2], Geraldine McCarthy[1], Juliet Compston[3], Caroline Sabin[4], Patrick W. Mallon[1]

[1]University College Dublin, Dublin, Ireland, [2]Mater Misericordiae University Hospital, Dublin, Ireland, [3]Cambridge University, Cambridge, UK, [4]University College London, London, UK

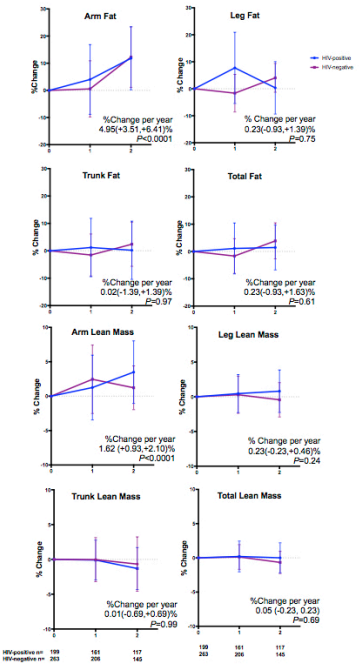
Background: Changes in body composition with antiretroviral therapy (ART) initiation have been well defined but long-term body composition changes in people living with HIV on stable ART compared to people without HIV remains unclear. With concerns regarding fat gain and sarcopenia in older PLWH, we aimed to compare changes in fat and lean mass in a large cohort of HIV+ and HIV- individuals.

Methods: In HIV UPBEAT, a prospective cohort of HIV+ and HIV- subjects from similar demographic backgrounds, subjects had annual dual energy Xray absorptiometry (DXA) to measure total and regional (arms, legs, trunk) fat and lean mass and provided clinical, demographic and laboratory data. We determined the absolute change in log-transformed body composition variables with longitudinal mixed effects models. Time-updated variables were included in models and removed if no difference in slope was determined. Data are presented as median(interquartile range) or %change(95% C.I.) unless otherwise specified.

Results: From February 2011-June 2014, 462, 367 and 262 subjects provided DXA data at 3 annual visits respectively. Compared to the HIV- group, the HIV+ group were younger (38.5 (33.3, 46.1) vs 41.7 (34.6, 48.4) years, P=0.03; 13.7% and 20.0% aged >50 respectively, P=0.07), more likely male (58.0% vs 43.4%, P=0.002) and of African ethnicity (39.2% vs 24.9%, P=0.001). While arm fat increased by +4.95(+3.51,+6.41)% per year (P<0.0001), there were no significant changes in leg, trunk or total fat (fig) and no significant between-group differences in annual %change in arm (+0.92(-1.86,+3.75)%), leg (-0.46(-2.57,+1.86)%), trunk (-0.69(-3.75,+2.09)%) or total fat (-0.09(-0.03,+2.33)%) between HIV+ and HIV- groups. Arm lean mass increased by +1.62(+0.93, +2.10)% per year (P<0.0001) but there was no significant change in leg, trunk or total lean mass (fig). There was no significant between-group difference in annual %change in arm (+0.23(-0.93,+1.39)%), leg (+0.46(-0.23,+0.93)%), trunk (-0.69 (-2.09,+0.93)%) or total lean mass (+0.23(-0.23,+0.69)%) between HIV+ and HIV- groups. Conclusions were unchanged after adjustment for age, gender or ethnicity.

Conclusion: While we observed increases in arm fat and lean mass, these did not differ between HIV+ and HIV- groups. We observed no significant change in other parameters of fat or lean mass either in the entire cohort or between groups. These data are reassuring; alterations in body composition in this cohort of PLWH reflect those observed in a relevant HIV- control group.

Figure. % change in body composition variables over time in HIV-positive and HIV-negative subjects

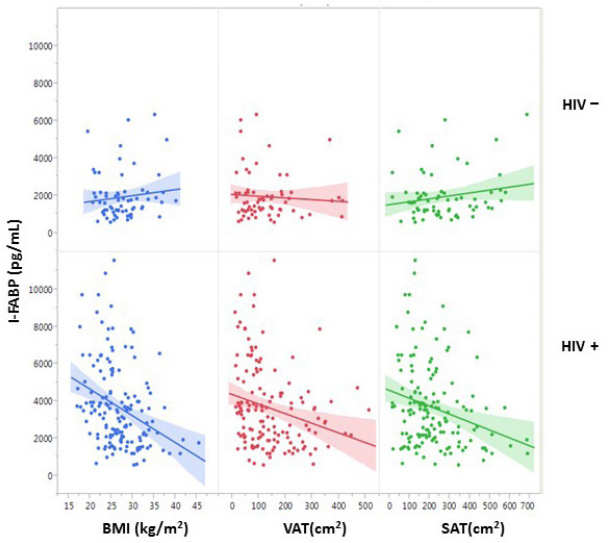


734 I-FABP IS ELEVATED AND IS INVERSELY RELATED TO BODY FAT IN HIV

Lediya Cheru[1], Elli Park[1], Charles Saylor[1], Kathleen V. Fitch[1], Tricia H. Burdo[2], Jake A. Robinson[2], Martin Torriani[1], Steven K. Grinspoon[1], Janet Lo[1]
[1]Massachusetts General Hospital, Boston, MA, USA, [2]Temple University, Philadelphia, PA, USA

Background: Intestinal damage occurs during acute and chronic HIV infection despite suppressive antiretroviral therapy and is posited to be one of the drivers of residual chronic immune activation and inflammation. Our study aims to assess intestinal damage as measured by serum intestinal fatty acid binding protein (I-FABP) to further elucidate its role on body composition in individuals living with HIV.
Methods: Observational cross-sectional analysis of 154 men and women living with chronic HIV (66% men, mean age 47±7 years) and 69 HIV negative controls (59% men, age 46±7 years) with similar BMI and cardiovascular risk factors was performed. Serum I-FABP was measured by ELISA. Markers of inflammation and immune activation as well as lipopolysaccharides (LPS) were measured. Anthropometric measurements, DXA and single slice abdominal CT were obtained to assess body composition and visceral and subcutaneous adipose tissue areas.
Results: Serum I-FABP was higher in the HIV-infected group (3373 pg/ml [1976-4527]) in comparison to the non-HIV control group (1633 pg/ml [1149-2127]) (p<0.0001). Serum I-FABP was negatively associated with BMI (ρ=-0.36, p=<0.0001), truncal fat (ρ=-0.47, p<0.0001), arm fat (ρ=-0.48, p<0.0001), SAT (ρ=-0.24, p=0.003), and VAT (ρ=-0.28, p=0.0005), and positively associated with adiponectin (ρ=0.20, p=0.04) in the HIV-infected group. These relationships were not seen in the HIV-negative control group. Serum I-FABP was positively related to MCP-1 (ρ=0.19, p=0.005), CXCL10 (ρ=0.30, p=0.008), sCD163 (ρ=0.26, p=<0.0001), LPS (ρ=0.16, p=0.03) and to the percent of HLA-DR+CD38+ CD4+ T cells (ρ=0.26, p=0.02) among all participants.
Conclusion: People living with chronic HIV have significantly higher I-FABP than HIV negative controls. I-FABP was also positively related to markers of microbial translocation, monocyte activation and T-cell activation markers. Interestingly, I-FABP was strongly negatively correlated with BMI and adiposity in subcutaneous and visceral fat compartments among people living with HIV, suggesting that intestinal damage from HIV infection may lead to impaired intestinal absorption and fat loss. Future studies to investigate the role of I-FABP or intestinal damage on fat metabolism are needed to elucidate mechanisms of this observed relationship in people living with HIV.

Relationship of I-FABP to BMI, VAT, and SAT



735 LOWER PRETREATMENT GUT INTEGRITY ASSOCIATED WITH FAT GAINS ON ANTIRETROVIRALS

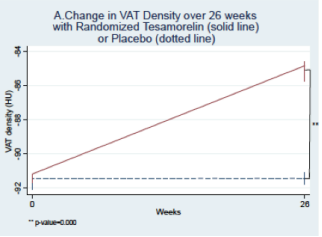
Vanessa El Kamari[1], Carlee Moser[2], Judith S. Currier[3], Todd T. Brown[2], Liz Johnston[2], Corrilynn O. Hileman[4], Peter W. Hunt[5], **Grace A. McComsey**[6]
[1]Case Western Reserve University, Cleveland, OH, USA, [2]Harvard University, Cambridge, MA, USA, [3]University of California Los Angeles, Los Angeles, CA, USA, [4]MetroHealth Medical Center, Cleveland, OH, USA, [5]University of California San Francisco, San Francisco, CA, USA, [6]University Hospitals Cleveland Medical Center, Cleveland, OH, USA

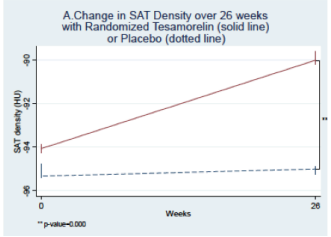
Background: Despite advances in antiretroviral therapy (ART), obesity and insulin resistance remain a threat to treatment success. HIV infection is known to disrupt gut barrier integrity, leading to microbial translocation. Little is known about the differential effect of integrase and protease inhibitors on gut integrity, and the role of gut dysfunction in metabolic complications associated with ART initiation.
Methods: In ACTG A5260, a substudy of A5257, HIV-infected treatment naïve participants were randomized to receive tenofovir-emtricitabine (TDF/FTC) plus atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), or raltegravir (RAL) for 96 weeks. Changes in gut integrity markers: intestinal fatty acid binding protein (I-FABP) and zonulin, markers of enterocyte damage and intestinal permeability, respectively, were assessed from baseline to 4, 24, and 96 weeks in all participants that achieved virologic suppression by week 24 and remained suppressed through week 96 on their randomized treatment. Wilcoxon Rank-Sum tests compared changes in gut markers between groups. Linear regression models quantified associations between gut markers, and the following: insulin resistance (by homeostatic model assessment HOMA-IR), BMI, visceral, subcutaneous, and total adipose tissue (VAT, SAT, and TAT by CT scan) adjusting for baseline age, sex, race/ethnicity, HIV-RNA, CD4 count, smoking, alcohol, drug use, and physical activity.
Results: 234 participants included; 90% were male, 48% were white, non-Hispanic. Median age was 36 years, HIV-1 RNA load 4.6 $\log_{10}$ opies/mL, and CD4 count 338 cells/μL. Overall I-FABP levels increased significantly from baseline throughout 96 weeks (1.7-fold change; 95% CI [1.53,1.78]), without significant difference between arms (p>0.2). Non-significant increases overtime in zonulin levels were observed; zonulin levels were higher in RAL vs DRV/r arm at week 24 (p<0.01), and in RAL vs ATV/r at week 96 (p=0.02). A two-fold higher baseline I-FABP levels were significantly associated with increases in VAT, TAT, and BMI (16%, 9%, 2.5%; p<0.04) over 96 weeks, even after adjusting for confounders. Gut markers levels were not associated with HOMA-IR (p≥0.2).
Conclusion: Disruption of gut barrier integrity persists after ART initiation in treatment-naïve participants, regardless of regimen used. Baseline gut dysfunction in ART-naïve individuals is associated with subsequent changes in BMI, total and central fat regardless of regimen used.

736 TESAMORELIN IMPROVES FAT QUALITY INDEPENDENT OF CHANGES IN FAT QUANTITY

Jordan E. Lake[1], Kristine M. Erlandson[2], Stefan Adrian[3], Abanti Sanyal[4], Ann Scherzinger[5], Michael Dube[6], Takara L. Stanley[7], Steven K. Grinspoon[7], Jean-Claude Mamputu[8], Christian Marsolais[8], Todd T. Brown[4], Grace A. McComsey[9]
[1]University of Texas at Houston, Houston, TX, USA, [2]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [3]University of Colorado Denver, Denver, CO, USA, [4]Johns Hopkins University, Baltimore, MD, USA, [5]University of Colorado, Aurora, CO, USA, [6]University of Southern California, Los Angeles, CA, USA, [7]Harvard University, Cambridge, MA, USA, [8]Theratechnologies, Inc, Montreal, QC, Canada, [9]Case Western Reserve University, Cleveland, OH, USA

Background: Fat quality may contribute to metabolic disease and inflammation as much or differently than fat quantity. HIV-infected (HIV+) adults have multiple risk factors for fat dysfunction, including HIV and antiretroviral therapy (ART). Both visceral (VAT) and subcutaneous (SAT) fat quality can be measured on computed tomography (CT) by measuring fat density (greater density=smaller, better quality adipocytes). Tesamorelin, a growth hormone-releasing hormone analogue, reduces VAT quantity in some HIV+ adults with central adiposity, but its effect on fat density is unknown.
Methods: Participants were selected from two completed, randomized (2:1) trials of tesamorelin vs placebo for the treatment of central adiposity in HIV+ adults. Included participants had a clinical response to tesamorelin (defined as a VAT area decrease ≥8%, ≈70% of tesamorelin-treated participants) or were randomized to placebo. Week 0 and 26 abdominal (L4-5) CT scans were re-analyzed for VAT and SAT density (in Hounsfield Units, HU) by a central lab blinded to treatment arm. Paired t tests and linear regression models assessed 26-week, between-group differences in fat density changes.
Results: Participants (193 responders, 148 placebo) were mostly male (87%) and Caucasian (83%). Arms were similar (p>0.10) at baseline in regards to sex, race/ethnicity, age, adiposity, concomitant medications, CD4+ T-cell count, HIV-1 RNA, ART, and time since HIV diagnosis. Baseline mean VAT and SAT HU were -91 and -94 in the tesamorelin arm, and -91 and -95 in the placebo arm (SAT p=0.29, VAT p=0.80). Over 26 weeks (Fig.), mean (SD) VAT density increased 6.2 (8.7) HU in the tesamorelin arm vs 0.3 (4.2) HU for placebo (p<0.0001). The effect was attenuated but persisted after controlling for baseline VAT HU and area, and VAT area change (2.3 HU, 95% CI [4.5, 7.3], p=0.001). Mean (SD) SAT density increased 4.0 (8.7) HU in the tesamorelin arm vs 0.3 (4.8) HU for placebo (p<0.0001), with no significant attenuation of effect after controlling for baseline SAT HU and area, and SAT area change (3.5 HU, 95% CI [2.3, 4.7], p<0.001).
Conclusion: In HIV+ adults with central adiposity who responded to tesamorelin, VAT and SAT density increased independent of changes in fat quantity. These findings suggest that tesamorelin improves VAT and SAT quality in HIV+ adults in addition to reducing VAT quantity. Additional studies will determine whether these changes in fat density are associated with improvements in cardiometabolic and inflammatory parameters.





737 FAT QUALITY IS INDEPENDENTLY ASSOCIATED WITH CARDIOMETABOLIC RISK IN HIV INFECTION

Jordan E. Lake[1], Carlee Moser[2], Liz Johnston[2], Clara Magyar[3], Scott D. Nelson[3], Kristine M. Erlandson[4], Todd T. Brown[5], Grace A. McComsey[6]
[1]University of Texas at Houston, Houston, TX, USA, [2]Harvard University, Cambridge, MA, USA, [3]University of California Los Angeles, Los Angeles, CA, USA, [4]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [5]Johns Hopkins Hospital, Baltimore, MD, USA, [6]Case Western Reserve University, Cleveland, OH, USA

Background: Adipose tissue (AT) quality and quantity may have independent metabolic effects. Computed tomography (CT)-quantified abdominal subcutaneous AT (SAT) density reflects biopsy-quantified SAT adipocyte size in HIV-infected adults, with lower density reflecting larger, poorer quality adipocytes. We assessed relationships between SAT and visceral AT (VAT) density and cardiometabolic and inflammatory parameters among HIV-1-infected adults enrolled in a completed ART initiation trial.
Methods: AIDS Clinical Trials Group study A5224s participants were included in baseline analyses (n=54) if they had both abdominal SAT biopsy and CT data, and 96-week analyses (n=30) if they remained on their original randomized antiretroviral therapy (ART) regimen, had HIV-1 RNA <50 copies/mL and had biopsy or CT data. Partial Spearman's correlations adjusting for AT area assessed relationships between AT density (in Hounsfield Units, HU) and metabolic and inflammatory parameters. The Jonckheere-Terpstra test assessed significance in metabolic syndrome analyses.
Results: At baseline, median age was 40 years, CD4+ T lymphocyte count 219 cells/mm^3, body mass index (BMI) 26.0 kg/m2, SAT area 199 cm2 and density -100 HU, VAT area 83 cm2 and density -83 HU; 89% were male and 67% white. Greater baseline SAT density correlated with lower triglyceride levels; greater VAT density correlated with higher HDL cholesterol (Table). Baseline AT density did not correlate with HOMA-IR nor inflammatory biomarker levels. The number of metabolic syndrome components (0, 1-2, 3+) at baseline increased as VAT density decreased (-75, -83 and -90 HU, p=0.002), irrespective of total adiposity (BMI <25 p=0.02, BMI 25+ p=0.04). Over 96 weeks of ART, SAT (+18%) and VAT (+35%) area increased, and SAT (-3%) and VAT (-6%) density decreased. Decreases in SAT HU correlated with increases in hs-CRP, IL-6, soluble TNFRI/II and sICAM-1 independent of SAT area (Table). Decreases in VAT HU correlated with increases in IL-6 and soluble TNFRII independent of VAT area.
Conclusion: SAT and VAT quality, as measured by CT density, are associated with metabolic disturbances in ART-naïve HIV-infected adults, and inflammatory biomarker concentrations on ART, independent of AT quantity. Increased AT area and decreased AT density on ART (suggestive of hypertrophic AT expansion) is associated with increased systemic inflammation and has important implications for comorbidity development following ART initiation.

	SAT HU		VAT HU	
	r	p value	r	p value
Baseline (n=53)*				
HDL (mg/dL)	0.117	0.41	0.314	0.02
Triglycerides (mg/dL)	-0.279	0.04	-0.114	0.42
HOMA-IR	0.012	0.94	-0.203	0.18
96-week change (n=24)**				
hs-CRP (µg/mL)	-0.518	0.01	-0.380	0.07
IL-6 (pg/mL)	-0.674	<0.001	-0.503	0.01
sTNFRI (pg/mL)	-0.416	0.04	-0.474	0.02
sTNFRII (pg/mL)	-0.469	0.02	-0.360	0.09
sICAM-1 (ng/mL)	-0.420	0.04	-0.139	0.52

r=Spearman correlation coefficient, SAT=subcutaneous adipose tissue, VAT=visceral adipose tissue, HDL=high-density lipoprotein cholesterol, HOMA-IR=homeostatic model assessment of insulin resistance, hs-CRP=high-sensitivity C-reactive protein, IL-6=interleukin-6, sTNFRI=soluble tumor necrosis factor receptor-1, sTNFRII= soluble tumor necrosis factor receptor-2, sICAM-1=soluble intracellular adhesion molecule-1
*adjusted for baseline SAT or VAT area
**adjusted for week 96 SAT or VAT area

738 HIV IMMUNE DYSREGULATION PREDICTS LEAN TISSUE AND FAT CHANGES DURING CHRONIC DISEASE

Louie M. Gangcuangco, Dominic Chow, Scott A. Souza, Glen M. Chew, Brooks I. Mitchell, Michelle L. D'Antoni, Jason T. Huynh, Lishomwa C. Ndhlovu, Cecilia Shikuma
University of Hawaii at Manoa, Honolulu, HI, USA

Background: Changes in body composition such as fat accumulation and lean tissue loss may impact physical function and mortality. We investigated the association between various HIV-associated immune parameters and 2-year body composition changes assessed by dual-energy x-ray absorptiometry (DXA) among HIV patients on stable ART.
Methods: Longitudinal analysis of HIV+ individuals ≥40 years old on stable ART ≥3 months in the Hawaii Aging with HIV cohort. Multiparametric flow cytometry was performed on cryopreserved year 1 peripheral blood mononuclear cells to quantitate the percentages of monocyte (MO) phenotypes, and T cells expressing activation (HLA-DR/CD38) and exhaustion markers (PD-1/TIM-3/TIGIT). Select plasma soluble biomarkers were measured by Luminex technology. Among subjects not on zidovudine and stavudine, multivariate linear regression analyses were performed to assess the association between T cell subsets with DXA changes.
Results: Of 97 subjects, median age at enrollment was 52 (48, 57) years, BMI 26.5 kg/m2, CD4 count 502 cells/uL, and nadir CD4 count 150 cells/uL. Majority were males (87.6%), Caucasian (56.7%), and 82.5% had undetectable HIV RNA < 50 copies/mL. Median (Q1, Q3) body composition changes: total fat 10.0

(-86.5, 11.4) mg/m2, peripheral fat 10.0 (-29.7, 46.7) mg/m2, truncal fat 10.0 (-48.1, 62.3) mg/m2, and lean tissue -33.0 (-86.8, 23.7) mg/m2. Multivariable linear regression adjusted for age, gender, and undetectable plasma HIV RNA showed that percent lean tissue change [(year3-year1)/year1] was associated with IL-10 (β=0.24, p=0.04), sE-selectin (β=-0.31, p=0.008), percentage of the inflammatory intermediate (CD14+CD16+) M0 (β=-0.24, p=0.04), and TIGIT+TIM-3+ CD8+ T cell (β=-0.52, p=0.03). Total fat change was associated with TIGIT+ CD4+ T cell (β=-0.58, p=0.01), PD-1+ CD4+ T cell (β=-0.46, p=0.04), and TIGIT+PD-1+ CD4+ T cell (β=-0.61, p=0.008). Peripheral fat change was associated with TIGIT+ CD4+ T cell (β=-0.61, p=0.007), PD-1+ CD4+ T cell (β=-0.54, p=0.01), and TIGIT+PD-1+ CD4+ T cell (β=-0.67, p=0.004). Truncal fat change was associated with TIGIT+ CD4+ T cell (β=-0.56, p=0.02) and TIGIT+PD-1+ CD4+ T cell (β=-0.58, p=0.01).

Conclusion: Over two years, modest changes in body composition was seen in our patients with chronic HIV. HIV-associated immune dysregulation, including higher T cell exhaustion, higher intermediate M0 subset levels as well as a pro-inflammatory cytokine profile were associated with lean tissue and fat loss.

739 DISPARITIES IN DIABETES SCREENING AND TREATMENT AMONG PATIENTS RECEIVING HIV CARE

Kassem Bourgi, Peter F. Rebeiro, John R. Koethe, Stephen P. Raffanti, Megan M. Turner, Sally S. Bebawy, Timothy R. Sterling
Vanderbilt University, Nashville, TN, USA

Background: The aging HIV population is at increased risk for diabetes mellitus (DM). Prior studies have demonstrated racial and gender disparities in HIV care. However, data regarding possible disparities in chronic non-communicable diseases, including DM, among persons living with HIV (PLWH) are limited.

Methods: We performed a retrospective cohort study of adult PLWH seen ≥2 times at the Vanderbilt Comprehensive Care Clinic from 2012 to 2015. Patients with prior DM diagnosis, abnormal hemoglobin A1C (A1C), and/or on antihyperglycemic drugs prior to 2012 were excluded. We assessed demographic and disease-specific factors associated with the likelihood of screening and the incidence of impaired glucose control (IGC) (A1C ≥5.7%). In patients identified as diabetic (A1C≥6.5%), we further examined disparities in the initiation of antihyperglycemic medications. We used multiple logistic regression, adjusting for relevant demographic and clinical factors, to evaluate the odds of screening, diagnosis and treatment.

Results: Among 2,944 patients included, 1,649 (56%) were screened for DM. Of those screened, 487 (30%) had incident IGC. Among the 112 (7%) diagnosed with DM, 70% (77/112) were subsequently started on antihyperglycemic drugs. In multivariable analyses, African American (AA) race, male sex, older age, and higher body mass index were significantly associated with higher likelihood of A1C screening, and among those screened, these same factors, with the exception of sex, were associated with a higher incidence of IGC (Table). In contrast, suppressed viremia (i.e., having >50% of HIV-1 RNA measurements <200 copies/mL) was significantly associated with higher likelihood of screening but lower incidence of IGC. While patients on protease inhibitors were more likely to be screened, no significant association was noted between antiretroviral regimen type and the incidence of either IGC or DM. Among patients diagnosed with DM, the odds of starting antihyperglycemic drugs was 52% lower for AA patients, although this was only marginally significant (p=0.08).

Conclusion: In our cohort of PLWH, overall DM screening was suboptimal and racial and sex disparities were apparent. Women were less likely to be screened for DM, and, despite AA patients being more likely to receive DM screening and have incident IGC and DM, they were less likely to be started on antihyperglycemic drugs. The reasons for these disparities should be explored in future studies to ensure improved and equitable DM screening and treatment.

Table. Disparities in Diabetes Screening and Treatment Among Patients Receiving HIV Care

Factor	Screening for Diabetes 1,649/2,944 Adjusted OR	Incident Impaired Glucose Control [α] 487/1,649 Adjusted OR	Incident Diabetes [β] 112/1,649 Adjusted OR	Treated Diabetes 77/112 Adjusted OR
African American race (vs. other)	**1.54***	**2.59***	1.04	0.48[ψ]
Female sex (vs. male)	**0.72***	0.81	0.79	1.51
Age (per 1-year)	**1.01***	**1.04***	**1.03***	0.98
Baseline BMI (per 1-kg/m^2)	**1.05***	**1.08***	**1.07***	
Baseline CD4+ count (per 1-cell/μL)	1.00	1.00	1.00	
Suppressed viremia (vs. unsuppressed) [φ]	**1.68***	**0.70***	0.91	
Clinic visit frequency (per 1-visit/year)	**1.05***			
Ever smoked (vs. never smoked)	1.08			

OR: odds ratio; BMI: body mass index
[α] Hemoglobin A1c ≥ 5.7% [β] Hemoglobin A1c ≥ 6.5%
[φ] suppressed viremia defined as >50% of viral loads in the baseline year <200 copies/mL
* estimates are statistically significant (p<0.05; 95% confidence interval does not contain 1.00)
[ψ] p-value = 0.08

Adjusted regression models for each outcome included those factors with associated point estimates depicted in the table; every adjusted model also included antiretroviral therapy regimen type (non-nucleoside reverse transcriptase inhibitor-, protease inhibitor-, or integrase inhibitor-based).

740 GESTATIONAL DIABETES IN WOMEN ON DOLUTEGRAVIR- OR EFAVIRENZ-BASED ART IN BOTSWANA

Keolebogile N. Mmasa[1], Kathleen M. Powis[2], Joseph Makhema[1], Sikhulile Moyo[1], Mariana Gerschenson[3], Terence Mohammed[1], Erik VanWidenfelt[1], Justine Legbedze[4], Elaine J. Abrams[5], Emilia Bagiella[4], Irwin J. Kurland[6], Mitchell Geffner[7], Jennifer Jao[4]
[1]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [2]Massachusetts General Hospital, Boston, MA, USA, [3]University of Hawaii at Manoa, Honolulu, HI, USA, [4]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [5]ICAP at Columbia University, New York, NY, USA, [6]Albert Einstein College of Medicine, Bronx, NY, USA, [7]University of Southern California, Los Angeles, CA, USA

Background: HIV and antiretroviral therapy (ART), including protease inhibitors, have been associated with gestational diabetes (GDM). Little data exist on GDM in pregnant women living with HIV (PWLHIV) in sub-Saharan Africa or on integrase strand transfer inhibitors such as Dolutegravir (DTG).

Methods: We prospectively enrolled PWLHIV and HIV-uninfected pregnant women >18 years from antenatal clinics in Gaborone, Botswana. Women with documented pre-existing diabetes were excluded. We screened for GDM using a 75-g Oral Glucose Tolerance Test (OGTT) performed at 24-28 weeks (wks) gestational age (GA) or at the earliest prenatal visit for those presenting after 28 wks. Fasting, 1-hour (hr), and 2-hr plasma glucose were measured. GDM was defined as meeting any of the following criteria: fasting glucose >92 mg/dL, 1-hr glucose >180 mg/dL, or 2-hr glucose >153 mg/dL. Data were compared between groups using Wilcoxon, Chi-square, or Fisher's exact test as appropriate. Logistic regression models were fit to assess the association between maternal HIV infection and GDM. Subgroup analyses were performed amongst PWLHIV to assess the association between maternal ART use in pregnancy [DTG- vs. Efavirenz (EFV)-based] and GDM.

Results: Of 178 women enrolled, 53% were PWLHIV. PWLHIV were older than HIV-uninfected women (median age 28 vs 24 yr, $p<0.01$) and more likely to have hypertension prior to pregnancy (5% vs 0%, $p=0.05$). Median gravida was higher in PWLHIV (3 vs 1, $p<0.01$). GA at OGTT and body mass index (BMI) did not differ between the two groups. Of PWLHIV, 95% had an HIV-1 RNA level <400 copies/mL and 95% were on ART (31% on EFV- and 69% on DTG-based ART) at the time of OGTT. All PWLHIV received a backbone ART of tenofovir/emcitritabine. Overall, 10.1% of women in the cohort had GDM. No significant difference between groups was seen (12% for PWLHIV vs 8% among HIV-uninfected women, $p=0.62$). This relationship persisted even after adjusting for confounders. In multivariable analysis, BMI was positively associated with GDM (Table). In addition, among PWLHIV, rates of GDM did not differ between women receiving DTG- vs. EFV-based ART (8% vs 18%, $p=0.27$).

Conclusion: PWLHIV in Botswana receiving EFV- or DTG-based ART were not at increased risk for GDM compared to uninfected women. These results are reassuring. Further studies in larger cohorts are warranted to confirm these findings with expanding global use of DTG in pregnancy.

Table. Logistic Regression Modeling for the Association of Maternal HIV Infection with Gestational Diabetes

Risk Factor	Odds Ratio (95% CI)	
	Unadjusted	Adjusted
Maternal HIV infection	1.42 (0.53, 3.85)	1.18 (0.38, 3.70)
Age, per 1 year increment	1.10 (1.02, 1.18)	1.08 (0.97, 1.20)
Gravidity, per unit increase	1.34 (0.95, 1.87)	0.97 (0.61, 1.54)
BMI at 24-28 weeks, per 1 kg/m² increment	1.11 (1.02, 1.19)	1.10 (1.01, 1.18)
HTN pre-pregnancy	2.29 (0.24, 21.7)	1.05 (0.09, 12.76)

BMI=Body Mass Index; CI=Confidence Interval; HTN=hypertension

741 RECOMMENDED ANTIRETROVIRAL REGIMENS AND DIABETES MELLITUS IN THAI HIV-INFECTED ADULTS

Ninutcha Paengsai[1], Gonzague Jourdain[2], Jean-Yves Mary[3], Nicolas Salvadori[2], Tim R. Cressey[2], Apichat Tantraworasin[1], Romanee Chaiwarith[1], Chureeratana Bowonwatanuwong[4], Sorakij Bhakeecheep[5], Natapong Kosachunhanun[1]
[1]Chiang Mai University, Chiang Mai, Thailand, [2]IRD, Chiang Mai, Thailand, [3]INSERM, Paris, France, [4]Mahidol University, Bangkok, Thailand, [5]National Health Security Office, Chiang Mai, Thailand

Background: Individual antiretroviral (ARV) drugs such as stavudine and didanosine have been associated with a higher risk of type 2 diabetes mellitus (T2DM) in HIV-infected patients. However, the risk of T2DM associated with different ARV drug combinations remains unclear. We investigated the risk of T2DM in Thai adults using the WHO recommended ARV drug combinations.
Methods: We searched all records of HIV infected adults who received antiretroviral therapy within the Thai National AIDS Program from October 1, 2006 to September 30, 2013. Evidence of T2DM diagnosis was defined as either fasting plasma glucose ≥126 mg/dl (following the 2013 American Diabetes Association criteria), or the 2010 WHO ICD10 criteria codes E11-E14, or treatment with anti-diabetic drugs. The T2DM incidence rate was estimated by the number of new diagnoses divided by the total number of person-years of follow-up (PYFU). We analyzed the association between the risk of T2DM and those first line combinations currently recommended by the 2016 WHO HIV treatment guidelines (zidovudine [AZT], lamivudine [3TC], tenofovir [TDF], nevirapine [NVP], efavirenz [EFV] and lopinavir/ritonavir [LPV/r]). We used competing risks survival regression (Fine-Gray), with death consider as a competing event, to identify risk factors of T2DM in univariable and multivariable analyses adjusting for sex, age, history of pancreatitis at baseline and time-updated existence of previous fasting plasma glucose records.
Results: Data of 504,027 PYFU from 130,950 patients, 5,878 cases were diagnosed with T2DM. The overall incidence was of 11.7 per 1,000 PYFU (95% confidence interval [CI] 11.4 to 12.0) and 15.4 per 1,000 PYFU (95% CI 14.9 to 15.9) in patients aged 35 to 60 years. 35,731 patients received one of the recommended WHO combinations. In multivariable analysis, where AZT+3TC+NVP was the reference combination, the following combination were associated with a higher risk of T2DM: TDF+3TC+EFV (adjusted sub-distribution hazard ratio 1.6; 95% CI 1.3 to 2.0), AZT+3TC+LPV/r (1.7, 1.2 to 2.4), AZT+3TC+EFV (2.1, 1.7 to 2.5), and TDF+3TC+LPV/r (2.6, 1.7 to 3.9). The risk was not associated with the use of TDF+3TC+NVP 1.0 (1.0, 0.6 to 1.5).
Conclusion: The incidence of T2DM was higher than in the general population aged 35 to 60 years (7.8-11.4 per 1,000 PYFU). Several of the WHO recommended ARV regimens may associated with an increased risk of T2DM in Thai adults.

742 GLP-1 AND C-PEPTIDE ARE ASSOCIATED WITH INSULIN RESISTANCE AMONG PLWH IN INDIA

Ivan Marbaniang[1], Shashikala Sangle[2], Dileep Kadam[2], Vandana Kulkarni[1], Dhananjay Shere[1], Nikhil Gupte[1], Amita Gupta[3], Vidya Mave[1]
[1]BJGMC Clinical Trials Unit, Pune, India, [2]Byramjee Jeejeebhoy Government Medical College, Pune, India, [3]Johns Hopkins University, Baltimore, MD, USA

Background: Incretins (Glucagon like peptide-1 [GLP-1] and glucose-dependent insulinotropic peptide [GIP]) regulate glucose homeostasis in HIV-uninfected individuals. Inflammation has been implicated as a cause for insulin resistance (IR) among PLWH. Little is known about IR among Asian Indian PLWH, even though India has the highest burden of diabetes and third highest number of PLWH globally. We aimed to assess the relationship between different hormonal and inflammatory markers with IR in Indian PLWH.
Methods: Cross-sectional, conveniently sampled non-diabetic HIV-infected adults (≥18 years) who received HAART≥1 year at a large public sector ART clinic in Pune, India were included. Participants whose Quantitative Insulin Sensitivity Check Index (QUICKI) <0.339 were classified as insulin resistant. Logistic regression was used to identify associations between fasting GIP, GLP-1, leptin, ghrelin, C-peptide, PAI-1 (plasminogen activator inhibitor-1), resistin, visfatin, IL-6, IL-10, TNF-α, MCP-1 and IR.
Results: Of 350 adults included, 115 (33%) were insulin resistant. Median age was 40 years (IQR:35-45), 157 (45%) were male, median time updated CD4 was 471 cells/μL (IQR:298 – 655), 221 (63%) had undetectable viral loads, 73 (21%) were receiving PI based regimens, median fasting insulin was 42 pmol/L (IQR:26-65). When compared to insulin sensitive individuals, those with IR had higher BMI (p<0.001), longer duration of ART use (p=0.008), a higher proportion were hypertensive (p=0.02) and dyslipidemic (p<0.001), had higher GIP (p<0.001), GLP-1 (p<0.001), C-peptide (p<0.001). In multivariable models adjusted for age, sex, BMI, CD4 count, viral load, HAART duration, dyslipidemia, PI use; C-peptide (Odds Ratio (OR), 95% Confidence Interval (95% CI):11.4, 4.9 – 26.3, p<0.001) and GLP-1 (OR, 95% CI: 1.004 , 1.002 – 1.006, p<0.001) were associated with IR. We found no association between GIP, IL-6, IL-10, TNF-α, MCP-1 and IR.
Conclusion: GLP-1 but not GIP was associated with IR. Furthermore, we found a strong association between C-peptide and IR. We found no association between inflammatory markers and IR in our population of non-diabetic PLWH. Elucidation of the pathways regulating IR in PLWH require further investigation.

743 T CELL SUBSETS ASSOCIATED WITH INCIDENT DIABETES RISK IN HIV+ AND HIV− VETERANS

Wyatt J. McDonnell[1], Kathleen McGinnis[2], Kaku So-Armah[3], Melissa Wellons[1], Glory Koerbel[1], Jeffrey Blume[1], Margaret F. Doyle[4], Nels C. Olson[4], Russell Tracy[4], Amy C. Justice[5], Simon Mallal[1], Matthew Freiberg[1], John R. Koethe[1]
[1]Vanderbilt University, Nashville, TN, USA, [2]VA Pittsburgh Healthcare System, Pittsburgh, PA, USA, [3]Boston University, Boston, MA, USA, [4]University of Vermont, Colchester, VT, USA, [5]Yale University, New Haven, CT, USA

Background: There is a growing burden of diabetes in the HIV+ population. In the general population an increased percentage of memory (CD45RO+) T cells is associated with higher diabetes risk, but there are no similar data for HIV+ persons. CD4+ and CD8+ subsets of pro-inflammatory effector memory (TEM) and effector memory RA+ (TEMRA) are described as expanded in HIV+ individuals, often in part in response to human cytomegalovirus. We assessed whether the proportional size of the TEM and TEMRA compartments are associated with an increased risk of incident diabetes in HIV+ and HIV− persons.
Methods: We analyzed data on 601 HIV+ and 322 HIV− subjects from the Veterans Aging Cohort Study – Biomarker Cohort, a longitudinal study of HIV+ veterans and matched HIV− veterans. We measured the proportion of 8 classes of CD4+ and CD8+ T cells: memory CD45RO+; TEM cells CD45RO+CD28−, TEMRA cells CD45RA+CD28−CD57+; and CD57+. Incident diabetes was ascertained by a computer algorithm incorporating ICD-9 codes, serum glucose, hemoglobin A1c%, and prescribed medications. Subjects with diabetes at baseline were excluded. We compared the median baseline proportions of T cell subsets among subjects who developed diabetes versus who did not, stratified by HIV status, using Mann-Whitney U tests.
Results: Subjects were predominantly male (95%) and African-American (72%). Of the selected T cell subsets, no single phenotype was significantly associated with incident diabetes in both the HIV+ and HIV− persons. As reported in prior studies, HIV- subjects who developed diabetes had higher proportions of CD4+ CD45RO+ memory cells. In contrast, HIV+ subjects who developed diabetes had higher proportions of CD8+CD57+ T cells and CD8+ TEMRA cells (see table). We did not adjust for multiple comparisons. Findings were similar in regression models adjusting for age, sex, race, alcohol use, and BMI.
Conclusion: In a preliminary analysis, higher proportions of CD8+CD57+ T cells and expansion of the CD8+ TEMRA compartment are associated with increased risk of developing diabetes in HIV+ persons. This differs from the CD4+ memory cell association observed in HIV- participants in our cohort and similar studies. The mechanisms through which these two pro-inflammatory CD8+ T cell subsets contribute to glucose intolerance, and the potential role of hepatic dysfunction and hepatitis C, in the context of HIV warrant further investigation.

Table

	HIV+			HIV-negative		
T cell subset, median percent	*Incident diabetes*	*No diabetes*	*p-value*	*Incident diabetes*	*No diabetes*	*p-value*
CD4+CD45RO+	57.9	52.9	0.36	62.9	56.8	**0.01**
CD8+CD45RO+	29.9	30.7	0.35	22.4	22.2	0.96
CD4+ T_{EM}	8.8	9.1	0.53	7.9	7.1	0.26
CD8+ T_{EM}	7.6	8.8	0.50	5.4	4.7	0.91
CD4+ T_{EMRA}	5.5	4.7	0.41	2.9	2.3	0.55
CD8+ T_{EMRA}	24.1	18.5	**0.02**	20.0	22.1	0.77
CD4+CD57+	27.1	29.3	0.56	17.4	18.3	0.88
CD8+CD57+	61.2	54.8	**0.03**	50.7	51.6	0.71

744 FOOD INSECURITY IS ASSOCIATED WITH INCREASED INFLAMMATION AMONG HIV-POSITIVE WOMEN

Anna Leddy[1], Annelys Roque[1], Lila A. Sheira[1], Edward A. Frongillo[2], Alan Landay[3], Mardge H. Cohen[3], Phyllis Tien[1], Janet M. Turan[4], Bulent Turan[4], Sheri Weiser[1]

[1]University of California San Francisco, San Francisco, CA, USA, [2]University of South Carolina at Columbia, Columbia, SC, USA, [3]Rush University, Chicago, IL, USA, [4]University of Alabama at Birmingham, Birmingham, AL, USA

Background: Chronic inflammation is associated with worse HIV clinical outcomes including opportunistic infections and non-HIV related comorbidities such as cardiovascular disease (CVD). Limited research has considered how social and structural factors influence chronic inflammation among people living with HIV. Food insecurity, which is associated with HIV-related morbidity and mortality, as well as increased risk of chronic diseases such as diabetes and CVD, may be one such factor. This study assessed whether food insecurity is associated with higher levels of inflammation among a large sample of HIV-infected women in the United States.

Methods: We analyzed cross-sectional data collected from April-September 2015 from participants of the Women's Interagency HIV Study, a multi-site prospective cohort study of women with or at risk for HIV at 9 sites in the United States. Our sample comprised 409 HIV-infected women on antiretroviral therapy, with available fasting blood, and without diagnoses of comorbidities associated with high levels of inflammation (e.g., cancer). The primary predictor was any food insecurity measured using the U.S. Household Food Security Survey. Outcomes were natural log transformations of pro-inflammatory cytokines IL-6 and tumor necrosis factor receptor 1 (TNFR1). We conducted multivariable linear regressions adjusting for age, race/ethnicity, education, income, smoking, and viral load.

Results: Nearly one-third of the women (30.8%) were food insecure. Less than one-quarter (21%) had detectable viral loads and 6% had CD4 less than 200 cells/mm^3. In adjusted analysis, any food insecurity was associated with 1.28 times the level of IL-6 (95% CI: 1.09, 1.51) and 1.14 times the level of TNFR1 (95% CI: 1.06, 1.23). In sensitivity analysis restricted to those who were virally suppressed and with CD4 cell count greater than 500 cells/mm^3, findings remained significant.

Conclusion: Food insecurity is associated with elevations in markers of inflammation in HIV-infected women independent of viral load or CD4 cell counts. Prior research shows that both IL-6 and TNFR1 are associated with increased HIV-related morbidity and mortality as well as increased risk of cardiometabolic disease. Longitudinal research to assess whether IL-6 and TNFR1 are on the causal pathway between food insecurity and negative HIV and chronic disease clinical outcomes is needed.

Table 1. Adjusted associations between food insecurity and IL-6 and TNFR1 among HIV-infected women in visit 42 in the WIHS (N=409)

	IL-6 Relative difference[a] (95% CI)	TNFR1 Relative difference[a] (95% CI)
Age at visit	1.01 (1.00, 1.02)	1.00 (1.00, 1.01)
High school education or higher	1.11 (0.94, 1.31)	1.08 (1.00, 1.17)
Race/ethnicity (White ref)		
Hispanic	1.18 (0.83, 1.66)	0.76 (0.64, 0.90)**
Black/African American	1.33 (1.01, 1.76)*	0.83 (0.72, 0.94)**
Other	1.13 (0.68, 1.88)	0.79 (0.62, 1.01)
Income (≤ $12,000 ref)		
$12,001-$24,000	0.78 (0.65, 0.94)**	1.07 (0.98, 1.17)
≥ $24,001	0.79 (0.65, 0.95)*	0.92 (0.84, 1.00)
Current Smoker	1.01 (0.86, 1.19)	1.07 (0.99, 1.15)
Log viral load	1.04 (1.00, 1.08)*	1.02 (1.01, 1.04)**
Any Food Insecurity	1.28 (1.09, 1.51)**	1.14 (1.06, 1.23)***

*p<0.05; **p<0.01; ***p<0.001

[a] The natural logarithm of IL-6 and TNFR1 was used to satisfy the assumption of a normal distribution, and the factors above are natural exponential "e" of the regression coefficients and are interpreted as multiplicative factors

745 PROGRESSION OF QUANTITATIVE EMPHYSEMA IN A HIV-INFECTED SPANISH COHORT

Francisco Fanjul[1], Gloria Samperiz[2], Helem Haydee Vilchez[1], María Leyes[1], Antoni Campins[1], Maria Angeles Ribas[1], María Peñaranda[1], Javier Murillas[1], Luisa Martin[1], Angel Ríos[1], Meritxell Lopez Zamora[1], Jose Luis Valera[1], Melchor Riera[1]

[1]Hospital Universitario de Son Espases, Palma de Mallorca, Spain, [2]Hospital Universitario Miguel Servet, Zaragoza, Spain

Background: Prevalence of radiological emphysema is higher among patients living with the HIV (PLWH) and could have important clinical implications as it´s been described that emphysema is associated with increased respiratory symptoms, risk of lung neoplasms and mortality when compared to uninfected populations. No previous study has described the radiological progression of emphysema measured quantitatively. Our objective was to report that progression and analyze possible risk factors for accelerated progression

Methods: Prospective cohort study started in 2009 including 285 randomly selected adult PLWH being followed at Hospital Son Espases, Spain. Patients underwent at inclusion high resolution chest tomography (HRCT), lung function tests and clinical questionnaires. Smoking status, epidemiologic and clinical variables were also registered. Between 2014-2016, patients who continued being followed-up were offered to repeat the initial evaluation tests. Quantitative emphysema was calculated as percentage of low-attenuation lung areas below -950 HU (%LLA). Progression of emphysema was compared between groups using Paired-Samples T test, Wilcoxon test or ANCOVA adjusted to basal measure for repeated measures depending on variable distribution. Bivariate and multivariate logistic regression analyses were used to explore the Odds Ratio (OR) between potential risk factors and progression of emphysema.

Results: 285 patients were included in 2009, 29 patients died during followup and 150 patients (55.37 +-6.64 years, 76.5% male) with at least two HRCT were included in the analysis. Smoking status was: 58.4% active, 26.8% former and 14.8% never. Baseline CD4 cell count and CD4/CD8 ratio was 583 cells/ul (IQR 394-814.5) and 0.70 (IQR 0.44-1.01) respectively. 96.4% patients were receiving HAART at inclusion in the cohort and 94.6% had HIV-VL <50 cp/ml. Median quantitative emphysema progression was 0.14% (IQR: 0.00-0.58). Prevalence of patients with >1% emphysema increased from 10,48% to 24,20%. Accumulated incidence rate of >1% emphysema was 20,3 cases/1000 patient-years. Differences between groups and risk factors are represented in [Table 1]

Conclusion: Higher progression of emphysema was associated with: (1) Traditional risk factors as smoking (2) Altered baseline spirometric variables as diffusion capacity, residual volume, FEF25-75 and TLC (3) Previous AIDS defining event (CDC C stage) (4) Lower CD4/CD8 ratio at baseline.

	Variable	Baseline (median %)	*Between groups p*	Progression (absolute change, %)	*Between groups p*	OR unadjusted	*p*	OR adjusted	*p*
CATEGORICAL	**Sex** - Male - Female	0,16 (0,05-0,51) 0,09 (0,02-0,31)	**0,02**	0,14 (0,00-0,59) 0,05 (-0,03-0,50)	0,642	1,6 (0,63-4,05) 1	0,32		
	Smoking - Active - Former - Never	0,15 (0,04-0,41) 0,18 (0,10-0,54) 0,10 (0,04-0,38)	0,11	0,21 (0,02-0,71) 0,14 (-0,05-0,40) 0,01 (-0,03-0,33)	**0,016**	3,65 (1,14-11,75) 1,71 (0,45-6,42) 1	**0,03** 0,42	2,21 (0,229-21,72) 1,29 (0,063-26,672) 1	0,49 0,86
	CDC stage - A - B - C	0,14 (0,04-0,29) 0,15 (0,03-0,44) 0,22 (0,10-0,75)	**0,04**	0,03 (-0,03-0,35) 0,14 (0,01-0,50) 0,28 (0,03-0,83)	**0,03**	1 2,45 (0,87-6,95) 4,53 (1,71-11,99)	0,09 **0,002**	1 2,12 (0,528-8,551) 4,95 (0,997-24,571)	0,289 0,05
QUANTITATIVE	**Age**					1,017 (0,96-1,08)	0,57		
	Baseline CD4					0,998 (0,997-1,000)	**0,03**	0,997 (0,996-0,999)	**0,005**
	Baseline CD4/CD8					0,223 (0,07-0,75)	**0,015**	0,092 (0,015-0,555)	**0,009**
	SGRQ (%) - Symptoms - Activity - Impact					1,016 (0,997-1,036) 0,996 (0,978-1,015) 1,004 (0,975-1,033)	0,09 0,69 0,81		
	KCO (% over predicted)					0,94 (0,91-0,97)	**<0,001**	0,92 (0,88-0,96)	**<0,001**
	FEF25-75 (% over predicted)					0,041 (0,009-0,195)	**<0,001**	0,05 (0,009-0,314)	**0,001**
	TLC					1,07 (1,029-1,113)	**<0,001**	1,09 (1,006-1,182)	**0,036**
	RV					1,02 (1,005-1,037)	**0,008**	1,04 (0,983-1,055)	0,295

746 SMOKING AND ACCELERATED LUNG FUNCTION DECLINE IN THE START PULMONARY SUBSTUDY

David MacDonald[1], Gary Collins[2], Nicholas Ingraham[1], Anne Melzer[1], Kristina Crothers[3], Anchalee Avihingsanon[4], Henry Mugerwa[5], Matti Ristola[6], Jonathan Shuter[7], Ken Kunisaki[1]

[1]Minneapolis VA Health Care System, Minneapolis, MN, USA, [2]University of Minnesota, Minneapolis, MN, USA, [3]University of Washington, Seattle, WA, USA, [4]HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [5]Joint Clinical Research Centre, Kampala, Uganda, [6]Helsinki University Central Hospital, Helsinki, Finland, [7]Montefiore Medical Center, Bronx, NY, USA

Background: Chronic obstructive pulmonary disease (COPD) is a leading cause of death and disability globally. Smoking tobacco is the major risk factor for

COPD, but HIV infection has also been identified as an independent COPD risk factor. There are scant longitudinal data on the pulmonary effects of smoking in HIV. We measured baseline and annual spirometry in the Strategic Timing of Antiretroviral Treatment (START) Pulmonary Substudy and found no difference in lung function decline between persons living with HIV (PLWH) randomized to immediate versus deferred antiretroviral therapy. We used these data to determine the impact of smoking on rate of lung function decline and incident COPD in PLWH.

Methods: We included individuals who contributed at least two spirometry measures during the study, and we restricted this analysis to spirometry data meeting international quality control standards. Slope of forced expiratory volume in 1 second (FEV1) was estimated using a repeated measures model with random intercept and slope and AR(1) covariance matrix adjusted for treatment group (immediate vs. deferred treatment arm of START), age, sex, race, and region. COPD was defined as an FEV1/Forced Vital Capacity (FVC) <lower limit of normal, as defined by Global Lung Function Initiative predictive equations. Incident COPD was modeled using Fisher's exact test and excluded those with COPD at study entry.

Results: Of 1,026 START Pulmonary Substudy participants, 915 were included in the slope analysis and 852 were included in the incident COPD analysis. Median follow up time was 3.9 years. Current smokers and never/former (non) smokers were similar in baseline age (median 36 y), but current smokers were more likely to be white, male, and from Europe/Israel/Australia. Current smokers had a faster rate of decline in FEV1 than non-smokers (-40.7 mL/y vs -25.9 mL/y, p=0.009 for difference) (Table) and more incident COPD, though with borderline statistical significance (9.7% vs 5.8%, p=0.06).

Conclusion: Among PLWH, current smokers experience faster decline in lung function than non-smokers. The magnitude of this difference (14.9 mL/y) is similar to that seen in HIV negative population samples. Although the difference in incident COPD was of borderline statistical significance, short follow-up reduced power for this outcome. These results underscore the need for improved interventions to reduce smoking among PLWH.

Table Comparison of forced expiratory volume in 1 second (FEV_1) slopes by smoking status, adjusted for treatment group (immediate vs. deferred treatment arm of START trial), age, sex, race, and region.

	N	Slope Estimate	95% C.I.	p-value
Smoker	247	-40.7 mL/yr	-50.1 to -31.4	--
Non-Smoker	668	-25.9 mL/yr	-31.8 to -19.9	--
Difference	--	-14.9 mL/yr	-26.0 to -3.8	0.009

747 MARIJUANA SMOKING IMPACTS PULMONARY DISEASE IN HIV-INFECTED MEN

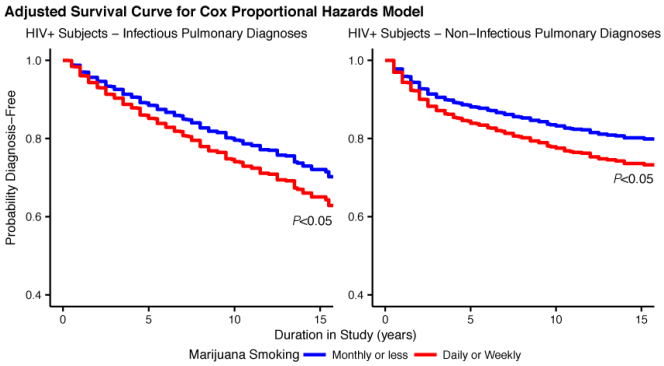
David Lorenz, Dana H. Gabuzda
Dana–Farber Cancer Institute, Boston, MA, USA

Background: Marijuana smoking is prevalent among HIV+ individuals, but its effects on pulmonary disease in the general population and people living with HIV remain unclear. This longitudinal prospective study examined the relationship between marijuana smoking, tobacco smoking, and pulmonary disease in HIV+ and HIV- men in the Multicenter AIDS Cohort Study.

Methods: 1404 HIV+ and 1352 HIV- men with follow-up between 1996-2014 and ≥1 year self-reported marijuana and smoking exposure data from biannual study visits were included (age ≥30, ART use at baseline for HIV+ subjects). Infectious (influenza, bacterial and other pneumonia, tuberculosis) and non-infectious (chronic bronchitis, COPD, emphysema, lung cancer, pulmonary hypertension) events were assessed from self-report and ICD-9 codes. Cox regression was used to estimate the association between marijuana use and first incident infectious and non-infectious pulmonary diagnosis in models adjusted for tobacco smoking, age, race, education, years of follow-up, calendar year, CD4 count, and HIV viral load.

Results: Median baseline age of participants was 43 years (IQR: 38-49); 69% were white, 82% had education >12 years, mean CD4 of HIV+ subjects was 454. 27% of HIV+ subjects reported ≥1 year of daily or weekly marijuana smoking, compared with 18% of HIV- subjects (p<0.001). During 25,788 person-years of follow-up, 407 HIV+ subjects had one or more infectious pulmonary diagnosis (27%, median follow-up 9 years), compared with 262 HIV- subjects (18%, median follow-up 11 years) (p<0.001), while non-infectious pulmonary diagnoses occurred at similar frequency between groups (19%, n=269 vs. 17%, n=232; p=0.19). Daily or weekly marijuana smoking in the prior 6 months was associated with higher adjusted hazard ratio (HR) for both infectious (HR 1.31, 95% CI 1.01-1.71) and non-infectious (HR 1.39, 95% CI 1.02-1.89) pulmonary diagnoses, independent of tobacco smoking and other risk factors. 2-year prior average marijuana use was associated with increased risk for both infectious and non-infectious pulmonary diagnoses when modeled as a continuous variable (HR 1.06, 95% CI 1.02-1.07, and HR 1.07, 95% CI 1.02-1.11, respectively, per 10 days use/month increase). There was no significant association between marijuana use and infectious or non-infectious events in HIV- participants.

Conclusion: Frequent marijuana smoking is a risk factor for infectious and non-infectious pulmonary disease in HIV-infected men, independent of tobacco smoking and other risk factors.



748 HIV INFECTION, SYSTEMIC INFLAMMATION AND LUNG FUNCTION IN RURAL UGANDA

Crystal North[1], Bernard Kakuhikire[2], Alexander C. Tsai[1], David C. Christiani[3], Douglas Kwon[4], Samson Okello[2], Mark J. Siedner[1], Russell Tracy[5]
[1]Massachusetts General Hospital, Boston, MA, USA, [2]Mbarara University of Science and Technology, Mbarara, Uganda, [3]Harvard University, Boston, MA, USA, [4]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [5]University of Vermont, Colchester, VT, USA

Background: Systemic inflammation is associated with impaired lung function in people living with HIV (PLWH) in high-income settings. Little is known about the relationship between systemic inflammation and lung function in PLWH in sub-Saharan Africa.

Methods: We measured lung function and serum hsCRP, IL-6, sCD14 and sCD163 in 126 PLWH at least 40 years of age who were on stable antiretroviral therapy (ART) and 111 age and gender matched HIV uninfected controls in rural Uganda. We modeled the relationship between lung function and systemic inflammation using linear regression, stratified by HIV serostatus, controlling for age, gender, height and smoking history.

Results: All 237 participants completed ATS-acceptable spirometry and 225 (95%) underwent phlebotomy for serum inflammatory markers. Those without phlebotomy results were slightly older than those with results (58 vs. 52 years, p = 0.01), otherwise there were no differences between those who did and did not have phlebotomy results. Median cohort age was 52 years (IQR 48-55), 46% (n=110) were women, and average lung function was normal, with no differences by HIV serostatus. HIV negative participants were more likely than PLWH to be current or former smokers (57%, n=63 vs. 43%, n=54; P=0.03). Most PLWH (92%, n=116) were virally suppressed, median CD4 count was 475 cells/mm^3 (IQR 374-627), and median time on first-line ART was 9 years (IQR 8-10). Median IL-6 and sCD163 concentrations were 0.3795pg/mL (IQR 0.273-0.568) and 454.695ng/mL (IQR 350.19-615.16), with no difference by HIV serostatus. Median hsCRP and sCD14 concentrations were higher among PLHW than HIV negative controls (hsCRP 1.325mg/L (IQR 0.6-3.15) vs. 0.44 (IQR 0.19-0.99), P<0.0001); sCD14 1458.09ng/mL (IQR 1162.735-1720.312) vs. 1213.82 (IQR 1005.92-1406.19), P<0.0001, respectively). In regression models controlled for age, gender, height, and smoking, increased IL-6 and sCD163 were associated with lower lung function among PLWH only, while increased hsCRP was associated with lower lung function in both PLWH and HIV negative controls. There was no association between sCD14 and lung function.

Conclusion: sCD163, IL-6 and hsCRP are associated with lower lung function in older age PLWH in rural Uganda. Further work is necessary to understand the mechanisms underlying differences in systemic inflammatory profiles among PLWH in sub-Saharan Africa and other non-African HIV cohorts.

Table 1: Change in lung function per interquartile range increase in each systemic inflammatory marker

	HIV +				HIV-			
	FEV1 (mL)	FEV1 (%pred)	FVC (mL)	FVC (%pred)	FEV1 (mL)	FEV1 (%pred)	FVC (mL)	FVC (%pred)
hsCRP	-38 (-82 - 6)	-1.7 (-3.3 - 0)	-44 (-89 - 0)	-1.4 (-2.8 - -0.1)*	-66 (-110 - -22)**	-3.0 (-5.0 - -1.1)**	-105 (-158 - -51)***	-3.8 (-5.6 - -1.9)***
IL6	-94 (-172 - -15)*	-3.4 (-6.4 - -0.4)*	-84 (-164- -5)*	-2.5 (-4.9 - -0.1)*	-30 (-77 - 17)	-1.3 (-3.4 - 0.7)	-34 (-93 - 26)	-1.1 (-3.1 - 1.0)
sCD14	33 (-90 - 156)	2.3 (-2.4 - 6.9)	64 (-61 - 188)	2.4 (-1.3 - 6.2)	49 (-38 - 137)	2.0 (-1.9 - 5.9)	70 (-40 - 180)	2.5 (-1.3 - 6.3)
sCD163	-100 (-223 - 24)	-2.8 (-7.6 - 1.9)	-136 (-260 - -12)*	-3.5 (-7.3 - 0.3)	-46 (-134 - 43)	-3.1 (-7.0 - 0.9)	-70 (-182 - 41)	- 3.4 (-7.2 - 0.4)

Effect estimate (95% confidence interval); All models adjusted for age, gender, height, smoking (current/former/never), and smoking duration (years); FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity; mL = milliliters; %pred = percent predicted using NHANESIII prediction equations
*p < 0.05, **p < 0.01, ***p < 0.001

749 DIFFERENCES IN THE ADENOSINE SIGNALING PATHWAY AMONG HIV+ INDIVIDUALS WITH COPD

Kiran Bandi, Seyed M. Nouraie, Edwin Jackson, Peter Nam, Delbert Gillespie, Cynthia Klamar-Blain, Cathy Kessinger, Sharon Riddler, Alison Morris, Bernard J. Macatangay
University of Pittsburgh, Pittsburgh, PA, USA

Background: Aberrant purinergic signaling is believed to play a role in COPD pathogenesis. CD39 has ATPase activity and is hypothesized to be protective in cigarette smoke-induced lung damage. CD73 is the rate-limiting enzyme that breaks down AMP to adenosine (ADO), which in turn has anti-inflammatory effects. CD26 binds ADO deaminase which metabolizes ADO and can influence extracellular ADO levels.

Methods: Using flow cytometry, we evaluated differences in the expression of CD39, CD73, and CD26 on peripheral CD4+/CD8+ T cells among ART-treated HIV(+) and HIV(-) individuals with and without COPD [HIV(+)COPD(+) n=16; HIV(+)COPD(-) n=14; HIV(-)COPD(+) n=11; HIV(-COPD(-) n=12], and determined whether expression is associated with plasma levels of inosine (surrogate for ADO; INO) obtained by mass spectrometry and with pulmonary function testing (PFT; forced expiratory volume, FEV1; forced vital capacity; diffusing capacity).

Results: With CD39 expression, HIV(-)COPD(+) had a trend for increased %CD4+CD39+ T cells compared to HIV(-)COPD(-) [12.7% vs 8.7, p=0.07; Kruskal-Wallis with Dunn's post-test]. However, HIV(+)COPD(+) did not have higher %CD4+CD39+ T cells compared to HIV(+)COPD(-). There were no associations between CD39 expression and PFTs. With CD73 expression, HIV(+) participants with or without COPD, had lower %CD4+CD73+ [p values=0.004-0.006] and %CD8+CD73+ [p values=0.001-0.015] compared to all HIV(-) participants. In all participants with COPD, %CD8+CD73+ T cells significantly correlated with FEV1 (Spearman r=0.45, p=0.01). This correlation was not observed among all COPD(-) participants. Expression of CD39 or CD73 did not correlate with plasma INO levels. With CD26 expression, HIV(+)COPD(+) had lower %CD4+CD26+ than HIV(+)COPD(-) [p=0.035], HIV(-)COPD(+) [p=0.0005], and HIV(-)COPD(-) [p=0.02]. Similarly, %CD8+CD73+ was lower in the HIV(+)COPD(+) group compared to the HIV(-) groups, but similar to the HIV(+)COPD(-) group. In all participants, %CD4+CD26+ T cells modestly correlated with INO levels (r=0.25, p=0.09); among all COPD(+) participants, INO levels in turn, modestly correlated with FEV1 (r=0.35, p=0.06).

Conclusion: Compared to HIV(-)COPD(+) individuals, HIV(+)COPD(+) individuals do not have increased CD39 expression relative to HIV(+)COPD(-) individuals and have lower frequencies of CD4+ and CD8+ T cells expressing CD73 or CD26. Given these differences, COPD therapeutic strategies targeting the ADO signaling pathway may result in different outcomes for the HIV(+) population.

750 PREDICTORS OF AIRFLOW OBSTRUCTION IN AN HIV TERTIARY CARE CLINIC

Cecilia Costiniuk[1], Roy Nitulescu[1], Christina de Castro[1], Natale Wasef[1], Syim Salahuddin[1], Jean-Pierre Routy[1], Bertrand Lebouché[1], Joseph Cox[1], Benjamin M. Smith[1], Jason Szabo[1], Alexandra de Pokomandy[1], Chris Tsoukas[2], Mohammad-Ali Jenabian[3], Jean Bourbeau[1], Marina Klein[1]
[1]McGill University Health Centre, Glen site, Montreal, QC, Canada, [2]McGill University, Montreal, QC, Canada, [3]Université du Québec à Montréal, Montreal, QC, Canada

Background: The reported prevalence of Chronic Obstructive Pulmonary Disease(COPD) in people living with HIV(PLWH) varies widely(7-60%) depending on the study population and methods used, underscoring the uncertainty of the estimates. Our objective was to estimate the prevalence of COPD in unselected PLWH and identify characteristics that increase the risk of non-reversible airflow obstruction using spirometry-the gold standard-in order to guide screening strategies for COPD.

Methods: This study was conducted at the Chronic Viral Illness Service at the McGill University Health Centre in Montreal, Canada(population≈2000 PLWH). All persons ≥18 years of age with HIV were invited to participate, regardless of smoking status or history of known COPD/asthma. Individuals with acute respiratory infection were excluded. Individuals underwent standard spirometric testing both pre and post salbutamol bronchodilator and completed the MRC dyspnea scale, which rates the severity of dyspnea on a scale of 1-5. The presence of COPD(FEV1/FEV<0.7 post-bronchodilator) was determined and multivariate logistic regression was used to evaluate risk factors associated with COPD, reported as adjusted odds ratios(aOR).

Results: There were 369 participants of whom 39(11%) had COPD on spirometry. Median age (Q1;Q3) was 51(44;58), and 30% were female. Most were Caucasian(57%), followed by Black African (22%). Participants had a median duration of HIV of 15 years(9; 22) and 94% were on antiretrovirals for a median duration of 10(6;16) years with 92% virally suppressed. Median CD4 count was 594(440;786) and nadir CD4 count was 234 (128;376) cells/uL. Median MRC dyspnea score was 1(1;2), implying a low burden of dyspnea. Results of spirometry testing are depicted in Table 1 and demonstrate a high proportion of patients with reversible airflow obstruction. The following risk factors for COPD were assessed: smoking history(aOR: 2.96, 95% CI: [1.36; 7.03]), age(2.02 [1.41; 2.97]), female sex(0.72 [0.23; 1.9]), and higher nadir CD4 count(0.85 [0.69; 1.03] per 100 cells).

Conclusion: Both smoking status and older age independently predicted the presence of non-reversible airflow obstruction in PLWH. Low nadir CD4 appeared to be associated with the presence of COPD. These findings suggest that PLWH who are ≥50 years, smokers and those with nadir CD4 counts ≤200 cells/μL should undergo spirometry screening for COPD. The high rate of reversible airflow obstruction is a novel finding and merits further exploration.

Table 1: Results of Spirometry Testing (N=369)

FEV1 % predicted pre-bronchodilator (%) (median (Q1; Q3))	91 (80; 102)
FEV1/FVC ratio (%) (median (Q1; Q3))	
Pre-bronchodilator / Post-bronchodilator	79 (74; 83) / 82 (76; 85)
FEV_1/FCV <70% post-bronchodilator (n (%))	39 (11%)
Mild / Moderate / Severe / Very Severe	12 (31%) / 24 (62%) / 3 (8%) / 0 (0%)
FEV_1/FEV <70% pre- and post-bronchodilator (n (%))	33 (9%)
Bronchodilator reversibility	
>12% increase FEV1 (pre to post)	11 (33%)
>200 mL increase in FEV1 (pre to post)	18 (55%)
>200 ml increase in FVC (pre to post)	14 (42%)
At least one of the above criteria	20 (61%)
At least two of the above criteria	13 (39%)

751 HIV IS INDEPENDENTLY ASSOCIATED WITH HIGHER ALPHA-1 ANTITRYPSIN

Rebekka F. Thudium[1], Jens D. Lundgren[1], Børge Nordestgaard[2], Jan Gerstoft[1], Susanne D. Nielsen[1], Andreas Ronit[1]
[1]Rigshospitalet, Copenhagen, Denmark, [2]University of Copenhagen, Copenhagen, Denmark

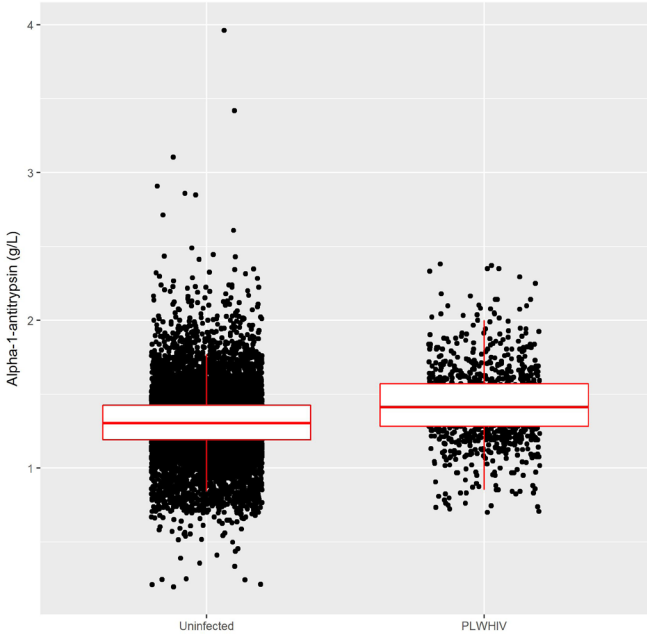
Background: Alpha-1 Antitrypsin (AAT) is the most abundant circulating serine protease inhibitor and its main function is to protect the lung against proteolytic damage. Little is known about AAT in people living with HIV (PLWH), but in theory: i) AAT may be associated with lower pulmonary function, ii) as an inducer of HIV inhibition in vitro, AAT may be associated with immune status, iii) as an acute phase reactant, AAT may be a novel biomarker for non-AIDS events. We measured AAT in PLWH and in uninfected controls and studied associations with pulmonary function and CD4 T-cell counts.

Methods: Using data from the Copenhagen comorbidity in HIV infection (COCOMO) study we assessed AAT levels in PLWH and age and sex matched uninfected controls. Low AAT was defined as below 1.0 g/L. Pulmonary function was measured by spirometry and airflow obstruction was defined by the lower limit of normal (LLN) of FEV1/FVC and by FEV1/FVC<70% plus FEV1-predicted <80% (fixed). We assessed whether AAT to a greater extend contribute to low FEV1-predicted in PLWH than in uninfected controls by studying the interaction

between HIV status and AAT in a linear regression model adjusting for age, sex, ethnicity and cumulative smoking. Controlling for the same variables, we assessed whether AAT was associated with current CD4 or CD4 nadir. Finally, we assessed whether HIV was independently associated with AAT controlling for the same variables and hsCRP.

Results: AAT was measured in 1011 PLWH and 11962 uninfected controls with mean (SD) age of 52 (11.5) and predominantly males (81.7%). PLWH had a higher median (interquartile range) AAT: 1.4 [95%CI: 1.3-1.6] vs. 1.3 [1.2-1-4], (p<0.0001). A total of 4.2% [3.1-5.6] PLWH and 6.6% [6.2-7.1] uninfected controls had low levels of AAT (p<0.01). Low AAT were not more common in PLWH with airflow obstruction assessed by LLN (p=0.57) or the fixed criterion (p=0.80). The effect of AAT on FEV1-predicted was similar in PLWH and uninfected controls (p-interaction=0.66). Also, AAT levels (per 1 g/L) did not affect current CD4 (adjusted β=12.2 [-86.2-61.5], p=0.74) or CD4 nadir (adjusted β= 6.7 [-38.9-52.2], p=0.77). HIV status was independently associated with higher AAT levels adjusted β (0.1 [0.01-1.36, p<0.001]).

Conclusion: AAT did not explain the excess pulmonary morbidity previously observed in PLWH. Also, AAT was not associated with immunological status. However, HIV was independently associated with higher levels of AAT and may be an interesting biomarker for other non-AIDS events.



752 DEPRESSION IS INDEPENDENTLY ASSOCIATED WITH NEAR DOUBLING OF HIV VIRAL LOAD

Susan M. Meffert[1], Thomas C. Neylan[1], Charles E. McCulloch[1], Jonah Jonah Maswai[2], John Owuoth[3], Francis Kiweewa[4], Lucas Maganga[5], Victor Valcour[1], Julie Ake[6]

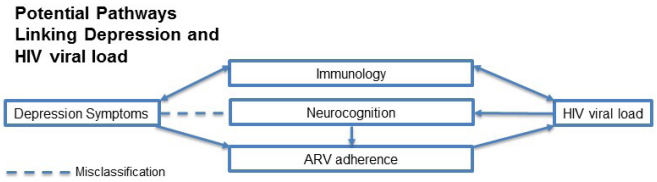
[1]University of California San Francisco, San Francisco, CA, USA, [2]KEMRI/Walter Reed Proj, Kericho, Kenya, [3]KEMRI/Walter Reed Proj, Kisumu, Kenya, [4]Makerere Univ Walter Reed Proj, Kampala, Uganda, [5]Mbeya Medical Research Programme, Mbeya, Tanzania, United Republic of, [6]US Military HIV Research Program, Bethesda, MD, USA

Background: Depression is a common co-morbidity for People Living With HIV (PLWH) and is associated with non-adherence to antiretrovirals (ARVs). Psychosocial interventions often focus on ARV adherence. However, depression may be associated with HIV outcomes (e.g., viral load) through other pathways, as well (Figure).

Methods: The African Cohort Study (AFRICOS) is prospective longitudinal cohort study at eleven HIV care sites in Kenya, Tanzania, Uganda, and Nigeria. For cultural consistency, we examined East African sites (Kenya, Uganda and Tanzania) (n=2,335). Using baseline data from HIV+ AFRICOS participants, all of whom are engaged in HIV care, we assessed cross-sectional relationships between depression, ARV adherence, HIV viral load and cognition. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale Revised (diagnostic cut-off > 16). Logistic regression was used to model self-report of complete/incomplete ARV adherence over the past month, and linear regression was used to model the $\log_{10}$ of HIV viral load and CESD-items (individually) among participants on ARVs for 6 months or more. Covariates included demographics, purchasing power, cognitive impairment and ARV adherence.

Results: The point prevalence of depression is 18% to 25% among East African HIV+ AFRICOS study participants-all enrolled in HIV care. Depression is associated with decreased ARV adherence (OR 0.39-0.88, p = 0.01) independently of cognitive impairment. Depression is associated with a nearly double the viral load of non-depressed counterparts, independently of ARV adherence and cognitive impairment (proportional increase 1.42-2.34, p= 0.00) for participants on ARVs > 6 months. Seven of the nine depression symptom clusters are significantly associated with viral load independently of ARV adherence and cognition for participants on ARVs > 6 months.

Conclusion: I HIV+ East African AFRICOS participants enrolled in HIV care have high prevalence of depression. I Depression is associated with viral load independently of pathways involved with ARV adherence or misclassification of cognitive impairment. I Depression and HIV viral load is associated across a wide spectrum of depressive symptoms, implying that comprehensive depression treatment is necessary to fully address the relationship between HIV viral load and depression. Future research should include scalable, evidence-based depression treatment for PLWH with assessment of impact on HIV viral load.



753 DEPRESSION IS ASSOCIATED WITH MISSED VISITS, EMERGENCY ROOM UTILIZATION, AND DRUG USE

Mamta K. Jain[1], Yordanos Tiruneh[2], Piper Duarte[3], Amneris Luque[1], Ank E. Nijhawan[1]

[1]University of Texas Southwestern, Dallas, TX, USA, [2]University of Texas at San Antonio, San Antonio, TX, USA, [3]Parkland Health and Hospital Systems, Dallas, TX, USA

Background: The US Preventive Service Task Force recommends screening all patients for depression. Depression has been associated with unsuppressed viral load. We collected data obtained from nurse-administered clinical tools in an urban HIV clinic to characterize the relationship of depression, HIV, and health care utilization.

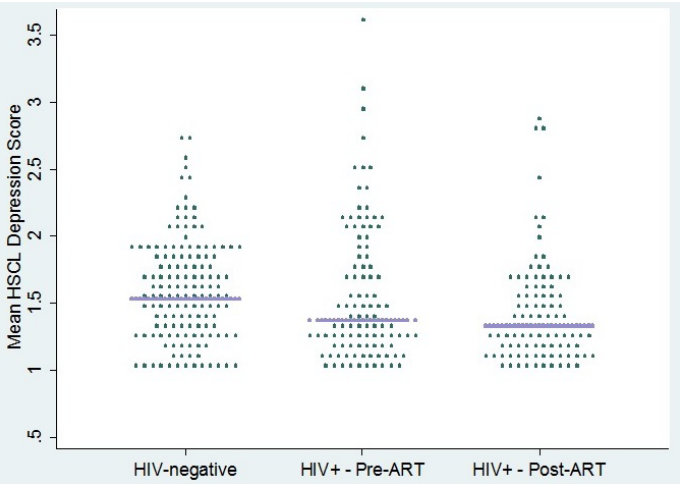
Methods: We retrospectively examined patients who had a Patient Health Questionnaire-9 (PHQ-9) administered during an HIV clinic visit to screen for depression symptoms. We also collected drug screen data from the Substance Abuse and Mental Illness Symptoms Screener (SAMISS). Data from 2014 and 2015 included demographics, HIV viral load, CD4 cell count, number of hospitalizations, number of missed visits, number of emergency room visits, and proportion of overall visits attended. Predictors of depression (defined as PHQ-9 ≥10) were examined by univariate and multivariate logistic regression.

Results: Of 5127 HIV-infected patients in our cohort, 21% had mild depression, 11% moderate depression, 7% moderately severe, and 6% severe. Overall the cohort was majority male (69%), black (56%) and 46% had viral suppression. Compared to those with CD4>500 cells/μL, those with CD4 between 351-500 cells/μL (Odds Ratio (OR) 0.89, 95% CI: 0.74-1.06) and 200 to 350 cells/μL (OR 0.95, 95% CI: 0.79-1.15) had no association with PHQ-9 score ≥10. Those with CD4 between 51-200 cells/μL (OR 1.44, 95% CI: 1.20-1.74) and <50 cells/μL (OR 1.78,95% CI: 1.42-2.26) were significantly more likely to have depression. Those with depression were significantly more likely to be female, have injection drug use or MSM as an HIV risk factor compared to heterosexual, be white compared to black, have a positive score for substance use by SAMISS, have a CD4 <200 cells/μL, have had one or more emergency room visits, and have missed one or more routine clinic visits (see Table). Depression was not associated with viral suppression.

Conclusion: Moderate to severe depression is prevalent among HIV clinic patients. Certain subgroups- women, whites and blacks (compared to Hispanics) and those with active substance use--were more likely to report depression. Depression was associated with missed routine clinic follow-up visits, more

frequent emergency room visits, and lower CD4 counts, but not with viral suppression. Further studies are needed to better understand who is at risk for depression and how depression affects healthcare utilization and HIV health outcomes.

Table	Overall n = 5127 N (%)	Moderate to severe depression n= 1272 N (%)	Odds Ratio (95% CI)	P value	Adjusted Odds Ratio (95% CI)	P value
Gender						
Male	3551 (69)	832 (65)	Reference	--		
Female	1497 (29)	418 (33)	1.27 (1.10-1.45)	<0.001	1.70 (1.34-2.14)	<0.001
Transgender	79 (1)	21 (2)	1.18 (0.71-1.96)	0.51	1.05 (0.58-1.90)	0.86
Age						
<30	747 (15)	192 (15)	1.06 (0.88-1.28)	0.52		
30-49	2583 (50)	634 (50)	Reference			
>50	1797 (35)	445 (35)	1.01 (0.88-1.16)	0.87		
HIV Risk Factor						
Heterosexual	2329 (46)	547 (43)	Reference	--	Reference	
IDU	309 (6)	106 (8)	1.70 (1.32-2.19)	<0.001	1.67 (1.17-2.38)	0.005
MSM	2289 (45)	566 (45)	1.07 (.94-1.22)	0.32	1.35 (1.08-1.79)	0.009
Other/unknown	200 (4)	52 (4)	1.14 (0.82-1.59)	0.42	1.01 (0.64-1.59)	0.98
Race/ethnicity						
Black	2885 (56)	719 (57)	Reference	--	Reference	
White	1251 (24)	367 (29)	1.25 (1.08-1.45)	0.003	1.22 (1.00-1.49)	0.05
Hispanic	912 (18)	172 (14)	0.70 (0.58-0.84)	<0.001	0.75 (0.58-.95)	0.02
Other	79 (2)	13 (1)	0.59 (0.32-1.08)	0.09	0.56 (0.25-1.28)	0.17
Viral suppression	2336 (46)	525 (41)	0.80 (0.70-0.90)	<0.001	1.00 (0.84-1.19)	0.99
CD4<200	1224 (24)	390 (31)	1.62 (1.40-1.86)	<0.001	1.36 (1.12-1.64)	0.002
Positive SAMISS drug screen	251 (8)	116 (14)	2.7 (2.09-3.53)	<0.001	2.32 (1.75-3.08)	<0.001
Positive SAMISS alcohol screen	378 (12)	113 (14)	1.27 (1.00-1.61)	0.05	1.15 (0.89-1.48)	0.28
Emergency room visit during year	1363 (27)	461 (36)	1.86 (1.62-2.13)	<0.001	1.64 (1.38-1.96)	<0.001
Hospitalized inpatient during year	699 (14)	240 (19)	1.72 (1.45-2.04)	<0.001	1.25 (0.99-1.59)	0.06
Show rate >80%	2782 (54)	592 (47)	0.66 (0.58-.0.75)	<0.001	0.90 (0.71-1.13)	0.36
Any missed visit in a year	2452 (48)	704 (55)	1.50 (1.32-1.70)	<0.001	1.26(1.01-1.59)	0.04



754 DEPRESSIVE SYMPTOMS AND HIV INFECTION IN AN AGING UGANDAN COHORT

Jennifer Manne-Goehler[1], Bernard Kakuhikire[2], Alexander C. Tsai[3], Till Bärnighausen[4], Samson Okello[2], Mark J. Siedner[3]
[1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]Mbarara University of Science and Technology, Mbarara, Uganda, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Heidelberg University, Heidelberg, Germany

Background: The measured prevalence of major depressive disorder has increased in sub-Saharan Africa in recent years, and depression is a common comorbidity among people living with HIV (PLWH) in the region. However, there are limited data regarding relationships between depression, engagement in HIV care, and use of antiretroviral therapy (ART), especially in low- and middle-income settings. This study aims to characterize associations between HIV infection & depressive symptoms in a cohort of aging PLWH on ART and among sex and age-matched, population-based, HIV-negative comparators.
Methods: We used data from the Ugandan Non-Communicable Diseases & Aging Cohort Study (UGANDAC) to estimate the association between HIV infection, ART use, and depressive symptoms. The study included 154 PLWH and 142 community-based, HIV-negative controls. The Hopkins Checklist (HSCL), a 15-item depression scale, was used to screen for probable depression. In a subset of PLWH (n=102), a pre-ART depression score was also available. We estimated differences in depressive symptoms by HIV status, comparing both pre-ART and post-ART depression scores among PLWH with those of the HIV-negative group. We then used multivariable adjusted log binomial regression to estimate the association between HIV infection and probable depression, adjusting for age, sex, education and wealth.
Results: PLWH on ART had significantly lower depression symptom scores than controls (median score: 1.38 [IQR 1.20 – 1.67] v. 1.53 [IQR 1.27 – 1.87], p=0.006) and a lower prevalence of probable depression (21.4 v. 33.8%, p=0.017). Among 102 PLWH with pre-ART depression screening scores available, the median depression score prior to ART was not significantly different from the median score in the HIV-negative group (1.38 v. 1.53, p=0.063) (see Figure 1). In multivariable adjusted log binomial regression models, PLWH on ART had a lower prevalence of probable depression than HIV-negative controls [adjusted prevalence ratio: 0.68 (95% CI: 0.47 – 0.99)].
Conclusion: Depressive symptoms were similar among pre-treatment PLWH & HIV-negative comparators. However, after enrollment in ART care, we found significantly lower depression scores and lower odds of probable depression, as compared to age & sex-matched, HIV-negative comparators. These data add to a growing body of literature showing improved physical & mental health indicators among PLWH on ART in sub-Saharan Africa. Further research is needed to elucidate the mechanisms underlying this phenomenon.

755 EFFECTS OF HIV STATUS ON FUNCTIONAL BENEFITS OF EXERCISE IN OLDER SEDENTARY ADULTS

Kristine M. Erlandson[1], Samantha MaWhinney[1], Melissa P. Wilson[1], Lilyana Gross[1], Sean A. McCandless[1], Wendy M. Kohrt[1], Robert Schwartz[1], Todd T. Brown[2], Thomas Campbell[1], Catherine M. Jankowski[1]
[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [2]Johns Hopkins Hospital, Baltimore, MD, USA

Background: Whether older, sedentary HIV+ adults can achieve similar functional benefits with exercise as their HIV- peers and the ideal intensity of exercise needed for these benefits is not known.
Methods: Older (50-75 years of age) sedentary HIV+ (undetectable HIV-1 RNA on antiretroviral therapy for ≥ 2 years) and HIV- participants were recruited for a 24 wk supervised, 3x/week cardiovascular and resistance exercise program. Participants exercised at moderate intensity for 0-12 wks, then were randomized to moderate (50% V02 maximum [V02max], 60-70% 1-repetition maximum [RM]) or high intensity (70% V02max, ≥80% 1-RM) exercise for an additional 12 wks. 10x chair rise time and 1-RM were measured every 3 wks; V02max and 400-m walk time at wk 0, 12, and 24. Outcomes by serostatus and exercise intensity were compared using linear and mixed effects regression models and adjusted for baseline values (for wk 0-12) or wk 12 (for 12-24 wk change).
Results: 28 HIV+ and 31 HIV- participants completed 12 wks; 27 HIV+ (12 moderate/15 high) and 30 HIV- (14 moderate/16 high) completed 24 wks of exercise. HIV+ participants were thinner (BMI 27 vs 30 kg/m2), younger (57 vs 60 years), less likely never smokers (39 vs 58%), and had more comorbidities (79 vs 55% with ≥3) compared to HIV-. Among HIV+ participants the CD4+ T-cell was 564 (467,682) cells/mm^3, and mean time since HIV diagnosis was 20 (17,23) yrs. At week 0, HIV+ participants had faster 400-m walk time but slower 10x chair rise (Table) compared to HIV- participants. Both groups had significant improvements in all physical function measures except V02max from 12-24 wks in HIV+ for moderate intensity (Table). HIV+ participants had significantly greater improvements than HIV- on V02 max between wk 0-12 (5 [0,10]% greater; p=0.04) and in 400-m walk between weeks 12-24 (-3 [-5,0]% faster; p=0.03). An interaction between exercise intensity and HIV serostatus was significant only on 1-RM measures: HIV+/high-intensity exercisers gained significantly more strength than HIV+/moderate exercises in bench press (6 [0, 12]% greater) and leg press (10 [2, 17]% greater; both p<0.05); HIV- had similar gains regardless of intensity.
Conclusion: Exercise training reverses physical function impairment to a similar extent in older, sedentary HIV+ and HIV- adults. HIV+ persons randomized to high intensity exercise showed greater gains in strength than HIV- persons, which may suggest an added benefit of high intensity exercise among older sedentary HIV+ adults.

Table. Baseline and % Change in Physical Function by HIV Serostatus and by 12-week Randomized Intensity

Out-come	HIV+ Week 0	HIV- Week 0	P value	Week	% Change in HIV+	% Change in HIV-	% Change in Mod Intensity	% Change in High Intensity
Chair rise	20 sec (18,22)	17 sec (16,19)	0.04	0-12	-20 (-24,-16)**	-20 (24,-16)**		
				12-24	-10 (-14,-5)**	-8 (-12,-4)**	-11 (-15,-7)**	-6 (-10,02)**
Bench press	106 lbs (94,120)	120 lbs (108,135)	0.10	0-12	27 (22,31)**	28 (24,32)**		
				12-24	16 (12,20)**	14 (10,17)**	14 (11,18)**	15 (12,19)**
Leg press	271 lbs (241,305)	312 lbs (284,342)	0.06	0-12	16 (11,22)**	16 (11,22)**		
				12-24	8 (3,12)**	9 (5,14)**	6 (2,11)**	11 (6,15)**
VO_2 max	26 ml/kg/min (24,29)	25 ml/kg/min (23,28)	0.58	0-12	11 (7, 15)**	6 (3, 9)**		
				12-24	3 (0, 7)#	3 (0,7)*	3 (-1, 6)	4 (0, 7)*
400-m walk	230 sec (220,240)	251 sec (241,262)	<0.01	0-12	-6 (-8, -3)**	-5 (-7, -3)**		
				12-24	-5 (-7, -2)**	-2 (-4, 0)*	-2 (-4, 0)*	-5 (-6, -3)**

All participants were on moderate intensity exercise weeks 0-12, then randomized to moderate or high intensity exercise for weeks 12-24. Values presented as geometric mean (95% confidence interval) or percent estimates (95% confidence interval); P values represent comparisons of baseline by HIV serostatus; * p <0.05, ** p<0.001, #p=0.07 for change from week 0 (adjusted for week 0 value), or change from week 12 (adjusted for week 12 value).

756 THE ASSOCIATION OF PAIN AND LONG-TERM OPIOID THERAPY WITH HIV TREATMENT OUTCOMES

Jessica Merlin[1], Dustin M. Long[1], William Becker[2], Edward R. Cachay[3], Katerina A. Christopoulos[4], Heidi M. Crane[5], E. J. Edelman[2], Richard Harding[6], Jane Liebschutz[7], W. C. Mathews[3], Michael J. Mugavero[1], Sonia Napravnik[8], Michael Saag[1], Joanna Starrels[9], **Robert Gross**[10]

[1]University of Alabama at Birmingham, Birmingham, AL, USA, [2]Yale University, New Haven, CT, USA, [3]University of California San Diego, San Diego, CA, USA, [4]University of California San Francisco, San Francisco, CA, USA, [5]University of Washington, Seattle, WA, USA, [6]King's College Hospital, London, UK, [7]University of Pittsburgh, Pittsburgh, PA, USA, [8]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [9]Albert Einstein College of Medicine, Bronx, NY, USA, [10]University of Pennsylvania, Philadelphia, PA, USA

Background: Chronic pain is common in persons living with HIV (PLWH) and is associated with impaired function and high care utilization. Few studies have investigated the impact of this important comorbidity on HIV outcomes. Long-term opioid therapy (LTOT) is commonly prescribed for chronic pain despite lack of evidence of benefit and known risks of misuse and addiction, but may keep patients in care due to the need for regular visits to obtain refills. We aimed to determine the impact of chronic pain and LTOT on HIV outcomes.

Methods: Between 7/2015-7/2016, we assessed pain in PLWH followed at 5 Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) sites using the Brief Chronic Pain Questionnaire (BCPQ) and the Pain and pain's impact on Enjoyment of life and General activity (PEG) questionnaire (scored 1-10). Chronic pain was defined as both ≥ moderate pain for ≥ 3 months on the BCPQ and ≥ 4/10 on the PEG. We used logistic regression to assess the relationship between chronic pain at an index visit and HIV outcomes over the subsequent year: plasma HIV RNA > 1000 copies/mL that did not suppress within a month (virologic failure) and no-shows without another visit within the next month (a measure of suboptimal retention). We also assessed the interaction between chronic pain and LTOT, defined as ≥ 90 consecutive days of prescribed opioids, for both outcomes.

Results: Among 2334 participants, 44% were ≥ 50 years old, 16% were female, 12% had virologic failure, 25% had chronic pain, and 19% were on LTOT. Chronic pain was associated with virologic failure (aOR 1.64, 95% CI 1.21-2.21, p=0.0014) and no-shows (aOR 1.45, 95% CI 1.15, 1.82, OR p=0.0016). Among PLWH with chronic pain, LTOT was not protective against no-shows (aOR 1.01, 95% CI 0.7-1.45, p=0.98), but was protective against virologic failure (aOR 0.53, 95% CI 0.33-0.88, p=0.013).

Conclusion: We found chronic pain to be associated with virologic failure. While virologic failure could lead to chronic pain, we hypothesize that chronic pain leads to virologic failure, as has been shown with similar comorbidities such as depression. If future studies confirm this hypothesis, potential next steps include developing chronic pain treatments in PLWH, and if effective, investigating whether they improve HIV-related outcomes. The protective association of LTOT on virologic failure warrants further research into the patient's lived experience and doctor-patient relationship to identify potential mechanisms of this effect.

757 REVERSING ACCELERATED AGING IN HIV PATIENTS: METABOLIC AND MITOCHONDRIAL MECHANISMS

Rajagopal V. Sekhar, Jean W. Hsu, James Suliburk, Ruya Liu, Charles G. Minard, Vijay K. Yechoor, Farook Jahoor, Chun Liu

Baylor College of Medicine, Houston, TX, USA

Background: HIV-infected patients are reported to have 'accelerated aging' based on rapid physical and functional decline. Such patients have muscle weakness, decreased exercise capacity, fat accumulation, muscle loss and impaired mitochondrial fuel oxidation (MFO), but underlying mechanisms are unknown and interventions lacking. We investigated deficiency of the intracellular antioxidant glutathione, GSH) and impaired MFO as metabolic and mitochondrial mechanisms contributing to accelerated aging and functional decline in HIV patients.

Methods: An open-label clinical trial (NCT02348775) in 8 older GSH-deficient HIV-infected patients of both genders (aged 50-64y), compared to 8 age, gender and BMI-matched non-HIV controls. HIV subjects were studied before and after 12-weeks of oral supplementation with N-acetylcysteine plus glycine (NAC-Gly, provided as GSH precursors), and again 8-weeks after stopping supplementation. Controls were not supplemented. All subjects underwent muscle biopsy, calorimetry, physical function measures (gait speed, chair-rise test, 6-min walk, grip strength), DEXA scan, anthropometry, and infusion of 2H3-3-methylhistidine tracer to measure the following: glutathione levels in muscle and red-cells, MFO, muscle strength, exercise capacity, body composition, waist-circumference and rate of muscle protein breakdown.

Results: Compared to non-HIV controls, 'older' HIV patients had significantly lower intracellular GSH, impaired MFO, lower gait speed, grip strength and 6-min walk times, higher fat mass and waist circumference, and increased muscle protein breakdown. Molecular analyses indicate a post-translational defect in genes regulating mitochondrial fuel oxidation. With NAC-Gly supplementation over 12weeks all these defects improved significantly; GSH, MFO and gait speed normalized to levels seen in non-HIV controls. Benefits began to recede on stopping supplementation. Results are summarized in attached table.

Conclusion: In HIV patients, deficiency of GSH and impaired mitochondrial fuel oxidation contribute to accelerated aging with decreased muscle strength and exercise capacity, increased muscle breakdown and fat accumulation. Supplementing NAC-Gly fully corrected intracellular GSH deficiency, impaired MFO and gait speed, and also improved strength, exercise capacity, fat mass, waist circumference and muscle loss. These findings suggest a key role for NAC-Gly supplementation and GSH on reversing accelerated aging in HIV, and warrants further investigation.

Parameters	Controls	HIV:0-wks	HIV:12-wks	P HIV 0 vs. 20wks
Age (y)	55 ± 1	55 ± 2	55 ± 2	
Sex distribution (M=male; F=female)	6M; 2F	6M; 2F	6M; 2F	
Red blood cell Reduced-Glutathione (µmol/g.Hb)	4.5 ± 0.6	2.8 ± 1.0	4.1 ± 0.6	P < 0.05
Red-blood cell Oxidized-Glutathione (µmol/g.Hb)	1.0 ± 0.4	0.4 ± 0.1	0.5 ± 0.2	P=0.9
Skeletal Muscle Total Glutathione (mmol/kg)	2.23 ± 0.29	0.47 ± 0.06	2.15 ± 0.33	P<0.001
Fasted fat oxidation (mg/kgLBM/min)	1.40 ± 0.09	0.86 ± 0.10	1.46 ± 0.09	P<0.01
Fasted carbohydrate oxidation (mg/kgLBM/min)	0.97 ± 0.10	2.61 ± 0.35	1.37 ± 0.17	P<0.05
Fasted Respiratory Quotient (RQ)	0.77 ± 0.01	0.86 ± 0.02	0.78 ± 0.01	P<0.01
Weight (kg)	90.5 ± 4.9	85.2 ± 2.7	81.7 ± 2.9	P=0.06
BMI	29.6 ± 1.2	29.1 ± 0.7	28.0 ± 1.0	P<0.05
Fat-mass (kg)	26.7 ± 2.4	30.5 ± 1.2	28.0 ± 1.3	P<0.05
Truncal-fat mass (kg)	13.3 ± 1.3	17.2 ± 0.9	15.4 ± 1.0	P<0.05
Waist circumferance (cm)	97.5 ± 2.4	105.4 ± 2.7	98.1 ± 2.8	P<0.001
Gait speed (metre/sec)	1.30 ± 0.07	1.03 ± 0.04	1.27 ± 0.06	P<0.01
6 minute walk test (metre)	644 ± 22	508 ± 8	542 ± 8	P<0.001
Chair-rise test (sec)	18.9 ± 1.2	28.8 ± 1.3	23.0 ± 1.0	P<0.01
Muscle strength, dominant forearm (lb)	102 ± 10	69 ± 7	86 ± 7	P<0.05
Muscle strength, nondominant forearm (lb)	92 ± 10	60 ± 7	78 ± 6	P<0.05
Muscle protein breakdown rate (mg/kgLBM/h)	105 ± 9	145 ± 13	96 ± 15	P<0.05

758 BLOOD TELOMERE LENGTH CHANGES AFTER DRV/R + EITHER RAL OR TDF/FTC AS FIRST-LINE ART

Natalia Stella-Ascariz[1], Rocio Montejano[1], Javier Rodriguez-Centeno[1], Belen Alejos[2], Christine Schwimmer[3], Jose I. Bernardino[1], Berta Rodes[1], Clotilde Allavena[4], Christian Hoffmann[5], Magnus Gisslén[6], Rosa de Miguel[1], Cédrick Wallet[7], François Raffi[8], Jose R. Arribas[1]

[1]Hospital La Paz Institute for Health Research, Madrid, Spain, [2]Institute of Health Carlos III, Madrid, Spain, [3]INSERM, Bordeaux, France, [4]CHU Hôtel-Dieu, Nantes, France, [5]ICH Study Center, Hamburg, Germany, [6]Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden, [7]CHU de Bordeaux, Bordeaux, France, [8]CHU de Nantes, Nantes, France

Background: In vitro tenofovir is a potent inhibitor of human telomerase. The in vivo relevance of this inhibition is unknown.

Methods: ANRS143/NEAT001 is a randomised trial that showed non-inferiority over 96 weeks of ritonavir-boosted darunavir (DRV/r) + raltegravir (RAL) vs tenofovir difumarate/emtricitabine (TDF/FTC) in 805 ART naïve HIV-infected adults. We compared changes in whole blood telomere length (TL) in 201 randomly selected participants who had stored samples available (baseline and 96 weeks). We measured TL (telomere to single copy gene ratio) with monochrome quantitative multiplex PCR. Samples were tested in triplicate and those with a coefficient of variation > 0.10 were retested. We performed multivariable estimative analysis and predictive linear regression adjusted by baseline TL to elucidate predictive factors of TL change

Results: Baseline characteristics of the 201 participants (104 RAL and 97 TDF/FTC) did not differ from the whole parent trial population: 89% male, median age 39 years, Caucasian 83.6%, sexual transmission 93%, median duration of known HIV infection 2.1 years, HIV-1 RNA load 4.7 log_{10} copies/mL, CD4 nadir/baseline 300/324 cells/µL. Blood TL did not differ between groups at baseline (Table). At W96, participants receiving TDF/FTC had a statistically significant higher gain in TL than participants receiving RAL. Intragroup change at W96 was significant only in the TDF/FTC group (p<0.001). Difference in mean TL change between groups (TDF/FTC minus RAL) from baseline to W96 adjusted by baseline TL was 0.031 (p=0.009). This difference was not significantly confounded by baseline age, gender, known duration of HIV infection, CD4 (baseline/nadir), CD8 cells, CD4/CD8 ratio, HIV viral load (baseline/W96), smoking, alcohol use, statins or hepatitis C. These results were unchanged when TL was analysed as a binary variable (TL shortened/not shortened). In the predictive model the only variables associated with TL gain at W96 were treatment with TDF/FTC, younger age (mean difference 0.001, p=0.042) and no current use of alcohol at baseline (mean difference 0.048, p=0.038)

Conclusion: This is the first clinical trial evaluating blood TL changes in naïve HIV participants starting ART. After 96 weeks participants receiving DRV/r + TDF/FTC had a significant higher gain in blood TL than those receiving DRV/r + RAL. The cause and clinical relevance of these differences between ART regimens are unknown and require further research.

Table. Blood telomere length changes

		RAL + DRV/r N=104	TDF/FTC + DRV/r N=97	p
Baseline	Mean TL (SD)	0.750 (0.154)	0.724 (0.149)	0.221
Week 96	Mean TL (SD)	0.760 (0.133)	0.772 (0.140)	
Change (week 96 TL minus baseline TL). Mean (95% CI)		0.009 (-0.007, 0.026)	0.048 (0.028, 0.067)	0.009
N (%) with shortening in TL at W96		45 (43.27)	28 (28.87)	0.034
N (%) with shortening >1 sd in TL at W96		13 (12.50)	6 (6.19)	0.126

759 THYMUS IS THE BAROMETER OF AGING IN HIV PATIENTS, ASSOCIATED WITH FRAILTY AND QOL

Giovanni Guaraldi, Giulia Besutti, Andrea Malagoli, Iacopo Franconi, Nicoletta Riva, Alessandro Raimondi, Riccardo Scaglioni, Guido Ligabue, Marianna Menozzi, Antonella Santoro, Federica Carli, Stefano Zona, Vanni Borghi, Andrea Cossarizza, Cristina Mussini

University of Modena and Reggio Emilia, Modena, Italy

Background: Age related thymus decline impact inability of adults to restore immune function following HIV infection and leads to increased morbidity and frailty. We sought to investigate the relationship between thymus imaging detection and structural changes with immunometabolic markers, multi-morbidity, frailty, and quality of life (QoL) in men with HIV.

Methods: This was a cross-sectional observational study including 665 consecutive HIV patients attending routine cardiovascular risk assessment with coronary artery calcium by mean of thoracic CT scan. Thymus detection and structural characteristics were retrospectively evaluated using a semiquantitative score based on the percentage of thymus solid tissue component (grade 0=no solid tissue; 1=1-25%; 2=26-50%; 3=51-75%; 4=76-100%; 5=100% solid tissue). Frailty was measured with the frailty phenotype and a 37-item Frailty index.

Results: 665 HIV infected patients (81% males), median age 53 years and median CD4=730/µL and HIV-RNA<40 c/mL in 98.5% were included. The table describes relevant immunometabolic markers. Thymus detection was also associated with lower prevalence of hypertension, diabetes, cardiovascular disease, MM, frailty and impaired QoL. In a multivariate logistic model, independent predictors for thymus detection were: male gender (OR=0.46, 0.22-0.93, p=0.03), BMI (OR=0.86, 0.81-0.98, p=0.03), IVDU (OR=0.22, 0.08-0.52, p<0.01), Frailty (FI>=0.4) (OR=0.95, 0.92-0.99, p=0.02), HIV duration (residual after correction for age) (OR=0.8, 0.65-0.97, p=0.03) and impaired QoL (OR=2.5, 1.19-5.78, p=0.02) after correction by Age (years) (OR=1.15, 0.95-1.38, p=0.15). Given the association between thymus structural characteristics and age a secondary sensitivity analyses was performed matching all the thymus detected cases with a subset of age and sex matched thymus not detected controls from the same cohort (180 cases +180 controls) confirming association with frailty and QoL. The impact of thymus on frailty was confirmed including thymus structural changes as predictors of most frail individuals (FI>=0.4) in multivariate logistic regression (mild or higher, OR=0.3, 0.12-0.93, p = 0.04) after correction for HIV duration (residual) (OR=1.10, 1.02-1.20, p=0.01), CD4/CD8 (OR=1.4, 0.6-3.3, p=0.38) and HIV late presentation (OR=0.5, 0.19-1.4, p=0.18)

Conclusion: Thymus detection and structural changes are associated with immunometabolic disarrangements and clinical spectrum of aging in HIV patients.

Table

		Thymus imaging appearance			Thymus imaging structural changes (compared to thymus non detected, No solid tissue component)		
	total (665)	Not detected 485 (72.93%)	detected 180 (27.07%)	p value	Grade 1-2 mild solid tissue component 128 (19.25%)	Grade ≥ 3 moderate/mass like solid tissue component 52 (7.82%)	p value
Age (years)	53.11 (7.98)	54.59 (7.86)	49.12 (6.89)	<0.001	50.92 (6.36)	44.69 (6.13)	<0.001
Female (n,%)	126 (18.95%)	73 (15.05%)	53 (29.44%)	<0.001	36 (28.12%)	17 (32.69%)	0.001
IVDU (n,%)	174 (26.17%)	141 (29.07%)	33 (18.33%)	<0.006	28 (21.88%)	5 (9.62%)	0.004
HIV duration (months)	262 (183-323)	267 (197-327)	222 (142-300)	<0.001	259 (180-319)	171 (87-251)	<0.001
CD4/CD8	0.96 (0.62)	0.96 (0.68)	0.96 (0.45)	0.267	0.95 (0.48)	0.97 (0.36)	0.398
HOMA	2.96 (5.31)	3.39 (6.09)	1.73 (1.12)	<0.001	1.87 (1.23)	1.38 (0.69)	<0.001
IFG1	163.33 (53.28)	158.7 (52.06)	178.24 (54.71)	0.002	173.97 (54.48)	191.02 (54.5)	0.004
Multi-Morbidities (MM) (>3 co-morbidities)	469 (70.53%)	368 (75.88%)	101 (56.11%)	<0.001	83 (64.84%)	18 (34.62%)	<0.001
37-item Frailty Index	0.29 (0.23-0.35)	0.3 (0.24-0.37)	0.24 (0.18-0.3)	<0.001	0.25 (0.19-0.32)	0.23 (0.16-0.26)	<0.000 1
Frailty Phenotype (≥ 3 *items*)	6 (2.17%)	6 (2.83%)	0 (0%)	0.38	0 (0%)	0 (0%)	0.38

Legend: IVDU: Intravenous Drug use risk factor

760 METHAMPHETAMINE USE INDEPENDENTLY PREDICTS PREMATURE AGING IN HIV+ INDIVIDUALS

Sanjay R. Mehta[1], Jennifer Iudicello[1], Ronald J. Ellis[1], Jue Lin[2], Erin Morgan[1], Debralee Cookson[1], Robert K. Heaton[1], Igor Grant[1], Scott L. Letendre[1]

[1]*University of California San Diego, La Jolla, CA, USA,* [2]*University of California San Francisco, San Francisco, CA, USA*

Background: As HIV+ adults grow older, aging-related comorbidities occur more frequently than in age-matched controls. Little is known about the role of substance use, which is common in this population, in this "premature" aging process. We examined the effects of methamphetamine (METH) dependence and HIV on physiologic and functional measures of aging.

Methods: Using clinical, demographic and laboratory measures obtained from 124 participants (HIV-/METH- n=31, HIV-/METH+ n=24, HIV+/METH- n=35, HIV+/METH+ n=34), we examined the impact of HIV serostatus and METH dependence in relation to epigenetic changes (telomere to single copy gene ratio [T/S], mitochondrial DNA [mtDNA] level, and relative abundance of the mitochondrial common deletion within the mtDNA population [RACD]) as well as to functional status, cardiovascular comorbidity (Framingham risk scores), renal functional changes, and age-related anthropometric (hip/waist ratio) changes.

Results: Controlling for age, HIV was associated with a lower Karnofsky rating (p<0.001), a larger hip/waist ratio (p=0.052), higher creatinine (p=0.002), and shorter T/S ratio (p=0.003). Similarly, controlling for age, METH use was associated with a shorter T/S ratio (p=0.002) but a lower creatinine (p=0.029). In multivariate regression including HIV, METH, and age, both METH+ and HIV+ remained significant predictors of shorter T/S ratios. In this model and within our study cohort, a 40-year-old HIV+/METH+ individual had a T/S ratio equivalent to a 44.5-year-old HIV+/METH-, a 45.2-year-old HIV-/METH+, and a 60.7-year-old HIV-/METH- individual. When examining RACD, another epigenetic marker of aging, METH+ participants had significantly smaller RACD (p=0.034) only in the HIV seronegative group. In a multivariate regression of creatinine adjusting for age and body mass index, both HIV and METH remained statistically significant, while tenofovir exposure was not a predictor of creatinine level.

Conclusion: Both HIV and METH contribute to premature biological aging with HIV having broader physiologic and epigenetic effects than METH. Consistent with earlier observations, METH was associated with less mtDNA damage, possibly due to induction of autophagy and cell turnover. This may explain the association with improved renal function in METH users, as mitochondrial dysfunction is known to play a significant role in renal disease.

761 SHORT-TERM OUTCOMES FOR MAJOR NON-CARDIAC SURGERY IN HIV INFECTION

Keith M. Sigel[1], Lesley Park[2], Michael Leapman[3], Amy C. Justice[3], Sheldon T. Brown[4], Joseph T. King[5]
[1]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [2]Stanford University, Stanford, CA, USA, [3]Yale University, New Haven, CT, USA, [4]James J. Peters VA Medical Center, Bronx, NY, USA, [5]VA Connecticut Healthcare System, West Haven, CT, USA

Background: The risk of surgical complications in HIV infected (HIV+) persons is unclear. We identified HIV+ patients on ART and uninfected comparators in a national cohort undergoing major non-cardiac surgeries to determine the rates and risk factors of major complications and death associated with HIV.

Methods: We linked clinical data from the Veterans Aging Cohort Study (VACS) to surgical outcomes from the Veterans Affairs Surgical Quality Improvement Project to identify VA patients undergoing major surgeries (2000-2015). We classified surgical procedures according to the Healthcare Cost and Utilization Project Clinical Classification System (CCS), and matched HIV+ patients on ART to uninfected subjects 1:2 by CCS category (N=13,071; 4,357 HIV+). We compared crude 30-day mortality, post-operative infection and other major complication rates by HIV status and fit multivariable logistic regression models, adjusting for confounders (including, but not limited to, age, smoking, surgery year, albumin level, anesthesia risk class, cancer diagnosis, diabetes, heart disease, recent chemotherapy or steroid use). We then evaluated risk of surgical complications in HIV+ subjects according to HIV-specific factors (recent CD4, viral suppression, VACS index score).

Results: Patients did not differ by HIV status in age (median 56 years) or race/ethnicity. HIV+ patients had higher preoperative anesthesia risk scores and more prevalent metastatic cancer, but had lower BMI and were less likely to be diabetic or taking corticosteroids. The most frequent surgical procedures were hernia repair, hip arthroplasty and cholecystectomy. Crude 30-day mortality and frequency of other complications (including infectious) did not differ by HIV status (Table 1). HIV was not significantly associated with increased short-term mortality (odds ratio: 1.4; 95% confidence interval: 0.8-2.4) or other complications after adjustment. Among HIV+ subjects low preoperative CD4 count, lack of HIV viral suppression, and higher VACS index values were associated with mortality in separate models, but in a mutually adjusted model only VACS index score retained significance as a predictor.

Conclusion: Compared with procedure-matched uninfected patients, HIV+ patients on antiretroviral therapy undergoing major non-cardiac surgery have similar rates of 30-day post-operative mortality, infections and other complications.

Table 1. 30-Day Complication Rate for Major Non-Cardiac Surgery by HIV Status

Complication	**HIV+** (n=4,357)	**HIV-** (n=8,714)	**p-value**
Death, n (%)	41 (0.94)	58 (0.67)	0.09
Infectious Complications			
Any Major Infection, n (%)	205 (4.7)	438 (5.0)	0.4
Superficial Wound infection, n (%)	66 (1.5)	160 (1.8)	0.2
Deep Wound Infection, n (%)	31 (0.71)	61 (0.70)	0.9
Urinary Tract Infection, n (%)	55 (1.3)	112 (1.3)	0.9
Pneumonia, n (%)	46 (1.1)	92 (1.1)	0.9
Sepsis, n (%)	40 (0.91)	82 (0.94)	0.9
Other Major Complications			
Myocardial Infarction, n (%)	9 (0.20)	13 (0.15)	0.5
Pulmonary Embolism, n (%)	9 (0.20)	25 (0.29)	0.4
Cerebrovascular Accident, n (%)	4 (0.10)	10 (0.11)	0.7
Renal Failure, n (%)	8 (0.18)	16 (0.18)	0.9
Reoperation, n (%)	205 (4.7)	419 (4.8)	0.8
Any Major Complication, n (%)	292 (6.7)	638 (7.3)	0.2

762 HOSPITALIZATION RATES AND OUTCOMES IN A SOUTHEASTERN US CLINICAL COHORT, 1996-2016

Thibaut Davy-Mendez, Sonia Napravnik, Oksana Zakharova, David Wohl, Claire E. Farel, Joseph J. Eron
University of North Carolina Chapel Hill, Chapel Hill, NC, USA

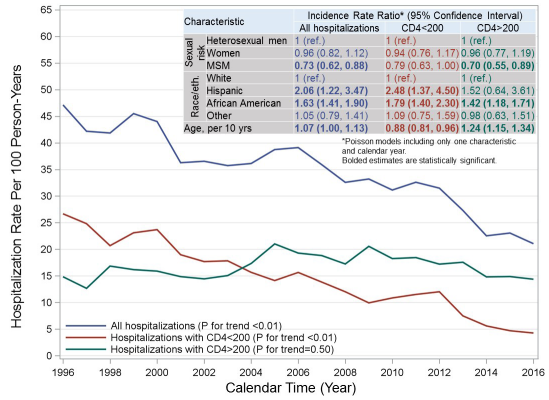
Background: Hospitalizations in the context of an aging HIV-infected population with increasing co-morbidities are not well known. We examined trends in hospitalization rates, outcomes, and risk factors in the UNC CFAR HIV Clinical Cohort (1996-2016).

Methods: Patients contributed time from latter of 01-1996 or HIV care initiation at UNC, until first of 12-2016, or death. Patient time was also censored at loss to follow-up (LTFU-18 months with no clinical visit), with patients contributing additional time if reentering HIV care. We calculated crude annual hospitalization rates per 100 person-years (PY), overall and stratified by CD4 at hospitalization (CD4

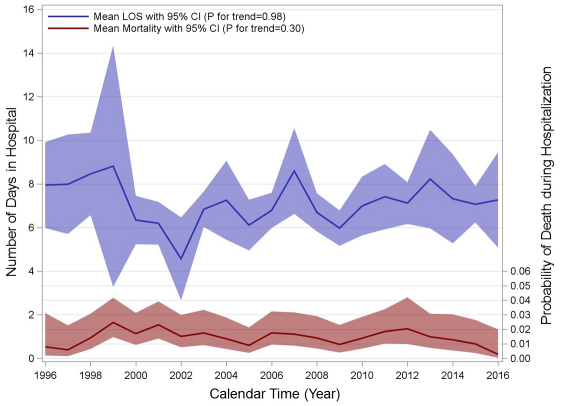
Results: The 4327 patients contributed 30,000 PY and were 29% female, 40% MSM, and 60% African-American. Patient CD4 counts increased in more recent calendar years (median 618, IQR 411-845, 6%<200 in 2016 vs 300, 130-464, 36%<200 in 1996, P<0.01). Crude hospitalization rate over the study period was 33.7/100 PY (95% CI 33.0-34.3). From 1996 to 2016, hospitalization rates per 100 PY overall and with CD4<200 decreased from 47.1 to 21.0 (41.5-53.3, 18.9-23.4), and 26.7 to 4.3 (22.4-31.4, 3.3-5.4), respectively, while hospitalizations with CD4>200 remained constant from 14.8 to 14.4 (11.7-18.5, 12.6-16.3) (Figure 1A, P<0.01, P<0.01, P=0.50, respectively). MSM had lower hospitalization rates than heterosexual men, and African-Americans and Hispanics had higher rates than whites (Figure 1A). Older age was associated with increased rates of hospitalization with CD4>200, but lower rates with CD4<200 (IRR per 10-year increase 1.24, 95% CI 1.15-1.34; 0.88, 0.81-0.96, respectively). Overall, mean LOS was 7.1 (95% CI 6.6-7.5) days, inpatient mortality was 1.5% (95% CI 1.3-1.7), with no change over time (Figure 1B, P=0.98 and P=0.30, respectively).

Conclusion: Among HIV-infected patients in care, overall hospitalizations decreased substantially over the last 20 years, largely driven by decreased hospitalizations with CD4<200; while hospitalizations with CD4>200 remained constant. Hospitalization outcomes did not change over calendar time.

A. Hospitalization rates among patients in care, overall and by proximal CD4



B. Length-of-stay (LOS) and mortality of hospitalizations among patients in care



763 NOVEL BIOMARKERS PREDICTIVE OF NON-AIDS EVENTS DURING ART-MEDIATED VIRAL SUPPRESSION

Martin Hoenigl[1], Carlee Moser[2], Nicholas Funderburg[3], Ronald Bosch[2], Amy Kantor[2], Yonglong Zhang[4], Jesper Eugen-Olsen[5], Malcolm Finkelman[4], Alan Landay[6], Michael M. Lederman[7], Sara Gianella[8]
[1]University of California San Diego, San Diego, CA, USA, [2]Harvard University, Cambridge, MA, USA, [3]The Ohio State University, Columbus, OH, USA, [4]Associates of Cape Cod, Inc, Falmouth, MA, USA, [5]Hvidovre Hospital, Hvidovre, Denmark, [6]Rush University Medical Center, Chicago, IL, USA, [7]Case Western Reserve University, Cleveland, OH, USA, [8]University of California San Diego, La Jolla, CA, USA

Background: Antiretroviral therapy (ART) treated HIV infection is associated with increased risk of morbidity/mortality, driven in part by increased inflammation. Potential contributors to inflammation include translocation of bacterial and fungal products from the gut into systemic circulation and pro-inflammatory lipids, but direct linkages between these indices and clinical events have not been adequately demonstrated. Here, in a case/control study, we measured levels of plasma biomarkers that have been associated previously with microbial translocation (i.e. lipopolysaccharide binding protein [LBP], beta-D-glucan [BDG], intestinal fatty acid binding protein [I-FABP]), oxidized [ox]LDL), and chronic inflammation and monocyte activation (soluble urokinase plasminogen activator receptor [suPAR], soluble CD163 [sCD163]), to identify potential associations among biomarker levels and non-AIDS events (myocardial infarction, stroke, cancer, serious bacterial infection and non-accidental death).
Methods: Participants (143 cases, 315 controls) were selected from the ACTG ALLRT trial; all were virally suppressed on ART at year 1, and thereafter (Tenorio, PMID:24795473). Plasma samples were selected: pre-ART initiation, 1-year post-ART, and immediately preceding an event (cases). Controls had an event-free follow-up equal or greater than that of the relevant case, and participants were matched on age (median 45 years), sex (85% male), pre-ART CD4+ count (median 215 cells/mm^3), ART regimen, and parent study. LBP, BDG, I-FABP, sCD163, and oxLDL were measured at all timepoints; suPAR was measured in baseline samples only. At each timepoint, conditional logistic regression analysis assessed associations of the biomarkers with events, and adjusted for relevant covariates.
Results: At baseline, higher levels of suPAR were associated with increased risk of non-AIDS events in both unadjusted and adjusted analyses (Table 1). At year 1 post-ART and pre-event, higher levels of BDG and LBP were associated with increased risk of non-AIDS events in unadjusted and adjusted analyses. Associations were not observed for I-FABP, sCD163 and oxLDL.
Conclusion: Elevated levels of suPAR pre-ART were associated with development of non-AIDS events post-ART. After 1 year of ART, elevated BDG and LBP were predictive of non-AIDS events, similar to IL-6, D-dimer, and sTNFR-I and –II (Tenorio, PMID: 24795473). These biomarkers may inform future interventional studies aimed at reducing morbidity and mortality in ART-treated HIV infection.

Table 1: Unadjusted and Adjusted Conditional Logistic Regression Models for Associations between Biomarkers and non-AIDS events at Three Time-points.

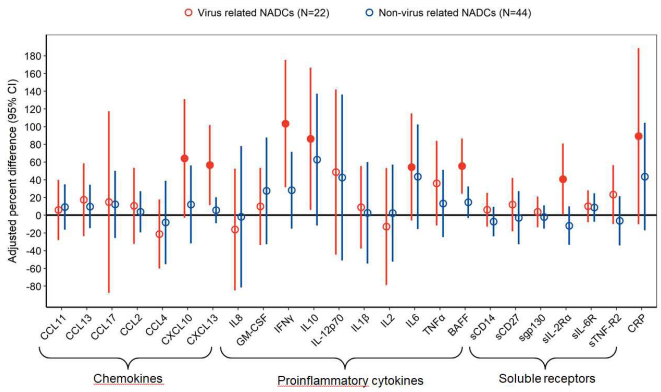
Biomarker	Baseline (i.e. before ART) N=325 *		Year 1 N=418 *		Pre-Event N=377 *	
	Unadjusted OR (95% CI) per one IQR; p-value *#	Range of Adjusted OR per one IQR §	Unadjusted OR (95% CI) per one IQR; p-value *#	Range of Adjusted OR per one IQR §	Unadjusted OR (95% CI) per one IQR; p-value *#	Range of Adjusted OR per one IQR §
LBP	1.1 (0.9-1.4); p=0.2	1.1 - 1.2	**1.4 (1.1-1.8); p=0.01**	**1.3 – 1.4**	**1.7 (1.3-2.3); p<0.001**	**1.6 – 1.8**
BDG	1.0 (0.8-1.3); p=0.83	1.0 – 1.1	**1.5 (1.1-2.0); p=0.008**	**1.4 – 1.6**	**1.4 (1.1-1.7); p=0.016**	**1.2-1.4**
suPAR	**1.7 (1.2-2.5); p=0.002**	**1.6 – 1.9**	-	-	-	-
I-FABP	0.9 (0.6-1.2); p=0.44	0.8 – 0.9	1.0 (0.7-1.3); p=0.98	0.9 – 1.0	0.9 (0.7-1.3); p=0.6	0.8 - 0.9
sCD163	1.2 (0.9-1.7); p=0.2	1.1 – 1.3	1.3 (1.0-1.6); p=0.08	1.2 – 1.3	1.2 (0.9-1.6); p=0.15	1.1 – 1.2
oxLDL	0.9 (0.7-1.2); p=0.46	0.8 – 0.9	0.8 (0.6 – 1.1); p=0.13	0.7 -0.8	0.7 (0.5-1.0); p=0.054	0.7 – 0.8

* = Baseline: N=111 cases and N=214 controls; Year 1: N=134 cases and N=284 controls; Pre-Event: N=122 cases and N=255 controls.
# = significant (p<0.05) results are bold
§ = Adjustments were done individually for the following covariates: i.) HIV-disease measure (Baseline: log-10 HIV RNA level, Year 1 and Pre-event: CD4 cell count); ii.) Time updated chronic Hepatitis B/C status; iii.) Time updated smoking status; iv.) Baseline injection drug use; v.) Time updated waist-to-hip ratio; vi.) Time updated diabetes status; vii.) Time updated hypertension status; viii.) Time updated use of antihypertensive or lipid lowering medications; and ix.) Time updated family history of myocardial infarction. The ranges of the 9 adjusted ORs are displayed in the Table.
Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio.

764 INFLAMMATION AND IMMUNE ACTIVATION MARKERS ASSOCIATED WITH NON-AIDS CANCERS IN HIV

Muhaimen Siddiqui[1], Elizabeth Breen[2], Jay Bream[1], Yue Chen[3], Dana H. Gabuzda[4], **Eric C. Seaberg**[1]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]University of California Los Angeles, Los Angeles, CA, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA, [4]Dana–Farber Cancer Institute, Boston, MA, USA

Background: The incidence of non-AIDS defining cancers (NADCs) is elevated among PLWH, and this difference may be promoted by persistent inflammation and immune activation during HIV infection. The objective of this study was to examine the association of inflammation and immune activation with incident NADCs among HIV+ men enrolled in the Multicenter AIDS Cohort Study (MACS).
Methods: Matched case-control study among MACS participants with 23 serum markers of inflammation and immune activation and C-reactive protein (CRP) tested in longitudinal samples obtained between 1984 and 2009. Cases included 66 HIV-infected men diagnosed with a NADC during follow-up who had serum markers measured 0-2 years before NADC diagnosis. Controls included cancer-free men who were individually matched (1:1) to cases on age, race, smoking history, BMI, CD4 T-cell count, HIV RNA level, duration of effective ART, and calendar year. We examined the association of the serum markers with incident NADCs both overall and separately for NADCs with and without a known viral etiology (i.e., HPV, HBV, HCV, and EBV). Marker levels were $\log_2$-transformed, and the adjusted percent difference (PD) in the mean levels between cases and controls was estimated using GEEs to account for matching. The Benjamini-Hochberg method was used to determine statistical significance (α=0.05) controlling for a false discovery rate of 25%.
Results: The mean age of cases was 52, 71% were Caucasian, 24% were eART naive, mean CD4 was 489, and 17% had CD4<200; controls were similar on all matching factors. CXCL13 (PD:23%), IFN-γ (PD:53%), IL-10 (PD:70%), IL-6 (PD:47%), BAFF (PD:27%), and CRP (PD:56%) were significantly elevated among NADC cases compared to controls. For NADCs with a known viral etiology, the same markers plus CXCL10 (PD:64%) and sIR-2Rα (PD:41%) were significantly (p<0.05) elevated among cases. In contrast, no significant differences were observed for NADCs without a known viral etiology (see figure).
Conclusion: Several inflammation and immune activation markers were elevated prior the diagnosis of incident NADC among men living with HIV. However, statistically significant elevation of these markers was observed only for NADCs with a known viral etiology. It remains to be determined whether the association between elevated serum markers and development of NADCs is due to HIV-related immune dysregulation, products of developing tumors or tumor microenvironment, or immune responses to coinfection with oncogenic viruses.



Solid circles indicate statistically significant (α=0.05) marker elevations based on Benjamini-Hochberg procedure with a 25% false discovery rate.

765 SERUM ALBUMIN AS A LONG TERM PREDICTOR OF SERIOUS NON-AIDS EVENTS

Andreas Ronit[1], Camilla Ingrid Hatleberg[1], Lene Ryom[1], Fabrice Bonnet[2], Wafaa M. El-Sadr[3], Peter Reiss[4], Rainer Weber[5], Christian Pradier[6], Stephane de Wit[7], Matthew Law[8], Antonella D'Arminio Monforte[9], Jens D. Lundgren[1], Andrew N. Phillips[10], Caroline Sabin[10]

[1]Rigshospitalet, Copenhagen, Denmark, [2]INSERM, Bordeaux, France, [3]ICAP at Columbia University, New York, NY, USA, [4]Academic Medical Center, Amsterdam, Netherlands, [5]University Hospital Zurich, Zurich, Switzerland, [6]Nice University Hospital, Nice, France, [7]Saint-Pierre University Hospital, Brussels, Belgium, [8]Kirby Institute, Sydney, NSW, Australia, [9]Azienda Ospedaliera San Paolo, Milan, Italy, [10]UCL Great Ormond Street Institute of Child Health, London, UK

Background: Lower serum albumin (sAlb) has been associated with an increased risk of mortality and AIDS in HIV-positive people and may be associated with the development of serious non-AIDS events (SNAEs). We evaluated the association between sAlb and the risk of SNAEs.

Methods: D:A:D participants free of SNAEs were followed from their first routine sAlb value (01/01 2004 onwards) to the first of a new centrally-validated SNAE (cardiovascular disease (CVD: myocardial infarction, stroke, invasive cardiovascular procedure), end-stage liver disease (ESLD), end-stage renal disease (ESRD), non-AIDS malignancy (NADM), death from any non-AIDS cause), AIDS death, 6 months after last clinic visit or 01/02/2016. Poisson regression models were used to determine associations between sAlb (fixed covariate) and a new i) SNAE, ii) CVD or iii) NADM event, with adjustment for potential confounders (including markers of HIV disease and other measures of organ system injury, Table 1). Models additionally tested whether the association varied with age, duration of follow-up, or smoking status.

Results: Of 16,350 participants (71.8% male, median (interquartile range, IQR) age 44 (37, 51), 50.5% white, 90.1% antiretroviral therapy experienced) 1,463 developed a SNAE (371 CVD, 200 ESLD, 40 ESRD, 553 NADM, 299 deaths from other non-AIDS causes) over 80,264 person-years. Median (IQR) sAlb was 43 (40-46) g/L). The SNAE rate was 1.82 [95% confidence interval 1.73-1.92]/100 person-years. Lower sAlb was associated with an increased risk of each event (Table 1). While there was no clear threshold effect of sAlb, there was a clear reduced risk across sAlb levels above 35 g/L (Table 1). The association between sAlb (per 5 g/L higher) and a SNAE was attenuated with older age as event rates increased (age in years<30: adjusted rate ratio 0.73 [0.54-0.99]; 30-50: 0.77 [0.74-0.81]; >50: 0.82 [0.78-0.87]; p-interaction=0.001) but did not appear to wane with additional years of follow-up (0-2: 0.75 [0.72-0.78]; 3-4: 0.88 [0.81-0.95]; 5-6: 0.83 [0.74-0.94]; >6: 0.82 [0.74-0.91], p-interaction=0.79). The association between sAlb and SNAE appeared stronger for current smokers (0.76 [0.73-0.80] than for never smokers 0.87 [0.8-0.95], p<0.01).

Conclusion: sAlb is an independent and long-term risk factor for SNAE. Future studies are needed to determine the mechanism underlying this association and risk-score studies should consider evaluating the potential role of sAlb in predicting SNAEs.

Table 1: Poisson regression analysis including unadjusted and adjusted rate ratio (RR) between baseline sAlb values and a) any SNAE (CVD, NADM, ESLD, ESRD, death from other non-AIDS causes), b) any CVD event and c) any NADM

		Rate (95% CI)/100 PYRS	Unadjusted RR (95% CI)	Adjusted[1] RR (95% CI)	P-value[2]
a) Any SNAE					
Albumin (g/L)	<30	7.37 (6.03, 8.71)	4.57 (3.74, 5.58)	3.49 (2.83, 4.31)	0.0001
	≥30, <35	4.07 (3.34, 4.79)	2.52 (2.07, 3.07)	2.30 (1.88, 2.81)	0.0001
	≥35, <40	2.42 (2.16, 2.68)	1.50 (1.31, 1.71)	1.32 (1.15, 1.51)	0.0001
	≥40, <45	1.61 (1.48, 1.75)	Ref.	Ref.	-
	≥45, <50	1.24 (1.10, 1.39)	0.77 (0.67, 0.89)	0.83 (0.72, 0.96)	0.01
	≥50	1.02 (0.68, 1.36)	0.63 (0.45, 0.89)	0.74 (0.52, 1.05)	0.09
Albumin (continuous, per 5g/L)			0.75 (0.73, 0.78)	0.79 (0.77, 0.82)	0.0001
b) Any CVD event					
Albumin (g/L)	<30	0.51 (0.22, 1.00)	1.12 (0.55, 2.29)	1.21 (0.59, 2.48)	0.60
	≥30, <35	0.81 (0.48, 1.13)	1.79 (1.16, 2.74)	2.28 (1.47, 3.55)	0.0002
	≥35, <40	0.61 (0.48, 0.74)	1.34 (1.03, 1.75)	1.29 (0.99, 1.69)	0.06
	≥40, <45	0.45 (0.38, 0.52)	Ref.	Ref.	-
	≥45, <50	0.37 (0.29, 0.45)	0.83 (0.64, 1.07)	0.82 (0.63, 1.07)	0.15
	≥50	0.27 (0.12, 0.51)	0.60 (0.30, 1.17)	0.64 (0.33, 1.27)	0.20
Albumin (continuous, per 5g/L)			0.87 (0.80, 0.94)	0.87 (0.80, 0.94)	0.0006
c) Any NADM event					
Albumin (g/L)	<30	1.65 (1.02, 2.29)	2.44 (1.63, 3.66)	2.00 (1.30, 3.08)	0.002
	≥30, <35	1.11 (0.73, 1.49)	1.64 (1.14, 2.36)	1.55 (1.07, 2.26)	0.02
	≥35, <40	0.76 (0.61, 0.91)	1.12 (0.89, 1.41)	1.00 (0.79, 1.26)	0.98
	≥40, <45	0.68 (0.59, 0.76)	Ref.	Ref.	-
	≥45, <50	0.57 (0.47, 0.67)	0.84 (0.68, 1.04)	0.92 (0.74, 1.14)	0.44
	≥50	0.54 (0.32, 0.85)	0.80 (0.49, 1.29)	0.95 (0.58, 1.54)	0.83
Albumin (continuous, per 5g/L)			0.84 (0.79, 0.89)	0.88 (0.82, 0.94)	0.0004

[1]Adjusted for participating cohort, gender, risk group, race and the following covariates defined at baseline: Age, body mass index, smoking status, dyslipidemia, total cholesterol, alanine aminotransferase, estimated glomerular filtration rate, hepatitis C, hepatitis B, CD4 count (cells/mm³), viral load ≤50 copies/ml, current exposure to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors and integrase inhibitors, [2]P-value for adjusted model.

766 MOBIILITY PREDICTS INCIDENT TB INFECTION IN CHILDREN & ADULTS IN RURAL UGANDA

Carina Marquez[1], Atukunda Mucunguzi[2], Gabriel Chamie[1], Laura B. Balzer[3], Joel Kironde[4], Theodore Ruel[1], Bridget Nzarubara[4], Dalsone Kwariisima[5], Edwin D. Charlebois[1], Maya L. Petersen[6], Diane V. Havlir[1]

[1]University of California San Francisco, San Francisco, CA, USA, [2]Makerere University–University of California San Francisco Research Collaboration, Kampala, Uganda, [3]University of Massachusetts Amherst, Amherst, MA, USA, [4]Makerere Univ and Univ of California San Francisco Rsr Collab, Mbarara, Uganda, [5]Makerere University Joint AIDS Program, Kampala, Uganda, [6]University of California Berkeley, Berkeley, CA, USA

Background: In sub-Saharan Africa, a significant portion of the large latent TB reservoir is established outside of the home. Data on TB risk among mobile children and adults who travel outside of the community for work or school is limited, but critical to targeting TB prevention efforts.

Methods: We assessed the association between mobility and incident TB infection in an ongoing longitudinal cohort of tuberculin skin test (TST) negative children (≥5 years) and adults in the SEARCH trial (NCT:01864603) in Eastern Uganda, this sample was enriched for HIV-infection. Participants were included in the TST negative cohort if they had no induration at their baseline TST. A follow-up TST was placed one year from baseline. Incident TB infection was defined as a change in TST induration from 0mm at baseline to ≥10mm at their annual follow up test. Mobility was defined as living outside of the community for more than 1 month in the last year, such as to attend boarding school or work. We used multivariate logistic regression and adjusted for confounding by age, gender, lowest wealth tertile, BCG vaccination, HIV status, living in household with HIV-infected adult, and household TB contact within the last year.

Results: One year follow-up TSTs were completed in 739 participants (age ≥5 years) from the TST negative cohort. Our definition of incident TB infection was met by 89 (12%) participants. Among those with incident TB infection: 48% were ages 5-14 years of age, 17% were 15-24 years, and 35% were older than 25 years, 65% were women, 93% had a BCG scar or record of vaccination, 10% were mobile, 6% reported a household contact within a year. In the adjusted model, mobility was associated with a 2.6-fold increased odds of incident TB infection (95% CI: 1.3-7.5, p<0.01). Reporting a household contact was also independently associated with TB infection (aOR 11.3, 95% CI: 2.1-62.2, p<0.01). HIV infection and living in a household with one or more HIV-infected adult was not associated with incident TB infection.

Conclusion: In a rural Ugandan cohort of children and adults where population based treatment of HIV is ongoing, mobility was a predictor of increased risk of incident TB infection. TB exposure outside of the community, such as in boarding schools, may drive a portion of TB infections in rural communities. Casual TB contacts within rural communities and undiagnosed household contacts may explain the incident infections not associated with a known household contacts or mobility.

767 IMPROVED SENSITIVITY OF A NOVEL RECOMBINANT PROTEIN SKIN TEST FOR THE DIAGNOSIS OF TB

Roberto Badaro[1], Corey Casper[2], Rhea Coler[2], C A. Araujo-Neto[1], Diana B. Pedral-Sampaio[1], Maria Nakatani[1], Antonio Campos Neto[3], Steven Reed[2]

[1]Federal University of Bahia, Salvador, Brazil, [2]Infectious Disease Research Institute, Seattle, WA, USA, [3]Forsyth Institute, Boston, MA, USA

Background: The tuberculin skin test (TST) or Mantoux reaction (MR) has been used worldwide in the diagnosis of M. tuberculosis infection for over 100 years. Many regions have experienced shortages of the purified protein derivative (PPD) TST in recent years as the number of suppliers has decreased. The accuracy of the PPD TST is limited by prior BCG vaccination, infection by other non-tuberculous mycobacteria, reduced sensitivity in immunocompromised hosts with a high risk of tuberculosis (TB) such as HIV, and limited ability to diagnose active TB. We previously described a recombinant protein ("DPPD") derived from M. tuberculosis (MTB) that can replace the classical PPD antigen used in TST.

Methods: We compared DDPD to PPD using MR in a population of 672 people in the state of Bahia, Brazil. Participants were divided among 5 specific groups: Group 1 - 232 BCG-vaccinated individuals with no signs or symptoms nor history of active TB; Group 2 - 40 HIV-negative patients with active TB as defined by a clinical isolate with a positive culture for MTB or positive acid fast stain; Group 3 - 38 HIV-positive individuals with active TB and MTB found on culture a positive acid fast stain; Group 4 - 182 HIV-positive patients with signs and symptoms compatible with active TB, but without microbiologic confirmation,

who responded to drug therapy for TB; Group 5 - 115 HIV-negative patients with a clinical diagnosis of active TB, without microbioloigc confirmation of MTB, who responded to drug therapy for active TB. PPD and DPPD were applied intradermally in contralateral arms using a standard Mantoux test technique.
Results: Among healthy people previously vaccinated with BCG (Group 1), 57% had positive PPD and 41% had positive DPPD with a good concordance index (Kappa = 0.90). In the context of active TB, DPPD was positive in 93% of patients with active co-infection HIV and TB (Groups 3 and 4), compared to 50% of PPD ($p < 0.001$). All (100%) of HIV negative patients with active TB (Groups 2 and 5) were both DPPD and PPD positive. No differences were noted when microbiologically-confirmed cases were compared to clinically-confirmed cases of active TB. Among HIV-positive patients with active TB, DPPD was significantly more sensitive than PPD when stratified by CD4 cell counts (P=0.0001).
Conclusion: The recombinant DPPD antigen may be an important tool in the diagnosis and control of TB, with improved sensitivity and enhanced specificity compared with PPD.

768 HIV-ASSOCIATED TB IN A LOW BURDEN COUNTRY: IS SCREENING FOR LATENT TB STILL NEEDED?

Enrico Girardi[1], Alessandro Cozzi-Lepri[2], Andrea Gori[3], Annalisa Saracino[4], Antonio Di Biagio[5], Giuseppe Lapadula[6], Giancarlo Orofino[7], Miriam Lichtner[8], Sergio Lo Caputo[4], Andrea Antinori[1], Antonella D'Arminio Monforte[3], Cristina Mussini[9]
[1]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, [2]University College London, London, UK, [3]University of Milan, Milan, Italy, [4]University of Bari, Bari, Italy, [5]University of Genoa, Genoa, Italy, [6]San Gerardo Hospital, Monza, Italy, [7]Amedeo di Savoia Hospital, Torino, Italy, [8]Sapienza University of Rome, Rome, Italy, [9]University of Modena and Reggio Emilia, Modena, Italy

Background: Combination antiretroviral therapy (cART) reduces the risk of developing tuberculosis (TB) in persons with HIV both in low and high TB burden countries. Nonetheless, some studies suggest that this risk may remain above that of background HIV -uninfected populations. It is not clear whether in low TB burden countries the recommendation to screen and treat for latent TB infection (LTBI) all persons with newly diagnosed HIV infection is presently justified
Methods: We analyzed data of persons enrolled in the ICONA cohort in 2006-2016 in Italy, diagnosed with HIV within 6 months of enrolment. We considered cases of TB diagnosed at first presentation or during follow-up. Factors associated with the risk of developing TB at enrolment were identified by multivariable logistic regression. Incidence rates of TB from enrolment were calculated, and Poisson regression model was used to identify factors associated with the incidence of TB in the study population
Results: Among 5,555 persons included in the analysis, 98 (2%) were diagnosed with TB: 72 (73%) were diagnosed at HIV diagnosis, 14 (14%) at least 3 month after HIV diagnosis and before cART start; 8 (8%) during the first 6 months of cART, and 4 (4%) more than 6 months after cART initiation. Factors associated with being diagnosed with TB at enrollment were being immigrants (OR 6.99 vs. Italians; 95%CI: 3.76- 13.02) and having a nadir CD4 cells count< 200/mm^3 (OR 3.17 vs. CD4 cells count > 200, 95%CI: 1.87-5.39). Incidence rates of TB per 1,000 person-years of follow-up were 12.8 (95%CI: 10.4 - 15.8) before cART 3.5 (95%CI: 1.8 - 7.0) during the first 6 months of cART and 0.3 (95%CI: 0.1, 0.8) more than 6 months after cART initiation. Incidence of TB decreased in more recent calendar years and was significantly associated with being immigrants and with a low CD4 cells count (Table)
Conclusion: Most of the cases of TB in our study were diagnosed before cART initiation, and the risk of presenting with TB significantly decreased over time. Promoting early HIV diagnosis and immediate initiation of cART appear to be the most important interventions to further decrease the risk of HIV-associated TB in a low TB burden country. Additional prevention efforts should be focused on persons born in high TB burden countries and on these with CD4 nadir below 200/mm^3, while the effectiveness of screening and treatment of LTBI among those from low TB burden countries and with less advanced immunosuppression should be reevaluated.

	Relative Rates of developing TB							
	No. TB	PYFU	Rates (95% CI)	Unadjusted (95% CI)	RR p-value	Adjusted* RR (95% CI)	p-value
Gender							
Male	51	17706	0.29 (0.22, 0.38)	1.00		1.00	
Female	47	4064	1.16 (0.87, 1.54)	4.01 (2.70, 5.97)	<.001	1.14 (0.70, 1.85)	0.606
Mode of HIV transmission							
PWID	20	1724	1.16 (0.75, 1.80)	1.00		1.00	
MSM	48	8908	0.54 (0.41, 0.71)	0.17 (0.05, 0.57)	0.004	0.14 (0.03, 0.57)	0.006
Heterosex	30	11138	0.27 (0.19, 0.39)	1.87 (0.68, 5.12)	0.222	0.98 (0.35, 2.76)	0.967
Other/Unknown	15	7162	0.21 (0.13, 0.35)	1.71 (0.55, 5.30)	0.353	0.90 (0.27, 3.00)	0.867
Nationality							
Italian	25	17591	0.14 (0.10, 0.21)	1.00		1.00	
Immigrant	73	4178	1.75 (1.39, 2.20)	12.29 (7.81, 19.36)	<.001	6.79 (3.94, 11.71)	<.001
Education							
Other/Unknown	41	6918	0.59 (0.44, 0.80)	1.00		1.00	
Primary	17	1213	1.40 (0.87, 2.25)	2.36 (1.34, 4.16)	0.003	0.77 (0.41, 1.45)	0.411
Secondary	20	3846	0.52 (0.34, 0.81)	0.88 (0.51, 1.50)	0.632	0.76 (0.41, 1.40)	0.382
College	15	7162	0.21 (0.13, 0.35)	0.35 (0.20, 0.64)	<.001	0.55 (0.28, 1.07)	0.079
University	5	2631	0.19 (0.08, 0.46)	0.32 (0.13, 0.81)	0.016	0.63 (0.22, 1.79)	0.383
CD4 count nadir							
200+	28	11627	0.24 (0.17, 0.35)	1.00		1.00	
0-200	53	5217	1.02 (0.78, 1.33)	4.22 (2.67, 6.67)	<.001	2.76 (1.73, 4.41)	<.001
Current period							
2006-2009	20	1724	1.16 (0.75, 1.80)	1.00		1.00	
2010-2013	48	8908	0.54 (0.41, 0.71)	0.46 (0.28, 0.78)	0.004	0.41 (0.23, 0.73)	0.002
2014-2016	30	11138	0.27 (0.19, 0.39)	0.23 (0.13, 0.41)	<.001	0.25 (0.13, 0.46)	<.001

*adjusted for all factors included in Table

769 A PILOT RCT OF GENEXPERT MTB/RIF ON A MOBILE HIV TESTING UNIT IN SOUTH AFRICA

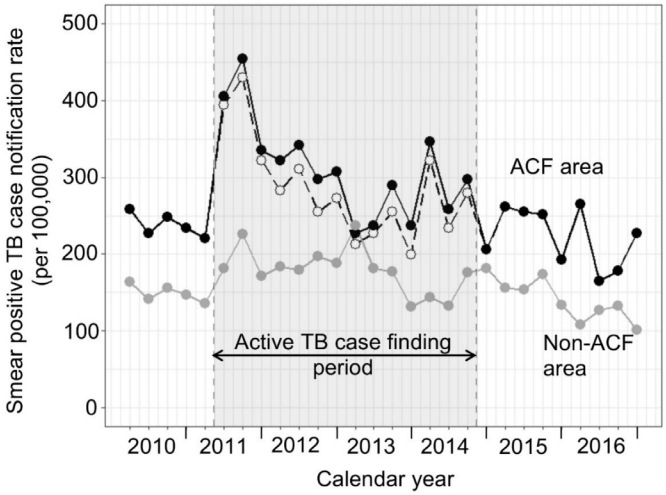
Ingrid V. Bassett[1], Leah S. Forman[2], Sabina Govere[3], Hilary Thulare[3], Simone C. Frank[1], Bright Mhlongo[3], Elena Losina[4]
[1]Massachusetts General Hospital, Boston, MA, USA, [2]Boston University, Boston, MA, USA, [3]AIDS Healthcare Foundation, Durban, South Africa, [4]Brigham and Women's Hospital, Boston, MA, USA

Background: TB is a leading cause of death in South Africa, yet often goes undiagnosed. Community-based GeneXpert MTB/RIF screening may expedite TB diagnosis and treatment.
Methods: We conducted a proof-of-concept randomized trial to evaluate the yield of GeneXpert screening on a mobile HIV testing unit at community venues in Umlazi Township, Durban. Eligible adults (≥18y) underwent rapid HIV testing and a TB symptom screen and were randomized to usual care or intervention. Participants with TB symptoms in the usual care arm were asked to produce a sputum sample, for GeneXpert testing at the provincial hospital laboratory; participants were contacted ~7 days later with results and treatment referral. In the "Test & Treat TB" intervention, all HIV-infected or HIV-uninfected/ TB symptomatic participants able to produce sputum underwent GeneXpert testing on the mobile unit. GeneXpert-positive participants received expedited TB treatment initiation on the mobile unit as well as monthly SMS reminders and non-cash incentives for picking up test results, linking to an initial clinic visit, and TB treatment completion. We assessed linkage to TB care and 6-month TB treatment outcomes.
Results: We screened 7,361 people over 20 months. 4,815 were eligible and enrolled; median age was 27 (IQR 22 to 35), 51% were male, and 95% reported prior HIV testing. TB symptoms included cough (5%), weight loss (4%), night sweats (4%), and fever (3%). Overall, 42% of eligible participants could produce sputum samples (intervention: 55%; usual care: 26%). Among intervention participants, 41% exhibiting no TB symptoms successfully produced sputum compared to those with 1 (48%), 2 (71%), 3 (72%), or 4 (89%) symptoms. Seven participants tested GeneXpert-positive, six in the intervention arm (3%, 95% CI 1%, 5%) and one in the usual care arm (1%, 95% CI 0%, 6%). All 6 in the intervention arm linked to care within 6 months, and 5 of the 6 completed treatment; the GeneXpert-positive participant in the control arm did not link to care and did not complete TB treatment.
Conclusion: Screening for TB on a mobile HIV testing unit in the community using GeneXpert is feasible, though likelihood of specimen production is higher among those with more TB symptoms. Overall yield for GeneXpert-positive TB was low, however, the expedited "Test & Treat TB" strategy led to rates of TB treatment completion comparable to clinic-initiated treatment in South Africa.

770 TRENDS IN HIV- AND SEX-STRATIFIED TUBERCULOSIS CASE NOTIFICATIONS IN BLANTYRE, MALAWI

Marriott Nliwasa[1], Augustine Choko[2], Mphatso Mwapasa[1], Daniel Grint[3], Peter MacPherson[4], Elizabeth L. Corbett[3]
[1]University of Malawi, Blantyre, Malawi, [2]Malawi–Liverpool–Wellcome Trust Clinical Rsr Prog, Blantyre, Malawi, [3]London School of Hygiene & Tropical Medicine, London, UK, [4]Liverpool School of Tropical Medicine, Liverpool, UK

Background: Understanding of tuberculosis (TB) epidemiology helps in the design of interventions to reduce disease burden in an area. The objective of the study was to describe trends in smear positive TB case notification rates (CNRs) in relation to an active case finding (ACF) intervention in Blantyre, Malawi and investigate TB case notification rate (CNR) ratios associated with sex, age and HIV status.
Methods: An extended monitoring and evaluation system was set up to improve reporting of TB cases (numerator for CNRs) in Blantyre in 2009-16. An electronic register was used to record TB patient's age, gender, HIV status and residence in ACF areas. Age-sex population sizes (denominators) were estimated using the national census and study area enumeration and HIV prevalence survey data, adjusting for yearly growth rate.
Results: In quarter 1 of 2011, before the introduction of TB ACF, the smear positive TB CNR in Blantyre was 220 per 100, 000 (95% CI: 169 to 282) - see Figure. When ACF was introduced in 2011, TB CNRs increased significantly in ACF areas to 405 per 100, 000 (95% CI: 335 to 486) and fell again to pre-ACF levels (206 per 100, 000 [95% CI: 157 to 266]) in 2014, when ACF was stopped. TB CNRs rose in all age and sex groups during ACF period, notably in 30 to 39-year-old men (from 360 per 100, 000 to 638 per 100,000, p=<0.001). Factors associated with higher adjusted TB CNR ratio were HIV positive status (12.7 [95% CI: 11.3 to 14.2]); male sex (2.32 [95% CI: 1.97 to 2.72]); and older age, for example, 40 to 49-year age group (1.34 [95% CI: 1.10 to 1.64]) versus 16 to 19-year age group.
Conclusion: The TB incidence in Blantyre is highest in men and those HIV-positive. Community TB ACF increased smear positive TB case detection in these key groups. Appropriately designed TB prevention and care strategies can reduce TB transmission in Africa's urban areas.



771 ROLE OF CHEST X-RAY IN DIAGNOSIS OF HIV-ASSOCIATED SMEAR-NEGATIVE TB IN UGANDA

Lydia Nakiyingi[1], John Mark Bwanika[1], Willy Ssengooba[2], Frank Mubiru[1], Harriet Mayanja-Kizza[2], Jerrold Ellner[3], Susan E. Dorman[4], Yukari C. Manabe[5]
[1]Infectious Disease Institute, Kampala, Uganda, [2]Makerere University College of Health Sciences, Kampala, Uganda, [3]Boston University, Boston, MA, USA, [4]Medical University of South Carolina, Charleston, SC, USA, [5]Johns Hopkins Hospital, Baltimore, MD, USA

Background: Chest X-ray (CXR) interpretation remains a central component of current World Health Organization recommendations for diagnosis of smear-negative tuberculosis (TB) in high HIV prevalence settings. National TB guidelines for most resource-limited settings still include use of CXR as part of their TB diagnostic algorithms. With its low specificity, high maintenance and operational costs, we evaluated accuracy of CXR for detecting culture-positive TB among HIV co-infected smear-negative presumptive TB patients in a high HIV/TB burden setting. We also evaluated the additive value of CXR to Xpert MTB/Rif test in smear-negative TB diagnosis in the same patient population.
Methods: HIV co-infected presumptive TB patients were recruited from the Infectious Diseases Institute outpatient clinic and medical wards of Mulago Hospital, Uganda. Chest radiographs were reviewed by two independent experienced radiologists using a standardised evaluation form. CXR interpretation with regard to TB was either positive (consistent with TB) or negative (normal or unlikely TB). Mycobacterial sputum and blood cultures were used as reference standard.
Results: 366 HIV co-infected smear-negative presumptive TB patients (female, 63.4%; hospitalized, 68.3%) had technically adequate chest radiographs. Median (IQR) age was 32 (28-39) years and CD4 count 106 (24-308) cells/mm^3. 81/366 (22.1%) had positive MTB cultures. 187/366 (51.1%) had CXR interpreted as consistent with TB, of which 55 (29.4%) had culture confirmed TB. Sensitivity and specificity of CXR interpretation in culture-positive, smear-negative TB diagnosis were 67.9% (95%CI 56.6-77.8) and 53.7% (95%CI 47.7-59.6) respectively while Xpert MTB/Rif sensitivity and specificity were 65.4% (95%CI 54.0-75.7) and 95.8% (95%CI 92.8-97.8) respectively. Addition of CXR to Xpert had overall sensitivity of 87.7% (95%CI 78.5-93.9) and specificity of 51.6% (95%CI 45.6-57.5); with 86.2% (95%CI 75.3-93.5) and 48.1% (95%CI 40.7-55.6) respectively among inpatients and 93.8% (95%CI 69.8-99.8) and 58.0% (95%CI 47.7-67.8) respectively among outpatients **(Table)**.
Conclusion: In this high HIV/TB burden setting, CXR interpretation by expert radiologists had low diagnostic utility in HIV co-infected patients presenting with TB symptoms and negative smear. Addition of CXR to Xpert MTB/Rif did not complement its performance in smear-negative TB diagnosis in HIV. CXR may not have a role in settings where Xpert MTB/Rif is available as a TB diagnostic.

Accuracy of Chest X-ray and Xpert MTB/Rif test when used as independent tests and in combination for smear-negative TB diagnosis in HIV using Mycobacterial cultures as reference standard

Setting	Accuracy Index	Chest X-ray	Xpert MTB/Rif test	CXR plus Xpert MTB/Rif test
Overall	Sensitivity (95% CI)	67.9% (56.6-77.8)	65.4% (54.0-75.7)	87.7% (78.5-93.9)
	Specificity ((95% CI)	53.7% (47.7-59.6)	95.8% (92.8-97.8)	51.6% (45.6-57.5)
	PPV (95% CI)	29.4% (23.0-36.5)	81.5% (70.0-90.1)	34.0% (27.6-40.8)
	NPV (95% CI)	85.5% (79.4-90.3)	90.7% (86.8-93.7)	93.6% (88.6-96.9)
Inpatients	Sensitivity	66.2% (53.4-77.4)	64.6% (51.8-76.1)	86.2% (75.3-93.5)
	Specificity	50.3% (42.8-57.7)	95.7% (91.7-98.1)	48.1% (40.7-55.6)
	PPV (95% CI)	31.9% (24.1-40.4)	84.0% (70.9-92.8)	36.8% (29.2-45.0)
Outpatients	Sensitivity	75.0% (47.6-92.7)	68.8% (41.3-89.0)	93.8% (69.8-99.8)
	Specificity	60.0% (49.7-69.7)	96.0% (90.1-98.9)	58.0% (47.7-67.8)
	PPV (95% CI)	23.1% (12.5-36.8)	73.3% (44.9-92.2)	26.3% (15.5-39.7)

Abbreviations: CI, Confidence Intervals; PPV, Positive predictive value; NPV, Negative predictive value

772 C-REACTIVE PROTEIN TO SCREEN FOR HIV-ASSOCIATED TUBERCULOSIS IN SOUTH AFRICA

Adrienne E. Shapiro[1], Ting Hong[1], Sabina Govere[2], Dumezweni Ntshangase[2], Hilary Thulare[2], Mahomed-Yunus Moosa[3], Afton Dorasamy[4], Connie L. Celum[1], Jacques H. Grosset[5], Paul K. Drain[1]
[1]University of Washington, Seattle, WA, USA, [2]AIDS Healthcare Foundation, Durban, South Africa, [3]University of KwaZulu-Natal, Durban, South Africa, [4]KwaZulu-Natal Research Institute for TB and HIV, Durban, South Africa, [5]The Johns Hopkins University, Baltimore, MD, USA

Background: A low-cost, point-of-care screening test for HIV-associated tuberculosis (TB) could accelerate antiretroviral therapy (ART) and isoniazid preventive therapy (IPT). C-reactive protein (CRP) is a non-specific inflammatory marker elevated during active TB and other pyogenic infections and can be measured using a rapid fingerstick assay. We assessed the diagnostic accuracy of CRP as a screening test for active TB in HIV-infected ambulatory adults.
Methods: We measured CRP levels in stored plasma specimens collected from HIV-infected adults at HIV testing at an urban clinic in KwaZulu-Natal, South Africa. We collected sputum from all participants for TB culture and measured CD4 T-cell counts. We calculated the diagnostic accuracy for HIV-associated pulmonary TB of: 1) CRP >5 mg/L (manufacturer threshold); and 2) the World Health Organization (WHO)-endorsed 4-symptom screen (cough, fever, night sweats, weight loss), compared to the diagnostic gold standard, a positive TB culture.
Results: Among 425 HIV-infected persons not on ART, 58% were female, median age was 32 years (IQR 27-39), and median CD4 was 306/mm^3 (IQR 176-

468). Overall, 279 (66%) had ≥1 TB-related symptom, 197 (46%) had a CRP >5 mg/L, and 42 (10%) had a positive TB culture. Sensitivity for TB of both CRP and the WHO symptom screen was 90.5% (95% CI 77.4-97.3), however the specificity of CRP was 58.5% (95% CI 53.4-63.5) compared to 37.1% (95% CI 32.2-42.1) for the symptom screen. The negative likelihood ratio (LR-) for CRP was lower than for symptom screen (0.16 vs. 0.26), indicating better performance of CRP as a "rule-out" test. CRP accuracy was similar to symptom screen in persons with CD4>200 (LR- 0.3 vs. 0.31) but better in those with CD4≤200 at highest risk for TB (LR- 0.11 vs. 0.36). Using CRP to screen for TB resulted in 228 persons screening negative, compared to 146 using the symptom screen - a 56% increase in persons eligible for IPT and ART without requiring confirmatory TB testing, and not missing any additional active TB cases.

Conclusion: CRP was as sensitive as the WHO symptom screen to diagnose TB in HIV-infected outpatients and was substantially more specific. Preserved sensitivity and higher specificity in higher CD4 strata are relevant for ART initiation in the growing proportion of persons eligible for ART with higher CD4 counts. Using CRP to exclude active TB in persons with HIV could reduce the need for time-consuming and costly diagnostic TB testing compared to current practice using the WHO symptom screen.

Screening test N=425	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)	LR- (95% CI)
CRP >5 mg/L	**90.5% (77.4-97.3)**	**58.5% (53.4-63.5)**	**98.2% (95.6-99.5)**	**0.16 (0.064-0.42)**
CD4≤200/mm³ (N=127)	*96.0% (79.6-99.9)*	*38.2% (28.8-48.4)*	*97.5% (86.8-99.9)*	*0.11 (0.015-0.73)*
CD4>200/mm³ (N=284)	*80.0% (51.9-95.7)*	*66.9% (60.9-72.5)*	*98.4% (95.3-99.7)*	*0.30 (0.11-0.83)*
WHO symptom screen (≥1)	**90.5% (77.4-97.3)**	**37.1% (32.2-42.1)**	**97.3% (93.1-99.2)**	**0.26 (0.1-0.66)**
CD4≤200/mm³ (N=127)	*92.0% (74.0-99.0)*	*22.5% (14.9-31.9)*	*92.0% (74.0-99.0)*	*0.36 (0.08-1.41)*
CD4>200/mm³ (N=284)	*86.7% (59.5-98.3)*	*43.5% (37.5-49.6)*	*98.3% (94.1-99.8)*	*0.31 (0.08-1.12)*

Table 1. Diagnostic accuracy of C-reactive protein (CRP) and symptoms to screen for tuberculosis in HIV-infected adults. CI: confidence interval; NPV: negative predictive value; LR-: negative likelihood ratio. WHO symptoms: cough, fever, night sweats, weight loss.

773 PLASMA INDOLEAMINE 2, 3-DIOXYGENASE, A BIOMARKER FOR TUBERCULOSIS IN HIV INFECTION

Clement G. Adu-Gyamfi[1], Tracy Snyman[1], Chris Hoffmann[2], Neil A. Martinson[1], Richard E. Chaisson[2], Jaya A. George[1], Melinda S. Suchard[1]
[1]University of the Witwatersrand, Johannesburg, South Africa, [2]Johns Hopkins University, Baltimore, MD, USA

Background: There exist no biomarker for diagnosing and/ or predicting active TB in HIV infected patients. Indoleamine 2, 3-dioxygenase (IDO) is an immunoregulatory enzyme which breaks down tryptophan to kynurenines. We evaluated whether IDO activity, as measured by Kynurenine-to-Tryptophan ratio, could diagnose or predict active TB disease in HIV infected adults.

Methods: Using ultra-performance liquid chromatography mass spectrometry, we measured Kynurenine and Tryptophan concentrations in plasma of 32 HIV infected patients who developed active TB followed up prospectively. We compared with 70 HIV infected control subjects from the same cohort who did not develop TB, matched by age, sex and CD4 count, and 37 unmatched HIV infected patients diagnosed with pneumonia.

Results: At time of TB diagnosis, IDO activity was significantly higher in TB patients than controls ($P < 0{\cdot}0001$). Six months prior to TB diagnosis IDO activity was significantly higher than controls in all those who later developed TB ($P < 0{\cdot}0001$). After 6 months of TB treatment, IDO activity in TB patients declined to similar levels as that of controls. IDO activity was 4 fold higher in TB patients than pneumonia patients, and could distinguish them. Using a receiver operating characteristic curve, IDO activity gave a sensitivity of 97%, specificity of 99% positive and negative predictive values of 89% and 100% for detecting active TB disease.

Conclusion: Plasma IDO activity is suitable as a biomarker of active TB in HIV positive patients.

774 HIV INFECTION IMPAIRS MYCOBACTERIUM TUBERCULOSIS-SPECIFIC CD4 T-CELL RESPONSES

Patrizia Amelio[1], Jerry Hella[2], Klaus Reither[3], Lujeko Kamwela[2], Omar Lweno[2], Anneth Tumbo[2], Linda Geoffrey[2], Song Ding[4], Giuseppe Pantaleo[1], Claudia Daubenberger[3], Matthieu Perreau[1]
[1]Lausanne University Hospital, Lausanne, Switzerland, [2]Ifakara Health Institute, Dar es Salaam, Tanzania, United Republic of, [3]Swiss Tropical and Public Health Institute, Basel, Switzerland, [4]EuroVacc Foundation, Amsterdam, Netherlands

Background: HIV infection is the major risk factor predisposing for 1) Mycobacterium tuberculosis (Mtb) infection and 2) progression from latent tuberculosis infection (LTBI) to tuberculosis disease (TB). Since, pulmonary TB (PTB) usually occurs in HIV-infected individuals with higher CD4 T-cell counts as compared to other opportunistic pulmonary infections such as Pneumocystis pneumonia, we hypothesized that progression from LTBI to PTB might not only be due to CD4 T-cell depletion but also to Mtb-specific CD4 T-cell impairment.

Methods: To test this hypothesis, Mtb-specific CD4 T-cell cytokine profiles and transcription factor expression profiles were investigated in untreated Tanzanian individuals suffering from LTBI or PTB and compared to those of untreated Mtb/HIV co-infected individuals suffering from LTBI or PTB.

Results: We show that Mtb-specific CD4 T-cell cytokine profiles of HIV negative individuals with LTBI or PTB are primarily composed of polyfunctional Th1 (IFN-γ/TNF-α/IL-2) and Th2 cells (IL-4/IL-5/IL-13). In contrast, the cytokine profiles of Mtb-specific CD4 T cells of Mtb/HIV co-infected individuals with LTBI or PTB were dominated by single TNF-α, single IFN-γ and dual IFN-γ/TNF-α, and reduction of polyfunctional Th1 and Th2 cells ($P<0.05$). The skewing of Mtb-specific CD4 T-cell cytokine profiles in Mtb/HIV co-infected individuals was associated with a significant increase of T-bet expression ($P<0.05$) and a significant reduction of Gata-3 expression in memory CD4 T cells ($P<0.05$). Taken together these results indicate that HIV infection significantly influences Mtb-specific CD4 T-cell cytokine and transcription factor expression profiles. Interestingly, the proportion of IL-2-producing Mtb-specific CD4 T cells inversely correlated with the percentage of Mtb-specific CD4 T cells expressing PD-1 ($r = -0.697$; $P<0.05$),. Finally, we showed that the serum levels of IL-1α, IL-6, IFN-α2, IFN-β, IFN-ω, IL-23, MCP-1, IP-10 and CRP were significantly reduced in Mtb/HIV co-infected individuals with PTB as compared to HIV negative individuals with PTB ($P<0.05$), suggesting that HIV infection significantly suppresses Mtb-induced systemic pro-inflammatory cytokine response.

Conclusion: Taken together, this study suggests that HIV infection significantly impairs functionally favourable Mtb-specific CD4 T-cell responses in Tanzanian individuals suffering from LTBI or PTB.

775 VARIATION IN THE NLRP3 GENE IS ASSOCIATED WITH INFLAMMATION AND MORTALITY IN HIV/TB

Shruthi Ravimohan[1], Kebatshabile Ngoni[2], Neo Tamuhla[2], Caroline Tiemessen[3], Drew Weissman[1], Gregory Bisson[1]
[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Botswana–UPenn Partnership, Gaborone, Botswana, [3]National Institute for Communicable Diseases, Johannesburg, South Africa

Background: Nearly 10-20% of advanced HIV/tuberculosis (TB) co-infected patients die despite antiretroviral therapy (ART) initiation. While hyper-inflammation likely contributes to death, the underlying mechanisms are unclear. We hypothesized that common variation in innate immune genes may play a role by modulating inflammation. As single nucleotide polymorphisms (SNP) in inflammasome pathway genes have been linked to increased risk for several inflammatory diseases and variable levels of inflammation, we investigated the association between these SNPs and early mortality in HIV/TB patients initiating ART.

Methods: We conducted a sub-analysis of a prospective cohort study of advanced HIV/TB patients initiating ART in Botswana. We determined variation at eight loci in the NLRP3, CARD8, IL1β, IL-18, and P2RX7 genes. We assumed a dominant model of inheritance for analyses, where patients homozygous for the major allele were compared to those heterozygous or homozygous for the minor allele. In unadjusted analyses, we determined the association between SNPs and death. We used a logistic regression model and adjusted for potential confounders of this association one at a time. For SNPs associated with death, we explored their relationship with pre- and post-ART levels of systemic inflammatory markers using Wilcoxon rank sum tests.

Results: Ninety-four (55%) of 170 patients enrolled in the parent study had samples available for analysis. Of the 94 patients, 82 (87%) were survivors

and 12 (13%) died within 6 months of starting ART. We found that carriers of the NLRP3 rs10754558 minor allele (G) were more likely to die soon after ART initiation than those who survived (p=0.032). In a logistic regression model, NLRP3 rs10754558 was associated with a 4.1-fold increased risk of death (Table 1). This association was strengthened after adjusting for nevirapine-based ART, baseline non-TB opportunistic infections, and pre-ART HIV viral load (Table 1). NLRP3 rs10754558-CG/GG patients had elevated levels of pre-ART MCP-1 (p=0.022) and IL-10 at week 4 post-ART (p=0.019) vs. CC patients. The CG/GG patients also tended to have elevated IL-18 at baseline (p=0.065) and week 4 post-ART (p=0.087) vs. the CC patients.

Conclusion: The NLRP3 rs10754558 SNP is associated with elevated levels of inflammasome markers and early mortality in HIV/TB patients initiating ART. Host-directed therapies that target NLRP3 could inhibit non-specific inflammation and improve outcomes in these patients.

Table 1. Logistic regression analysis of the association between *NLRP3* rs10754558 and early mortality in advanced HIV/TB co-infected patients initiating ART

Gene	RS ID (exposure)	Outcome	Factors#	Odds ratio (95% CI)	P value
NLRP3	rs10754558	Death	Base model	4.1 (1.04-16.5)	0.043
			Baseline CD4	4.3 (1.1-17.1)	0.041
			TB smear/Xpert status	4.0 (1.0-16.1)	0.051
			ATT-ART interval	4.2 (1.0-17.7)	0.049
			Baseline OI	4.8 (1.1-20.3)*	0.032
			Baseline HIV VL	4.9 (1.2-20.1)*	0.029
			NVP	7.0 (1.4-34.9)*	0.018

Potential confounders were adjusted for one at a time in the logistic regression model. *unadjusted odds ratio changed >10% after including this variable in the model.
Abbreviations: CI=confidence interval; Xpert=GeneXpert; ATT=anti-tuberculosis therapy; ART=antiretroviral therapy; OI=opportunistic infection; VL=viral load; NVP=nevirapine based ART regimen

776 DECAY OF INFLAMMATION MARKERS IN HIV-1/TB COINFECTED INDIVIDUALS INITIATING ART

Heloise M. Delagreverie[1], Claire Bauduin[2], Nathalie De Castro[1], Beatriz Grinsztejn[3], Marc Chevrier[1], Samia Mourah[1], Issa Kalidi[1], Jose H. Pilotto[4], Carlos Brites[5], Nemora T. Barcellos[6], Genevieve Chene[2], Linda Wittkop[2], Jean-Michel Molina[7], Constance Delaugerre[7]
[1]St. Louis Hospital, Paris, France, [2]L'Université de Bordeaux, Bordeaux, France, [3]Institute Nacional de Infectologia Evandro Chagas (INI/Fiocruz), Rio de Janeiro, Brazil, [4]Hospital Geral de Nova Iguaçu, Rio de Janeiro, Brazil, [5]Hospital Universitário Prof. Edgar Santos, Bahia, Brazil, [6]Secretaria de Estado da Saúde do Rio Grande do Sul, Porto Alegre, Brazil, [7]Hôpital Saint-Louis, Paris, France

Background: REFLATE-TB ANRS 12-180 was an international clinical trial of non-nucleoside reverse transcriptase inhibitor- or integrase inhibitor-based antiretroviral therapy (ART) initiation, in participants co-infected with HIV-1 and tuberculosis and treated with rifampicin. We report here the effects of efavirenz (qd) and raltegravir (400mg bid or 800mg bid) regimens on inflammation biomarkers levels up to 48 weeks after ART initiation.

Methods: The REFLATE-TB study was a phase 2 non-comparative, open-label, randomized trial including antiretroviral-naive patients with HIV and TB to receive raltegravir 400mg bid (RAL400, n=51), raltegravir 800mg bid (RAL800, n=51) or efavirenz (EFV, n=51) with tenofovir and lamivudine. Ultrasensitive C-reactive protein (usCRP), D-Dimers, IL-6 and sCD14 levels were measured in plasma samples obtained at week (W) 0, W4, W12, W24 and W48 of ART. Plasma levels were described at each time point in each arm and level changes W0-W48 were compared within each arm with two-sided Wilcoxon signed-rank tests. Plasma levels and changes over time in the 3 treatment groups were also compared with linear mixed models including random effects on intercept and slope.

Results: 141 participants with available W0 plasma samples were included, respectively 49 in EFV, 47 in RAL400 and 45 in RAL800 arms. 72% were males, median age was 38 years. At ART initiation, TB had been treated for a median 6 weeks. The baseline (W0) median viral load was 4.9log RNA copies/mL, and the median CD4+ count was 140/µL. All usCRP, IL-6, D-Dimers and sCD14 levels were above normal values at W0. Of note, usCRP levels increased significantly in all arms by week 4 of ART before subsiding. The inflammatory state improved significantly between W0 to W48 (Table 1). Notably, from W12 on, median usCRP and IL-6 levels were below 5mg/L and 5pg/mL, respectively; D-Dimers had normalized below 500ng/mL. The decay of inflammation was consistent across treatment arms and linear mixed models did not reveal differences in the dynamics or amplitude of markers decrease according to the ART regimen.

Conclusion: In HIV-1/TB co-infected participants, ART initiation with EFV, RAL400 or RAL800 effectively reduced the levels of systemic inflammation in blood as measured by usCRP, D-Dimers, IL-6 and sCD14 with no difference between treatment arms. All 4 markers normalized within one year on ART despite elevated initial values.

Table 1: Median plasma levels of inflammation and coagulation markers over 48 weeks following ART initiation

	usCRP (mg/L)			IL-6 (pg/mL)			D-Dimers (ng/mL)			sCD14 (ng/mL)		
Timepoint	EFV	RAL400	RAL800	EFV	RAL400	RAL800	EFV	RAL400	RAL800	EFV	RAL400	RAL800
W0	5.4	8.5	10.6	6.3	7.3	8.3	890	1200	985	3490	3025	3137
W4	12.6	12.4	13.6	5.7	9.9	6.5	700	1060	790	3300	2599	2900
W12	4.9	5.2	3.9	2.8	3.2	3.4	380	460	470	2923	2374	2376
W24	3.1	2.8	3.4	2.2	2.3	2.5	320	350	360	2250	1650	1740
W48	3.2	2.1	2.6	1.9	2.1	2.6	400	285	350	1763	1525	1475
W0-W48	-1.7	-2.5	-7.7	-2.9	-3.0	-3.8	-380	-505	-590	-1414	-1377	-1713
p(Wilcoxon) =	0.05	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

777 ANALYSIS OF PHAGOCYTE FUNCTION IN HIV/TB CO-INFECTION USING A NOVEL WHOLE BLOOD ASSAY

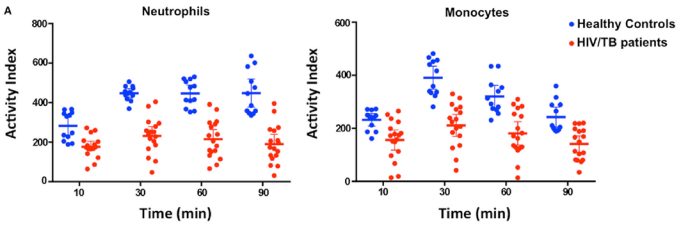
Ankur Gupta-Wright[1], Dumizulu Tembo[2], Kondwani C. Jambo[3], Elizabeth Chimbayo[4], David G. Russell[2], Henry Mwandumba[3]
[1]London School of Hygiene & Tropical Medicine, London, UK, [2]Cornell University, Ithaca, NY, USA, [3]Liverpool School of Tropical Medicine, Liverpool, UK, [4]Malawi–Liverpool–Wellcome Trust Clinical Rsr Prog, Blantyre, Malawi

Background: Mortality in patients hospitalised with HIV-associated tuberculosis (TB) remains unacceptably high, usually due to overwhelming TB infection and/or super added bacterial infection. Studies examining immune responses in this population focus on cytokine production, with few studies investigating functional immune responses, especially phagocytosis which is an important mechanism of microbial killing. We aimed to develop a novel whole blood assay to assess phagocytic function in HIV/TB co-infected patients in Malawi, a high burden setting.

Methods: We utilised the inflammatory inducer zymosan coupled to OxyBURST-SE, a fluorescent reporter of phagosomal oxidase activity. The reporter particles were incubated with whole blood, and phagocytic uptake and superoxide burst were measured after 10, 30, 60 and 90 minutes. Blood was stained with anti-CD45, anti-CD66b and anti-CD14 antibodies to allow identification of leukocytes, neutrophils and monocytes respectively before acquisition by flow cytometry. An 'activity index' (AI) of phagocytosis was calculated based on fluorescence of cells with and without reporter particles. The assay was optimised using whole blood from healthy (HIV-negative) volunteers, and then compared to hospitalised patients with HIV/TB co-infection.

Results: The assay was highly reproducible in healthy volunteers (n=4 in triplicate). Phagocytosis of zymosan reporter particles was highly dependent on particle and phagocytic cell concentration. However, AI remained constant despite the concentration of reporter particles, indicating the assay was able to measure phagosomal activity and superoxide burst at an individual cell level. The assay was performed on 18 hospitalised HIV+ patients with laboratory confirmed TB (median CD4 cell count 108.5 cell/mm^3). Kinetics of phagocytic function over time were similar to healthy volunteers, but overall intensity of superoxide burst was substantially reduced (figure, p<0.0001). Furthermore, monocyte phagocytic activity was strongly correlated with higher proportions "classical" CD14 ++CD16− monocytes (linear regression coefficient 0.0014, 95% CI 0.0005–0.0024, p=0.006), thought to specialise in phagocytosis compared to other subsets.

Conclusion: This assay demonstrated impaired whole blood phagocyte function in patients with advanced HIV-TB co-infection. It has the potential to be used to identify patient subsets with impaired functional immune responses who may benefit from adjunctive interventions aimed at reducing mortality.



778 SPATIAL OVERLAP LINKS SEEMINGLY UNCONNECTED GENOTYPE-MATCHED TB CASES IN RURAL UGANDA

Gabriel Chamie[1], Midori Kato-Maeda[1], Devy Emperador[1], Bonnie Wandera[2], John Crandall[3], Michael Janes[1], Carina Marquez[1], Moses R. Kamya[4], Edwin D. Charlebois[1], Diane V. Havlir[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]Makerere University–University of California San Francisco Research Collaboration, Kampala, Uganda, [3]California Department of Public Health, Richmond, CA, USA, [4]Makerere University, Kampala, Uganda

Background: Incomplete understanding of TB transmission in high HIV prevalence settings remains an obstacle for TB prevention efforts. Understanding where TB transmission occurs could provide a platform for optimizing approaches to case finding and interrupt transmission.
Methods: From 2012–2015, we sought to recruit all adults (≥18) starting TB treatment in a rural Ugandan community. Participants underwent household (HH) contact investigation, and provided names of frequent social contacts, sites of work, health care and socializing, and 2 sputum samples. Mycobacterium tuberculosis culture-positive (MTB Cx+) specimens underwent 24-loci MIRU-VNTR and spoligotyping to identify genotype-matched strains. We sought to identify epidemiologic links between genotype-matched cases by analyzing social networks and GPS mapping every location where TB cases reported spending ≥12 hours in total over the 1-month pre-treatment. Sites of spatial overlap (≤100m) between genotype-matched cases were considered potential transmission sites. We analyzed social networks stratified by genotype clustering status, with cases linked by shared locations, and compared network density (i.e. proportion of potential network connections that are actual connections) by location type between clustered vs. non-clustered cases.
Results: Of 173 adults with TB, 131 (76%) were enrolled, 108 provided sputum, and 84/131 (78%) were MTB Cx+: 52% (66/131) tested HIV positive. Of 118 adult HH contacts, 105 (89%) were screened and 3 (2.5%) newly diagnosed with active TB. Overall, 33 TB cases (39%; 95% CI:29-51%) belonged to 15 distinct MTB genotype-matched clusters. Within each cluster, no cases shared a HH or reported shared non-HH contacts. In 6/15 (40%) clusters, potential epidemiologic links were identified by spatial overlap at specific locations: 5/6 clusters with links based on spatial overlap involved health care settings. Genotype-clustered TB social networks had significantly greater network density based on shared clinics ($p<0.001$) and decreased density based on shared marketplaces ($p<0.001$), compared to non-clustered TB networks (Table).
Conclusion: In this molecular epidemiologic study, potential epidemiologic links between MTB genotype-matched cases were only identifiable via shared locations, health care locations in particular, rather than named contacts. This suggests most transmission is occurring between casual contacts, and emphasizes the continuing need for improved infection control in health care settings in rural Africa.

Table: Comparative network density of MTB genotype-clustered and non-clustered TB cases, within social networks that linked TB cases by shared location, based on location type of network connection. Network density here defined as the proportion of potential connections in a network that are actual connections (i.e. higher density represents a higher connectedness among nodes in a network).

	Non-clustered *N=634**		Clustered *N=241**		p-value**
Connection type	No. (%) connections	Density (SD)	No. (%) connections	Density (SD)	
Clinic	253 (40)	0.108 (0.001)	117 (49)	0.118 (0.006)	<0.001
Market	263 (41)	0.112 (0.015)	82 (34)	0.083 (0.003)	<0.001
Church	68 (11)	0.028 (0.005)	31 (13)	0.030 (0.121)	0.244
Bar/Restaurant/Vid Hall	44 (7)	0.019 (0.015)	9 (4)	0.009 (0.239)	0.110
School	2 (<1)	0.001 (0.000)	0 (0)	-	-
Non-household contact	2 (<1)	0.001 (0.148)	2 (<1)	0.002 (0.141)	0.995

*Total number of connections in each network. **T-test comparing network densities and bootstrapped standard deviations based on connection type.

779 SPATIAL DISTRIBUTION OF RIFAMPICIN-RESISTANT TB IN WESTERN CAPE, SOUTH AFRICA

Avery McIntosh[1], Helen E. Jenkins[1], Laura F. White[1], Elizabeth J. Ragan[2], Tania Dolby[3], John Simpson[3], Megan B. Murray[4], Rob Warren[5], **Karen R. Jacobson**[2]
[1]Boston University, Boston, MA, USA, [2]Boston Medical Center, Boston, MA, USA, [3]National Health Laboratory Service, Cape Town, South Africa, [4]Harvard University, Cambridge, MA, USA, [5]Stellenbosch University, Tygerberg, South Africa

Background: South Africa has the highest tuberculosis (TB) incidence globally (834/100,000), with an estimated 4.3% of cases being rifampicin resistant (RR) and 57% HIV co-infected. We demonstrate a method to enable drug resistant TB monitoring by identifying high-burden communities in the Western Cape Province using routinely collected laboratory data.
Methods: We retrospectively identified microbiologically-confirmed and RR-TB cases from all biological samples submitted for TB testing (n=2,219,891) to the Western Cape National Health Laboratory Services (NHLS) between January 2008 and June 2013. As the NHLS database lacks unique patient identifiers, we performed a series of record-linking processes to match specimen records to individual patients. We allowed patients to have multiple episodes of disease but removed those in consecutive years to avoid duplicate counting of the same episode. We aggregated cases by clinic location (n=302) to estimate the proportion of TB cases with rifampicin resistance ("RR-TB proportion") per clinic. We used inverse distance weighting to produce heat maps of the RR-TB proportion across the province. We used regression to estimate annual changes in the RR-TB proportion by clinic and mapped the estimated average size and direction of change.
Results: We identified 799,779 individuals who had specimens submitted from clinics for testing, of whom 222,735 (27.8%) had microbiologically-confirmed TB. The study population was 43% female and median age was 36 years (IQR 27-44). A total of 4.6% (95% CI: 4.6-4.7) of cases were RR (Figure 1). Among individuals with microbiologically-confirmed TB, 8,947 (4.0%) had more than one episode of disease during the study period. The RR-TB proportion among these individuals was 11.4% (95% CI: 10.7-12.0). Overall, the RR-TB proportion was spatially heterogeneous, ranging from 0% to 25% across the province. Our maps revealed significant year-on-year fluctuations in RR-TB proportions at several locations. Additionally, the directions of change in RR-TB proportion were not uniform.
Conclusion: Our maps revealed striking spatial and temporal heterogeneity in RR-TB proportions across this province. We demonstrate the potential to monitor RR-TB spatially and temporally with routinely collected laboratory data, enabling improved resource targeting and more rapid locally-appropriate interventions in a high TB and HIV burden setting.

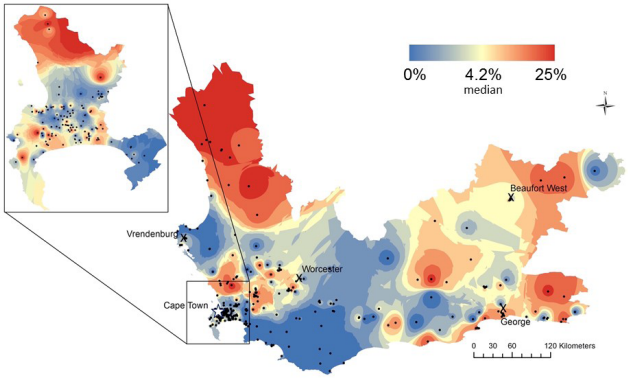


Figure 1: Inverse Distance Weighting interpolation heatmap of the proportion of total clinic-diagnosed tuberculosis cases found to be rifampicin-resistant in Western Cape Province between 2008 to 2013. Colors are broken by quantiles. Black dots denote clinic locations. Zoom to Cape Town Metropole.

780 TREATING RIFAMPICIN-RESISTANT TB WITH DELAMANID IN A HIGH HIV PREVALENCE SETTING

Erika K. Mohr[1], Anja Reuter[1], Jennifer Hughes[1], Justine Fargher[1], Johnny Daniels[1], Bongani Chabalala[1], Gabriella Ferlazzo[1], Virginia de Azevedo[2], Amir Shroufi[1], Laura Trivino Duran[1], Petros Isaakidis[1]
[1]MSF, Cape Town, South Africa, [2]City of Cape Town Department of Health, Cape Town, South Africa

Background: Delamanid (DLM) was recommended by the World Health Organization in 2014 for the treatment of rifampicin-resistant tuberculosis (RR-TB). Experience with DLM has been limited, particularly among patients with HIV. We aim to describe interim treatment outcomes using DLM in a high HIV burden programmatic setting in Khayelitsha, South Africa.
Methods: This was an observational cohort of patients who had DLM started as part of their RR-TB treatment regimen between November 1 2015 and July 31 2017. Participants were followed to September 13, 2017; interim treatment outcomes and sputum culture status at 6 months were described, stratified by HIV status.

Results: Overall, 102 patients initiated RR-TB treatment containing DLM within a median of 1.6 months (IQR 0.8-3.2) after treatment initiation; 62 (61%) were male, 91 (89%) were >19 years, 79 (77%) were HIV-positive, and 40% and 35% had multi-drug resistant tuberculosis (MDR-TB) and MDR-TB with second-line resistance, respectively. The median baseline CD4-count was 141 cells/mm^3 (n=70, IQR 61-252) and 94% of the HIV-positive patients were on ART at DLM initiation. Patients received DLM due to intolerance to drugs in the standard RR-TB regimen (n=57, 56%), limited therapeutic options (n=38, 37%), or treatment failure (n=7, 7%). Patients' interim treatment outcomes are summarized in Table 1. Among the 30/102 patients with a positive culture at DLM initiation (22/30 HIV-positive), 25 (83%) converted to negative by month 6 (19/25 HIV-positive). Time to culture conversion 6-months after delamanid initiation did not significantly differ based on HIV-status (P>0.05).
Conclusion: Early treatment outcomes among patients on DLM-containing regimens in a programmatic, primary care setting with high HIV prevalence were promising, regardless of HIV-status. As DLM has fewer drug-drug interactions with antiretroviral agents than the other novel TB drug bedaquiline, it may be an important therapeutic option for HIV/RR-TB co-infected individuals.

Interim Outcomes	HIV-Positive N=79 (100%)	HIV-Negative N=23 (100%)	Cumulative Median (IQR) time from DLM initiation to Final Outcome
Still on Treatment	52 (66)	17 (73)	--
Treatment Success	4 (5)	1 (4)	10.1 (IQR 7.1-10.3)
Loss to Follow-Up	11 (14)	1 (4)	3.1 (IQR 1.0-7.6)
Death	9 (11)	2 (9)	2.3 (IQR 0.9-3.8)
Failure	2 (3)	0 (0)	10.4 (IQR 8.1-12.6)
Transfer Out	1 (1)	2 (9)	4.1 (IQR 0.4-5.9)

781 PHARMACOKINETICS OF RIFABUTIN 150 MG QD VS 300 MG TIW WITH LPV/R IN HIV/TB PATIENTS

Chris Fujitnirun[1], Weerawat Manosuthi[2], Sivaporn Gatechompol[3], Phornchai Pingsusaen[3], Narukjaporn Thammajaruk[3], Angela Colbers[4], Rob Aarnoutse[4], Kiat Ruxrungtham[1], David M. Burger[4], Anchalee Avihingsanon[3], Opass Putcharoen[1]
[1]Chulalongkorn University, Bangkok, Thailand, [2]Bamrasnaradura Infectious Diseases Institute, Bangkok, Thailand, [3]HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [4]Radboud University, Nijmegen, Netherlands

Background: Rifabutin(RFB) based anti TB is an alternative when boosted protease inhibitors (PIs) are in need. RFB 150mg QD, 150mg three times a week (TIW) or 300mg TIW are recommended in different guidelines. However, the TIW dose of 150mg RFB was suggested to be sub-therapeutic . The objective of this study was to compare pharmacokinetics of RFB 150mg QD, vs 300mg TIW in combination with lopinavir/ritonavir (LPV/r) 400/100mg based cART in HIV/TB co-infected Thai patients.
Methods: This was a randomized, open-label, 2- arm, intensive pharmacokinetic study, as well as a 24 week efficacy study, conducted in Thai HIV and TB co-infected patients. RFB pharmacokinetics were evaluated before and between week 2 to week 8 after coadministration of LPV/r. We used a an LC-MS/MS method to determine RFB and 25-O-desacetyl RFB (desmetRFB) at Radboud university and and HPLC method to determine LPV/r concentrations
Results: A total of 21 patients were enrolled in the study. 10 patients were randomized to RFB 150mg QD and 11 patients received RFB 300mg TIW. AUC of RFB 150mg QD combined with LPV/r is moderately higher than RFB alone (41.9%). and AUC over 48 hours in patients with RFB 300 mg TIW combined with LPV/r is 23% higher than RFB alone. Geometric mean Cmax (CV) of RFB 150mg QD +LPV/r and 300mg QD alone were similar 0.65 mg/L versus 0.66mg/L, whereas the Cmax after RFB 300mg TIW + LPV/r was 24% higher.Exposure to desmetRFB was 1060% and 837% higher for 150mgRFB QD+LPV/r and 300mgRFB TIW+LPV/r. Overall RFB and desmetRFB exposure were 14% and 22% lower for the 300mgRFB TIW group compared to the 150mgRFB QD group. Pharmacokinetic parameters of LPV/r are in therapeutic level and were similar in both arms. Every patient in this study was cured from TB but uveitis which is associated to rifabutin developed in two patients who received RFB 300mg TIW.
Conclusion: Our study suggests that RFB 150mg QD and 300mg TIW could result in adequate exposure in Thai patients who concurrently use LPV/r. Moreover, this study shows that LPV/r 400/100 mg BID can give adequate lopinavir levels in HIV and TB co-infected patients who were treated with RFB both 150 mg QD and 300 mg TIW.

Table 1. Pharmacokinetic parameters of rifabutin and 25-O-desacetylrifabutin, geometric means and CV%.

	Rifabutin			25-O-desacetyl-rifabutin		
	Alone	With LPV/r		Alone	With LPV/r	
	300 mg QD	150 mg QD	300 mg TIW	300 mg QD	150 mg QD	300 mg TIW
C_{max} (mg/L)	0.66 (42%)	0.65 (36%)	0.82 (30%)	0.06 (49%)	0.33 (25%)	0.3 (39%)
T_{max} (h)	2 (1-4.0)	3 (1-8)	2 (2-6)	2.03 (1-6)	4.02 (2-10)	4 (4-12)
AUC_{0-48} (mg.h/L)	12.6 (35%)	17.94 (37%)	15.5 (43%)	1.16 (64%)	12.30 (27%)	9.71 (45%)

LPV/r: lopinavir/ritonavir, QD: once daily, TIW: thrice weekly, Cmax: maximum concentration, Tmax: time to maximum concentration, AUC0-48: area under the curve

Table 2. Pharmacokinetics of lopinavir and ritonavir, median and range

	Lopinavir (µg/mL) (range)		Ritonavir (µg/mL) (range)	
	150 mg QD RFB	300 mg TIW RFB	150 mg QD RFB	300 mg TIW RFB
C_{max}	13.455 (8.84- 16.54)	14.027 (10.6- 21.95)	0.946 (0.71- 1.38)	0.786 (0.54- 1.14)
C_{min}	5.287 (2.93- 7.92)	4.155 (1.33- 5.91)	0.223 (0.15- 0.31)	0.178 (0.07- 0.26)
C_{ave}	9.695 (5.75- 11.51)	10.252 (8.06- 15.24)	0.545 (0.39- 0.82)	0.468 (0.34- 0.66)

QD: once daily, TIW: thrice weekly, Cmax: maximum concentration, Cmin: minimum concentration, Cave: average concentration, RFB: rifabutin

782 WIRELESSLY OBSERVED THERAPY VS DIRECTLY OBSERVED THERAPY FOR TB MEDICATION ADHERENCE

Sara H. Browne[1], Charles A. Peloquin[2], Amanda J. Tucker[1], Kathleen Moser[3], Julie Low[4], Anya Umlauf[5], Florin Vaida[1], Constance A. Benson[1]
[1]University of California San Diego, La Jolla, CA, USA, [2]University of Florida, Gainesville, FL, USA, [3]Health and Human Services Agency, San Diego, CA, USA, [4]Orange County Health Care Agency, Santa Ana, CA, USA, [5]University of California San Diego, San Diego, CA, USA

Background: Directly Observed Therapy (DOT) is universally recommended to ensure Mycobacterium Tuberculosis Complex (TB) treatment adherence. DOT is resource intensive, intrusive and expensive, limiting implementation in high burden areas. Mobile technologies to confirm medication adherence have emerged recently. However, technology validation and comparison to the existing DOT Gold Standard is lacking. FDA approved Wirelessly Observed Therapy (WOT) is the first digital technology to detect medication ingestion and provide a stand-alone system to track TB medication adherence. WOT consists of an edible ingestion sensor (IS), external wearable patch and paired mobile device, it time-and-date stamps ingestions; recordings are uploaded to a secure Internet server, for remote viewing. We have previously 'digitized' fixed-dose Isoniazid/Rifampin (IS-INH/RIF) by co-encapsulation with IS (see doi:10.1002/cpt.760) and have validated WOT ingestion detection accuracy using IS-INH/RIF as 98.4% (CI 97.5-99%). We now report findings from a randomized controlled trial performed in highly funded US DOT programs comparing the proficiency of WOT and DOT to confirm TB medication adherence.
Methods: Sixty-one subjects with active MTB in the continuation phase of treatment were randomized 2:1 to receive WOT using IS-INH/RIF or standard of care DOT (5 days per week). In the WOT arm, if ingestions were not remotely confirmed, the subject was contacted within 24-48 hrs. The number of doses taken confirmed by DOT versus WOT were collected, length of observation varied according to treatment prescribed. The percentage of prescribed doses that were confirmed by DOT or WOT was calculated separately for each arm, using 7 and 5 days a week comparisons. Wilcoxon rank sum test was used to compare arms.

Results: The subjects' demographics were: mean age 41.9 years, 54% male, 77% reported income < $2000/month, 61% GED or less education. Duration of observation in days was Mean (SD) 97.1 (44.8), DOT 95 (30.1), WOT 98.1 (50.8). Table 1 shows the percentage of confirmed/prescribed doses for DOT and WOT analyzed at the group and individual subject level. WOT associated adverse events were skin rash and pruritus (10%).
Conclusion: WOT remotely confirmed a significantly greater percentage of prescribed doses than DOT over both 7 and 5 day analysis periods within highly funded US TB DOT programs. WOT is highly accurate and was a superior alternative to DOT for confirming adherence to TB medication in the continuation phase of treatment.

Table 1: The percentage of confirmed /prescribed doses for DOT and WOT analyzed at the group and individual level

		DOT (N=20 patients)	WOT (N=41 patients)	P-value
7 days	Total number of confirmed doses/ prescribed doses	2372/3808 Mean 62.3 %	7326/7574 Mean 96.7%	
	Median percent (%) of confirmed doses for each subject (95% CI)[a]	63.6 (58.3, 67.6)	97.7 (95.5, 98.3)	<0.001
5 days	Total number of confirmed doses/ prescribed doses	2372/2720 Mean 87.2%	5263/5436 Mean 96.8%	
	Median percent (%) of confirmed doses for each subject (95% CI)[a]	89.9 (82.2, 95.2)	97.9 (95.7, 98.8)	<0.001

Notes: [a] Percent calculated at the subject level (total number of confirmed doses/ total number of prescribed doses for each subject) CI = confidence interval

783 DIAGNOSTIC UTILITY OF MULTIPLEX PCR IN AN HIV-INFECTED POPULATION WITH MENINGITIS

Sarah Bridge[1], Kathy Huppler Hullsiek[2], Richard Kwizera[3], Edwin Nuwagira[1], Anna Stadelman[2], Tadeo K. Kiiza[3], Liberica Ndyatunga[1], Kenneth Ssebambulidde[3], James Mwesigye[1], Edward Mpoza[3], Mahsa Abassi[2], David Meya[3], Conrad Muzoora[1], David R. Boulware[2], Joshua Rhein[2]
[1]Mbarara University of Science and Technology, Mbarara, Uganda, [2]University of Minnesota, Minneapolis, MN, USA, [3]Infectious Disease Institute, Kampala, Uganda

Background: Meningitis remains a frequent cause of mortality among HIV-infected people in sub-Saharan Africa. We evaluated the utility of a commercial multiplex PCR assay (BioFire FilmArray® Meningitis/Encephalitis (ME) panel, Salt Lake City, Utah) in HIV-infected individuals with suspected meningitis in Uganda.
Methods: We collected CSF samples from 211 HIV-infected Ugandan adults with suspected meningitis from January 2016 to May 2017. We collected CSF samples at diagnosis in first episode of meningitis (n=129), recurrent cryptococcosis (N=6), and during therapeutic LPs following cryptococcal diagnosis (N=76). Standard bacterial, mycobacterial, and fungal CSF diagnostics were performed on site. The prevalence of Cryptococcus, bacterial, and viral pathogens in CSF were determined using the FilmArray® ME panel, run on-site in real time. We assessed the diagnostic performance of the panel for Cryptococcus.
Results: Cryptococcal meningitis was common in this population with 57% (74/129) of baseline specimens having a positive CSF cryptococcal antigen (CrAg). The sensitivity of the PCR panel for first cryptococcal episode was 85% (63/74) and the specificity was 98% (54/55) compared to CSF CrAg. All but one false negative baseline PCR result occurred when corresponding CSF cultures were either sterile (n=7) or had a quantitative cryptococcal count ≤ 100 CFU/mL (n=3). The single false positive result occurred in a subject with a positive serum CrAg but no other evidence of CNS infection. In those with a previous history of Cryptococcus (symptomatic relapse), multiplex PCR identified 3 of 5 cases of relapse. In follow-up samples obtained during therapeutic LPs, FilmArray® predicted conversion to culture sterility with 89% (34/38) negative predictive value (a negative FilmArray® = sterile culture). Other pathogens detected by PCR included CMV (n=6), HHV-6 (n=6), HSV-1 (n=5), S. pneumoniae (n=4), H. influenzae (n=3), HSV-2 (n=3), and VZV (n=3) (Table).
Conclusion: The FilmArray® ME panel appears to be a useful platform for the rapid diagnosis of CNS infections in an HIV-infected population. Commercial PCR testing is sensitive for detecting Cryptococcus in CSF when fungal burden is high, though sensitivity may be decreased at lower fungal burdens. PCR may predict conversion to culture sterility after cryptococcal meningitis diagnosis.

Table: Pathogens detected in CSF, with and without *Cryptococcus* coinfection

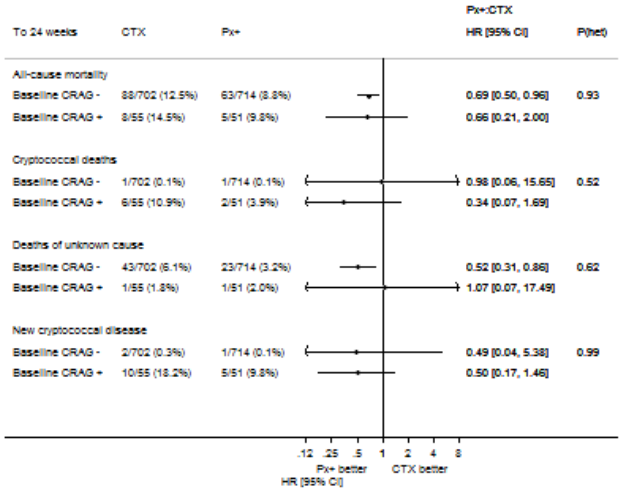
	Cryptococcus coinfection* N=105		No *Cryptococcus* coinfection* N=106		Total N=211	
	n	%	n	%	n	%
Viral pathogens detected						
Cytomegalovirus (CMV)	3	3%	6	6%	9	4%
Human herpesvirus 6 (HHV-6)	3	3%	6	6%	9	4%
Herpes simplex virus 1 (HSV-1)	1	1%	5	5%	6	3%
Herpes simplex virus 2 (HSV-2)	2	2%	2	2%	4	2%
Varicella zoster virus (VZV)	2	2%	2	2%	4	2%
Bacterial pathogens detected						
Streptococcus pneumoniae †	2	2%	3	3%	5	2%
Haemophilus influenzae †	4	4%	1	1%	5	2%

*By FilmArray® multiplex PCR
†All PCR results for bacterial pathogens were temporally clumped together, and thought to represent contamination

784 CRAG STATUS AND EFFECT ON BENEFITS FROM ENHANCED PROPHYLAXIS IN THE REALITY TRIAL

Sarah Pett[1], Lewis Haddow[2], Ruth Nhema[3], Moira J. Spyer[1], Laura Benjamin[2], Grace Najjuka[4], Ibrahim Daud[5], Jay Berkley[6], Juliet Kitabalwa[4], James G. Hakim[3], Rob Heyderman[2], Sarah Walker[1], Diana Gibb[1]
[1]MRC Clinical Trials Unit at UCL, London, UK, [2]University College London, London, UK, [3]University of Zimbabwe, Harare, Zimbabwe, [4]Joint Clinical Research Centre, Kampala, Uganda, [5]Moi University, Eldoret, Kenya, [6]KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya

Background: In HIV-infected adults/children with CD4<100 cells/ul starting ART in sub-Saharan Africa, the REALITY trial (ISRCTN43622374) showed that an enhanced prophylaxis (Px+) package (minimum cost $5.6) including 12 weeks' fluconazole 100mg OD at ART initiation significantly reduced all-cause mortality, mortality from unknown causes and cryptococcus, and incidence of new cryptococcal disease vs cotrimoxazole alone (CTX). We assessed the impact of enrolment cryptococcal antigen (CRAG) status on these outcomes.
Methods: Stored enrolment plasma was tested using the IMMY CrAg lateral flow assay. Logistic regression with backwards elimination (p>0.1) identified independent predictors of baseline CRAG status, and proportional hazards models estimated the impact of Px+ vs CTX on all, cryptococcal and unknown deaths, and new cryptococcal disease, through 24 weeks by baseline CRAG.
Results: 1550(86%) adults from Kenya, Uganda and Zimbabwe (Malawi results pending) with median baseline CD4 36 cells/ul (IQR 16-63) and VL 275,700 c/ml, were randomized to CTX (n=771) vs Px+ (n=779). Excluding 23 (1.5%) with active cryptococcal disease at enrolment, 55(7.3%) vs 51(6.7%) were CRAG+ in CTX vs Px+ respectively. CRAG+ patients had lower CD4 (OR=0.90 per 10 cells/ul higher (95% CI 0.83-0.97) p=0.006) and were less often female (OR vs male=0.68 (0.45-1.02) p=0.06). Over 24 weeks on ART, there were 96 CTX vs 68 Px+ deaths. 6 of 7 CTX deaths and 2 of 3 Px+ deaths due to cryptococcal disease were CRAG+, whereas there was only 1 CRAG+ among 44 deaths from unknown causes in CTX vs 1 among 24 on Px+. Over 24 weeks, there were 12 CTX vs 6 Px+ new cryptococcal meningitis cases; 10 vs 5 respectively were baseline CRAG+. Px+ reduced new cryptococcal disease equally in CRAG+ (HR=0.50) and CRAG- (HR=0.49) (interaction p=0.99) (figure); similarly for all deaths (interaction p=0.93). Of 49 patients treated for cryptococcal disease post-enrolment, only 12(24%) were CRAG+ at enrolment.
Conclusion: ~7% patients were CRAG+ pre-ART, without overt cryptococcal disease. CRAG+ was rare among unknown deaths suggesting these were unlikely due to cryptococcus. The relative benefits of fluconazole-containing Px+ were similar among CRAG+ and CRAG- patients. These data support the use of this affordable fluconazole-containing enhanced Px+ bundle in this severely immunocompromized group, particularly where costs of tests are similar to costs of fluconazole ($2.6) or where availability is limited.



785 EVALUATION OF A CRYPTOCOCCAL SCREENING AND TREATMENT PROGRAM IN HIV CLINICS IN UGANDA

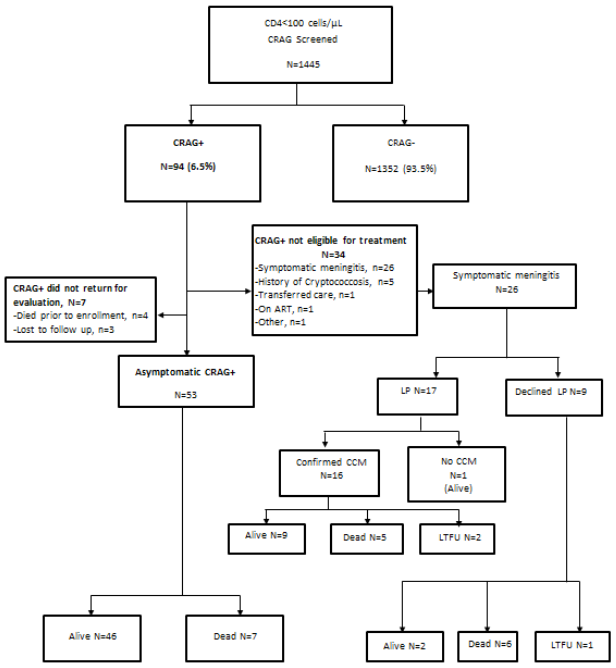
Elizabeth Nalintya[1], David Meya[1], Sarah Lofgren[2], Kathy Huppler Hullsiek[2], David R. Boulware[2], **Radha Rajasingham**[2]
[1]Infectious Disease Institute, Kampala, Uganda, [2]University of Minnesota, Minneapolis, MN, USA

Background: Screening for cryptococcal antigen (CRAG) among those with a CD4 cell count <100 cells/μL, and treating asymptomatic CRAG+ with fluconazole saves lives and is recommended by the WHO. However, implementation and uptake have been slow outside of clinical trials. Programs with high rates of loss to follow up or delayed ART initiation do not demonstrate the same survival benefit as seen in clinical trials. Few studies have evaluated optimal programmatic implementation to maximize survival amongst CRAG+. We designed a CRAG screening program, and evaluated implementation and clinical outcomes in routine care in Kampala.

Methods: At 11 HIV clinics, CD4 results<100 cells/μL were reflexively tested for CRAG using remaining plasma. Preemptive fluconazole treatment was given to asymptomatic CRAG+ persons. Our screening program included a) clinic-wide education, b) laboratory staff training, c) identification of a responsible clinic point-person, trained in operational aspects, and d) a system for ongoing review and feedback. If participants lost to follow up were not found after active tracing, they were presumed dead.

Results: Between December 2015 and January 2017, 1446 persons with a CD4<100 cells/μL were screened for CRAG, with a median CD4 cell count of 40 (IQR: 17 to 70) cells/μL. Prevalence of CRAG+ was 6.5% (n=94/1446) (Figure 1). Seven CRAG+ persons died or were lost to follow up prior to further clinic evaluation. Of the 53 asymptomatic CRAG+, median CD4 cell count was 20 cells/μL (IQR: 5 to 45), and median plasma CRAG titer was 1:40 (IQR: 1:20 to 1:160). 100% were prescribed fluconazole therapy and ART, a median of 14 days and 28 days after CRAG screening, respectively. Six-month survival was 87% (46/53). Of 26 symptomatic CRAG+, 17 consented to a lumbar puncture, and 16 had confirmed cryptococcal meningitis with a median CD4 cell count of 27 cells/μL (IQR: 10 to 45) and median plasma CRAG titer of 1:160 (IQR: 1:40 to 1:1120). For those with confirmed meningitis, mortality was 44% at 6 months despite amphotericin-based treatment. Of those symptomatic who declined lumbar puncture (n=9), 78% (7/9) died.

Conclusion: Our CRAG screening program resulted in 87% survival for asymptomatic CRAG+ persons who received timely fluconazole and ART, however 13% CRAG+ died before returning for evaluation. Mortality from symptomatic meningitis was 44% despite amphotericin therapy. Access to standard meningitis treatment is desperately needed to further reduce mortality.



786 CLINIC-BASED LATERAL FLOW CRYPTOCOCCAL ANTIGEN TESTING AT HIV DIAGNOSIS, SOUTH AFRICA

Paul K. Drain[1], Ting Hong[1], Hilary Thulare[2], Mahomed-Yunus Moosa[3], Connie L. Celum[1]
[1]University of Washington, Seattle, WA, USA, [2]AIDS Healthcare Foundation, Durban, South Africa, [3]University of KwaZulu-Natal, Durban, South Africa

Background: The World Health Organization (WHO) recommends screening HIV-infected people for cryptococcal antigens to identify cryptococcosis, a major cause of AIDS-related deaths. A point-of-care assay to detect cryptococcal antigens may be beneficial, but has not been validation at the clinical point of care following HIV testing. We sought to determine the feasibility and validation of a lateral flow assay for cryptococcal antigenemia among newly-diagnosed HIV-infected adults in South Africa.

Methods: We conducted a cross-sectional study of newly-diagnosed HIV-infected adults who received voluntary HIV testing in an outpatient clinic. A trained nurse obtained urine, finger-prick and venous whole blood and performed clinic-based testing with a rapid cryptococcal antigen lateral flow assay (Immy Inc., Norman, USA) per manufacturer's specifications. We also performed lab-based serum cryptococcal antigen testing with an ELISA-based assay, as developed by the same manufacturer, as the gold standard. We assessed diagnostic accuracy of the rapid cryptococcal assay, and stratified results by CD4 categories.

Results: We enrolled 5,618 participants, among whom 1,588 were HIV-infected and screen for cryptococcal antigenemia. The mean age was 33.6 (SD ±9.2) years, 1,184 (59.8%) were female, and median CD4 count was 309 cells/mm^3 (interquartile range: 162–477 cells/mm^3). Among those, 133 (8.4%), 48 (3.0%), and 31 (2.0%) were cryptococcal antigen positive by the lateral flow assay for urine, finger-prick blood, and venous whole blood samples, respectively. The urine, finger-prick blood, and venous whole blood had a overall sensitivity of 50% (95% CI 23-77%), 36% (95% CI 13-65%), and 43% (18-71%), and likelihood ratio positive values of 4.90, 10.8, and 22.3, respectively. When frozen serum samples were tested using the lateral flow assay, the assay sensitivity was 93% (95% CI 66-100%) and specificity was 100% (95% CI 88-100%). Two independent readers had very high agreement for lateral flow assay results (p<0.0001).

Conclusion: The performance of the lateral flow cryptococcal antigen assay was moderately sensitive for both finger-prick and venous whole blood, but was too non-specific for urine samples, among untreated HIV-infected adults in South Africa. However, the performance of the cryptococcal antigen assay was excellent for serum samples. While clinic-based cryptococcal antigenemia

screening may accelerate appropriate treatment, serum-based testing may be preferred where resources are available.

Table. Overall sensitivity, specificity, and likelihood ratios of the lateral flow cryptococcal antigen assay.

	Sensitivity	# TP/ (#TP+#FN)	Likelihood ratio positive	Specificity	# TN/ (#TN+#FP)**	Likelihood ratio negative
Urine	0.5 (0.23, 0.77)	7/14	4.90	0.9 (0.88, 0.91)	1021/1137	0.56
Finger-prick whole blood	0.36 (0.13, 0.65)	5/14	10.80	0.97 (0.95, 0.98)	1111/1149	0.66
Intra-venous whole blood	0.43 (0.18, 0.71)	6/14	22.38	0.98 (0.97, 0.99)	1127/1149	0.58
Serum	0.93 (0.66, 1)	13/14	.	1 (0.88, 1)	29/29	0.07

787 SYMPTOMATIC CRYPTOCOCCAL ANTIGENEMIA PRESENTING AS EARLY CRYPTOCOCCAL MENINGITIS

Kenneth Ssebambulidde[1], Mahsa Abassi[2], Joshua Rhein[2], Ananta Bangdiwala[2], Darlisha A. Williams[2], Edward Mpoza[1], Lillian Tugume[1], Richard Kwizera[1], Abdu Musubire[3], Fiona Cresswell[4], Sarah Lofgren[2], Kathy Huppler Hullsiek[2], David R. Boulware[2], David Meya[1]

[1]Infectious Disease Institute, Kampala, Uganda, [2]University of Minnesota, Minneapolis, MN, USA, [3]Makerere University College of Health Sciences, Kampala, Uganda, [4]London School of Hygiene & Tropical Medicine, London, UK

Background: Individuals with cryptococcal antigenemia are at high risk for developing cryptococcal meningitis (CM) if left untreated. It is unknown if meningitis may precede the detection of cryptococcal antigen (CrAg) in cerebrospinal fluid (CSF). We present a sub-population of individuals with symptomatic cryptococcal antigenemia, but negative CSF CrAg.

Methods: We evaluated serum and CSF CrAg among 1,236 HIV-seropositive individuals presenting with suspected meningitis in Kampala and Mbarara, Uganda between August 2013 and May 2017. Baseline characteristics and clinical outcomes of individuals with symptomatic cryptococcal antigenemia with negative CSF CrAg were compared to individuals with confirmed CM, (positive CSF CrAg). Wilcoxon rank sum tests were used to compare continuous variables and chi-square or Fisher's exact tests were used to compare categorical variables.

Results: We found 44% (547/1,236) of individuals screened had CM and 4.3% (53/1,236; 95% CI 3.2%-5.4%) had symptomatic cryptococcal antigenemia with negative CSF CrAg. The median CD4 count was higher for individuals with negative CSF CrAg compared to those with CM (29 (IQR 7, 86) versus 16 (IQR 6, 48) cells/μL; p=0.09), and headache was a less common symptom (81% vs 97%; p<0.01) (table). More individuals with negative CSF CrAg presented with normal CSF WBC (<5 cells/μL) (78% vs 60%; p<0.01) and normal OP (<20cmH20) (87% vs 39%; p<0.01). Of those presenting with negative CSF CrAg, 26% (14/53) were diagnosed with tuberculous meningitis (TBM) and 5.6% (3/53) subsequently grew Cryptococcus on CSF culture. Of those with TBM, 7 were detected by CSF Gene-Xpert, 2 by MTB culture, and 1 by AFB smears; 6 were purely empirical diagnoses. We had no cases of bacterial or viral meningitis on CSF PCR or culture, and 68% (36/53) had no known etiology. Among those with known in-hospital outcome, mortality was similar in those with symptomatic antigenemia with negative CSF CrAg and those with cryptococcal meningitis (39% (16/41) vs 32% (168/522); p=0.37); 23% of those with negative CSF CrAg had unknown outcome.

Conclusion: Symptomatic cryptococcal antigenemia with a negative CSF CrAg is a relatively common presentation. We hypothesize this represents early cryptococcal CNS infection. We observed a similar high in-hospital mortality in individuals with CrAg antigenemia regardless of CSF CrAg positivity. Further studies to better understand the clinical course and optimal management of this subset of individuals are warranted.

Table: Baseline characteristics and outcomes of symptomatic antigenemia compared to confirmed cryptococcal meningitis

	N with data	Symptomatic antigenemia CSF CrAg(-) (N=53)	Cryptococcal meningitis CSF CrAg (+) (N=547)	p-value
CSF WBC < 5	53	42 (79%)	309 (60%)	<.01
CSF OP < 200	53	46 (87%)	215 (39%)	<.01
CD4	49	29 (7, 84)	16 (6, 48)	0.09
Fever	53	34 (64%)	264 (48%)	0.03
Headache	53	43 (81%)	530 (97%)	<.01
Photophobia	53	7 (13%)	141 (26%)	0.04
GCS < 15	51	29 (57%)	233 (43%)	0.06
Diagnosed with TBM	53	14 (26%)	5 (1%)	<.01
Status at discharge	53			0.37*
Alive		25 (47%)	354 (65%)	
Dead		16 (30%)	168 (31%)	
Unknown		12 (23%)	25 (5%)	

Percents displayed are out of N with data in group group; Median (IQR) displayed for continuous variables. P-values are from Wilcoxon Rank Sum tests for continuous variables, and Chisq or Fisher's exact tests for categorical variables. *P-value comparing the proportion died among known outcomes (n=41).

788 POSTMORTEM CRYPTOCOCCAL MENINGITIS FOLLOWING TREATMENT FOR CRYPTOCOCCAL ANTIGENAEMIA

Rachel M. Wake[1], Tanvier Omar[2], Aaron S. Karat[3], Joseph N. Jarvis[4], **Nelesh P. Govender**[5], Thomas S. Harrison[1]

[1]St. George's University of London, London, UK, [2]University of the Witwatersrand, Johannesburg, South Africa, [3]London School of Hygiene & Tropical Medicine, London, UK, [4]University of Pennsylvania in Botswana, Gaborone, Botswana, [5]National Institute for Communicable Diseases, Johannesburg, South Africa

Background: Cryptococcal antigen (CrAg) screening and treatment with pre-emptive fluconazole reduces the incidence of evident cryptococcal meningitis and death among adults with advanced HIV. However, mortality remains higher in CrAg-positive than in CrAg-negative patients with similar CD4+ T-lymphocyte counts. Causes of this residual high mortality remain unclear.

Methods: Minimally-invasive autopsies (MIA) were performed on patients enrolled in a prospective cohort study in Johannesburg, who died following CrAg screening. Samples obtained by needle biopsy or aspiration, included lung, liver, spleen, kidney, and skin tissue, and blood, pericardial and cerebrospinal fluid (CSF). Samples underwent microbiological testing at the National Institute for Communicable Disease, and histological analysis at the University of the Witwatersrand. Investigators performing analyses were not aware of the patients' ante mortem CrAg test status.

Results: Death within 6 months occurred in 15/68 (22%) CrAg-positive and 12/129 (9%) CrAg-negative patients (adjusted HR 2.6, 95% CI 1.1 – 6.1, p=0.036). MIA was performed on four CrAg-positive and two CrAg-negative patients, none of whom had symptoms or signs of meningitis at the time of CrAg screening. Two patients were on antiretroviral therapy (ART) at enrolment, two commenced after 14 and 22 days, and two never received ART prior to death. CrAg-positive patients started antifungal therapy (fluconazole 800mg daily for two weeks, followed by 400mg for two months, then 200mg daily) in accordance with national CrAg screen-and-treat guidelines. All CrAg positive patients had lumbar punctures; one was diagnosed with subclinical cryptococcal meningitis and started on amphotericin B and fluconazole. Death occurred at median 35 days (IQR 34 – 38) after CrAg screening. Post-mortem cryptococcal meningitis was diagnosed in all four CrAg-positive patients by CSF CrAg test (n=4) and culture (n=1). Cryptococcosis was also identified histologically in lung tissue (n=1). Although other pathogens that likely contributed to death were identified in autopsy samples, there was no evidence of cryptococcal disease in either CrAg-negative patient.

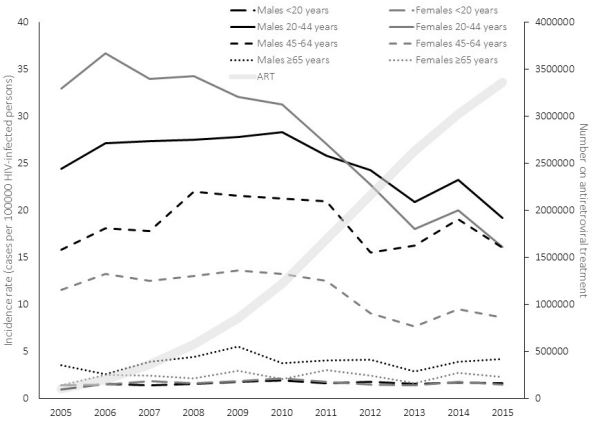
Conclusion: Undiagnosed cryptococcal meningitis may contribute to mortality among CrAg-positive patients despite the currently recommended pre-emptive fluconazole regimen. More aggressive antifungal therapy, for example combination therapy with flucytosine, may prevent death among asymptomatic CrAg-positive patients identified through screening.

789 DECLINING INCIDENCE OF HIV-ASSOCIATED CRYPTOCOCCOSIS IN SOUTH AFRICA, 2005-2015

Nelesh P. Govender[1], Cheryl Cohen[1], Phelly Matlapeng[1], Penny Crowther-Gibson[1], Susan Meiring[1], Alan Karstaedt[2], Halima Dawood[3], Kerrigan McCarthy[1], Graeme Meintjes[4], Vanessa Quan[1]
[1]National Institute for Communicable Diseases, Johannesburg, South Africa, [2]University of the Witwatersrand, Johannesburg, South Africa, [3]University of KwaZulu-Natal, Durban, South Africa, [4]University of Cape Town, Cape Town, South Africa

Background: The annual incidence rate of cryptococcosis was 139 cases per 100000 HIV-infected persons in Gauteng province during South Africa's pre-antiretroviral treatment (ART) era, 2002-2004. By 2015, an estimated 3.3 million of 6.9 million HIV-infected persons were on ART vs. approximately 100000 in 2005. We hypothesised that increased ART coverage would be associated with a decline in the incidence rate of cryptococcosis.
Methods: We conducted national active population-based laboratory surveillance for cryptococcosis, 2005-2015. A case was defined as a person diagnosed with a first episode at any public-or private-sector laboratory with a positive cerebrospinal fluid India ink/ cryptococcal antigen (CrAg) test or culture of Cryptococcus from any specimen. We excluded patients with isolated cryptococcal antigenemia across the period because routine CrAg screening was initiated in 2012, initially in a few health districts. Annual incidence rates were calculated using mid-year HIV population denominators from the Thembisa model. We collected data on in-hospital management and outcome from a subset of cases at sentinel urban hospitals.
Results: Over 11 years, 85969 incident cases were detected, the vast majority (81912; 95%) with cryptococcal meningitis. The national annual incidence rate peaked at 162 cases per 100000 HIV-infected persons (95%CI, 158-165) in 2006, declined to 127 cases per 100000 (95%CI, 125-130) in 2011 and to 90 cases per 100000 (95%CI, 88-92) in 2015. A reduction from the peak annual incidence rate was documented across all provinces in 2015 (range, 45% to 67%). Annual incidence was higher among males across all adult age groups in 2015; the most marked reduction in annual incidence occurred among women aged 20-44 years (Fig. 1). While a significantly higher proportion of patients was prescribed amphotericin B-based induction treatment (vs. fluconazole) each year (2005: 371/1204 [31%] vs. 2015: 355/391 [91%]; p<0.001), there was no corresponding reduction in the annual in-hospital case-fatality ratio (2005: 418/807 [34%]; 2015: 165/437 [38%]; p=0.06). More than half were ART-experienced in 2015 (204/379 [54%]).
Conclusion: We demonstrated a 44% reduction in the national annual incidence rate of cryptococcosis from a peak in 2006 to below pre-ART levels in 2015, temporally associated with ART program expansion. Focused interventions, including HIV test and treat, could reduce the incidence among adult males and national CrAg screening may reduce cryptococcosis-related mortality.

Figure 1: Age- and sex-specific incidence rates for cryptococcosis, South Africa, 2005-2015



790 ETIOLOGIES OF SYMPTOMATIC RECURRENCE OF HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS

Emily Evans[1], Kathy Huppler Hullsiek[2], Edwin Nuwagira[1], Edward Mpoza[3], Kenneth Ssebambulidde[3], Lillian Tugume[3], Bozena M. Morawski[2], Sarah Lofgren[2], Mahsa Abassi[2], Darlisha A. Williams[3], Conrad Muzoora[1], David Meya[3], David R. Boulware[2], Joshua Rhein[2]
[1]Mbarara University of Science and Technology, Mbarara, Uganda, [2]University of Minnesota, Minneapolis, MN, USA, [3]Infectious Disease Institute, Kampala, Uganda

Background: Recurrence of cryptococcal meningitis (CM) after initial therapy causes substantial mortality among HIV-infected patients. Differentiating cases of immune reconstitution inflammatory syndrome (IRIS) from relapse, persistent infection, or new opportunistic infections presents a diagnostic challenge. We assessed clinical characteristics and etiologies of HIV-infected Ugandans with symptomatic CM recurrence.
Methods: We enrolled a prospective cohort of 75 HIV-infected persons with recurrent symptoms of cryptococcal meningitis in Uganda from August 2013 to May 2017. All cases were reviewed by two experts, who provided a consensus diagnosis of relapse, persistence, CM-IRIS, or "other". Statistical comparisons were made with Kruskal-Wallis, linear regression and chi-squared tests. An objective classification system based on CSF culture growth, timing of previous cryptococcal meningitis episodes and antiretroviral (ART) initiation was used to categorize cases, and the accuracy of this system was assessed.
Results: CSF cultures were positive in 76% (57/75) of participants, reflecting frequent occurrence of relapse (40%; 30/75) or persistence of prior infection (36%; 27/75). Those with positive cultures had lower CD4 counts than those with negative cultures (18 (IQR 7-55) vs 76 (IQR 35-148) cells/μL; p=0.01). Compared to those with persistence, participants with relapse presented later (8.0 (IQR 5.2-13.3) vs 2.1 (IQR 1.4-3.6) months from initial diagnosis; p<0.001), were more likely to have been previously treated with amphotericin B (90% vs 26%; p<0.001), and were less likely to be currently receiving fluconazole (33% vs 52%; p=0.16). CSF cultures were negative in 24% (18/75) of participants, of which 39% (7/18) were thought to represent paradoxical CM-IRIS. Individuals with CM-IRIS presented a median of 3.0 (IQR 1.1-3.7) months after initial cryptococcal meningitis diagnosis. A classification system utilizing culture results and the timing of previous cryptococcal meningitis and ART initiation optimally differentiated etiology in 85% (64/75) of the cases.
Conclusion: The causes of recurrent symptoms after cryptococcal meningitis include relapse following early discontinuation of fluconazole prophylaxis, persistence with substandard induction therapy, and CM-IRIS. Culture, together with a detailed patient history, remains central to determining the etiology of symptomatic cryptococcal meningitis recurrence. Additional studies aimed at improving diagnostics in this diverse population are needed.

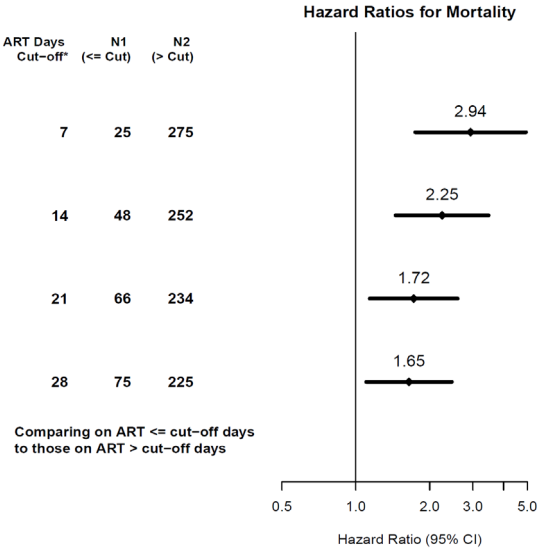
791 HIGH MORTALITY ASSOCIATED WITH UNMASKING CRYPTOCOCCAL MENINGITIS

Joshua Rhein[1], **Kathy Huppler Hullsiek**[1], Nathan C. Bahr[1], Lillian Tugume[2], Edwin Nuwagira[3], Kenneth Ssebambulidde[2], Reuben Kiggundu[2], Emily Evans[3], Edward Mpoza[2], Darlisha A. Williams[2], Mahsa Abassi[1], Abdu Musubire[2], Conrad Muzoora[3], David Meya[2], David R. Boulware[1]
[1]University of Minnesota, Minneapolis, MN, USA, [2]Infectious Disease Institute, Kampala, Uganda, [3]Mbarara University of Science and Technology, Mbarara, Uganda

Background: Increased antiretroviral therapy (ART) availability in Africa has led to more patients developing cryptococcosis after ART initiation. Despite this changing epidemiology, data regarding cryptococcal meningitis (CM) in those already receiving ART are lacking. Preliminary analyses (2015; n=172) suggested poor outcomes of unmasking CM with recent ART initiation. We sought to confirm and further characterize this observation by comparing clinical presentation and outcomes in a large cohort of ART-naïve and ART-experienced adults.
Methods: We prospectively enrolled 626 HIV-infected persons with CM in Uganda from August 2013 to May 2017. Participants were classified by ART status and the timing of ART initiation. Statistical comparisons were made with Kruskal-Wallis or Fisher's Exact tests, with a primary endpoint of 2-week survival.
Results: Overall, 48% (300/626) of participants were receiving ART at presentation, having initiated ART a median of 122 (IQR, 28-760) days prior to CM diagnosis. Compared with those not receiving ART, participants receiving ART had higher CD4 counts (median 30 (IQR, 10-79) vs 12 (IQR, 6-46) cells/μL; *p*=.02) and lower CSF fungal burdens (median 4.1 (IQR, 2.1-5.2) vs 5.0 (IQR,

4.0-5.6) $\log_{10}$ CFU/mL CSF; $p<.001$). Of those receiving ART, 50% (151/300) had initiated ART ≤ 4 months, and 16% (48/300) had initiated ART ≤ 14 days. Persons starting ART ≤ 4 months prior were more likely to present with CSF pleocytosis (47% vs 30%; $p=.003$) compared to those initiating ART > 4 months prior to diagnosis. Among persons receiving ART for > 4 months, 82% had HIV viral loads > 1000 copies/mL. Two-week mortality did not differ by overall ART status (27% vs 26%; $p=.86$). However, 50% (24/48) of those receiving ART for ≤ 14 days died within 2-weeks compared with 18% (19/103) of those receiving ART for 15-122 days and 23% (35/149) of those receiving ART for > 4 months ($p<.001$). Hazard ratio for mortality decreased as the duration from ART initiation to development of CM increased from 7 to 28 days (**Figure**).

Conclusion: Cryptococcosis after ART initiation is common in Africa. Patients initiating ART who unmask cryptococcal meningitis are at a high risk of death. Immune recovery in the setting of CNS infection is detrimental, and management of this population requires further study. Implementing pre-ART cryptococcal antigen screening is urgently needed to prevent CM after ART initiation.



792 CUSTOMIZED AMPHOTERICIN DURATION FOR CRYPTOCOCCAL MENINGITIS BASED ON FUNGAL BURDEN

Darlisha A. Williams[1], Kathy Huppler Hullsiek[2], Andrew Akampurira[1], Tonny Luggya[1], Edwin Nuwagira[3], Lillian Tugume[1], Edward Mpoza[1], Reuben Kiggundu[1], Kenneth Ssebambulidde[1], Mahsa Abassi[2], Conrad Muzoora[3], David Meya[1], David R. Boulware[2], Joshua Rhein[2]

[1]Infectious Disease Institute, Kampala, Uganda, [2]University of Minnesota, Minneapolis, MN, USA, [3]Mbarara University of Science and Technology, Mbarara, Uganda

Background: Successful induction therapy for cryptococcal meningitis (CM) relies on finding a balance between achieving fungal clearance and minimizing severe and potentially life-threatening amphotericin toxicity. In the ASTRO-CM trial, a customized approach to amphotericin induction therapy was employed based on initial fungal burden in cerebral spinal fluid (CSF). Here we report the feasibility and clinical outcomes of a customized approach to CM induction therapy.

Methods: We prospectively enrolled 460 HIV-infected CM patients in Uganda from March 2015 to May 2017. Cryptococcal cultures were obtained at baseline. Amphotericin was discontinued after 7 days if there was no fungal growth after 7 days of culture, or discontinued after 10 days if cultures were < 10,000 CFU/mL after 10 days of culture. Participants otherwise received 14 days of amphotericin. Participants were classified as receiving short (7-8 days; sterile culture), intermediate (9-12 days; <10,000 CFU/mL) or standard (13-14 days; ≥10,000 CFU/mL) durations of amphotericin. Clinical outcomes were compared.

Results: A total of 319 (69%) persons survived to 2 weeks. Of survivors, 69% (219/319) received the intended duration of amphotericin per the outlined algorithm. In those following the intended algorithm, 5% (11/219) received short duration, 23% (50/219) received intermediate duration, and 72% (158/219) received standard duration of amphotericin induction therapy. Persons receiving abbreviated durations of amphotericin had shorter median days of hospitalization [8 (IQR 7-14), 11 (10-14) or 15 (14-18)] days by respective duration group; p<.001), a lower incidence of phlebitis (0%, 8%, 20%; p=.04), and better 18-day CSF sterilization rates (72% in intermediate group vs. 50% in standard group; p=<.01). The incidence of CM relapse and grade ≥3 adverse events were similar across groups. Among 2-week survivors, there was no significant difference in 18-week mortality across customization groups (46%, 32% and 26% for short, intermediate, and standard groups; p=0.31).

Conclusion: Patients with CM present with varying CSF fungal burdens. We have demonstrated the ability to attain adequate CSF sterility with shortened courses of amphotericin by following a customized approach to therapy based on initial fungal burden. While this approach may be challenging to follow in resource-limited settings, it could maximize therapeutic efficiency while minimizing adverse events and hospitalization costs.

793 PCR AND URINE ANTIGEN FOR DIAGNOSIS OF DISSEMINATED HISTOPLASMOSIS IN AIDS PATIENTS

Maria D. Niembro-Ortega[1], Rosa A. Martínez-Gamboa[1], Brenda Crabtree-Ramírez[1], Pedro Martínez-Ayala[2], Andrea Rangel-Cordero[1], Nancy G. Velázquez-Zavala[1], Janet Santiago-Cruz[1], Paulette G. Díaz-Lomelí[1], Armando Gamboa-Domínguez[1], Edgardo F. Reyes-Gutiérrez[1], Pedro Torres-González[1], José Sifuentes-Osornio[1], Luis A. Ponce de Leon-Garduño[1]

[1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Hospital Civil Fray Antonio Alcalde, Guadalajara, Mexico

Background: Disseminated histoplasmosis (DH) is an AIDS-defining infection and the most common endemic fungal infection in North America. The current diagnostic tests for DH are time-consuming, expensive and not widely available. Recently a nested PCR targeting a 100-kDa protein (Hc100) from H. capsulatum was described for DH diagnosis. Additionally an urine antigen for DH diagnosis (IMMY alpha) is recently available for in-site use. We aim to determine the diagnostic performance of Hc100 PCR and IMMY alpha urine antigen in comparison with culture for DH in HIV infected patients.

Methods: We conducted a double-blind, multicenter, prospective, diagnostic tests study from December 2015 to June 2017. Adult HIV-positive patients presenting with fever and at least two of the following criteria: lymphadenopathy, hepatomegaly, splenomegaly, mucosal ulcers, dermatologic lesions, gastrointestinal bleeding; cytopenias, elevation of AST, LDH or ferritin levels; or radiographic findings suggestive of extrapulmonary infection were included from 10 hospitals in Mexico. At least a BACTEC MYCO/F Lytic blood culture and a blood sample for Hc100 amplification were required for inclusion. Additional samples (bone marrow, urine, tissue) for each case were obtained according with the in-site physician´s criteria. Fungal culture and Hc100 were performed to every additional sample. All clinical specimens were analyzed at a central laboratory.

Results: 270 patients with probable DH were included in the study. Fifty-four patients resulted in an alternative diagnosis (50% had mycobacterial infection). Seventy-seven cases were confirmed with DH (67 of them through culture isolation and 10 by histopathology only); 218 blood cultures, 171 bone marrow cultures and 53 cultures of tissue were compared with its corresponding Hc100 nested PCR, and 246 urine samples for the IMMY ALPHA Antigen EIA. (Table 1). The positivity rate of Hc100 PCR varied depending on the sample. The highest sensitivity (90%) and negative predictive value (96.7%) were observed from tissue samples. Specificity of the IMMY ALPHA Histoplasma antigen EIA when compared to any positive culture was 95% (95% CI 91.8-97.3).

Conclusion: In HIV patients with suspected DH, Hc100 PCR and IMMY ALPHA Histoplasma antigen EIA had a good diagnostic performance in terms of sensitivity and negative predictive value. Both tests were rapid and accessible to implement in endemic areas were mycology laboratories are not available.

	Hc100 nested PCR in blood samples vs BACTEC MYCO/F Lytic blood culture (n=218)	Hc100 nested PCR in bone marrow samples vs bone marrow culture (n=171)	Hc100 nested PCR in tissue samples vs culture of tissue (n=53)	IMMY ALPHA Histoplasma Antigen EIA in urine samples vs any positive culture (n=246)
Sensitivity (95% CI)	70.5 (56.7-81.7)	80.0 (68.6-88.5)	90.0 (57.4-99.5)	70.8 (61.9-77.1)
Specificity (95% CI)	80.5 (77.0-83.3)	83.5 (78.8-87.0)	67.4 (59.9-69.6)	95.0 (91.8-97.3)
PPV (95% CI)	47.7 (35.2-60.5)	66.7 (53.3-78.3)	39.1 (19.7-61.5)	83.6 (71.2-92.2)
NPV (95% CI)	91.5 (85.9-95.4)	91.0 (84.1-95.6)	96.7 (82.8-99.9)	90.1 (84.9-93.9)

794 ANTIFUNGAL DRUG SUSCEPTIBILITY OF TALAROMYCES MARNEFFEI CLINICAL ISOLATES, GUANGDONG

Linghua Li, Wanshan Chen, Fengyu Hu, Xiejie Chen, Weiping Cai, Xiaoping Tang
Guangzhou Eighth People's Hospital, Guangzhou, China

Background: Talaromyces marneffei can cause a fatal systemic mycosis in AIDS patients in Southeast Asia and Southern China. In Guangdong, the number of case is increasing, with many patients remain culture-positive after two weeks of antifungal therapy. We aim to investigate the antifungal susceptibility of T. marneffei strains with preliminary analysis of clinical correlation to inform treatment strategies.

Methods: 192 T. marneffei strains were obtained from bone marrow or peripheral blood of AIDS patients admitted at Guangzhou Eighth People's Hospital, the largest AIDS hospital in Guangdong. All isolates were identified by conventional culture, microscopic characteristics, and ITS sequencing. Blood and bone marrow culture were obtained before antifungal therapy, followed by blood culture weekly and bone marrow culture every two weeks until cultures became negative. Trains were categorized into two groups according to culture status at two weeks. The profiles of antifungal susceptibility at the yeast phase were generated using the Sensititre YeastOneTM YO10 assay, and the frequency of high MICs were compared between the groups using Chi Square test.

Results: Strains from 192 patients were collected from 2013 to 2016. 145/192 (76%) patients were male. The median age was 36 years. The median CD4 cell count was 9 cells/mm^3. 85 patients received amphotericin B; 46 received itraconazole, and 78 received voriconazole for a median duration of 30 days. The differences in gender, age, CD4 count, antifungal duration, and antifungal drugs between the two groups were not statistically significant (all P>0.05). The baseline MICs from low-to-high were as follows: posaconazole and voriconazole ≤0.008—0.06 µg/ml, itraconazole ≤0.015—0.03 µg/ml, amphotericin ≤0.25—1 µg/ml, anidulafungin 4—8 µg/ml and caspofungin 2—8 µg/ml, micafungin >8 µg/ml, and fluconazole 1—16 µg/ml. 89 strains were culture-negative at two weeks (Group A) and 103 strains were culture-positive (Group B). Group B had higher proportion of isolates with MICs above 0.015 ($\chi2$=4.819, P=0.028) for voriconazole, and MICs above 4 ($\chi2$=8.945, P=0.003) for fluconazole.

Conclusion: The T. marneffei isolates from Guangdong are susceptible to posaconazole, voriconazole, itraconazole, and amphotericin B but are resistant to the echinocandins and fluconazole. Persistent culture positivity is seen in isolates with higher MICs against azole drugs.

795 RISK FACTORS FOR IRIS IN HIV-ASSOCIATED PNEUMOCYSTIS PNEUMONIA AFTER ART INITIATION

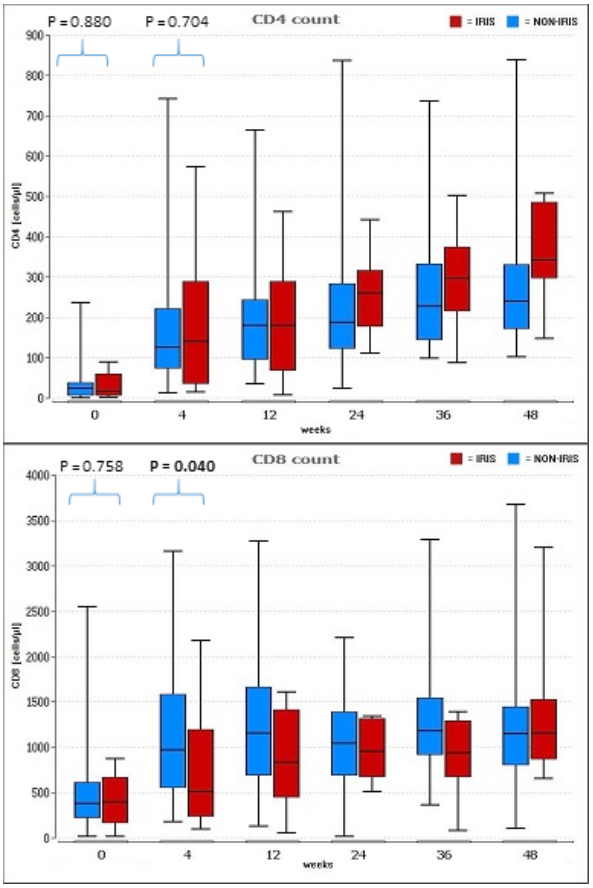
Gerrit Kann, Hannah Bielke, Philipp De Leuw, Gundolf Schuettfort, Annette E. Haberl, Junaid Owasil, Claus P. Kuepper-Tetzel, Nils Wetzstein, Imke Wieters, Johanna Kessel, Markus Bickel, Pavel Khaykin, Christoph Stephan
University Hospital Frankfurt, Frankfurt, Germany

Background: HIV-infected patients with Pneumocystis-pneumonia (PCP) due to Pneumocystis jirovecii-infection may develop immune reconstitution inflammatory syndrome (IRIS), following combination antiretroviral therapy (cART)-initiation. Though starting cART early is standard of care, PCP-associated IRIS could counteract its benefit. The aim of this study was to identify possible predictors and susceptible risk factors.

Methods: Frankfurt HIV Cohort patients with PCP were identified by hospital database query between January 2010 and June 2016. Among 108 individuals with HIV-associated PCP, 97 started off cART in the course of PCP-treatment (PCPT) and were evaluated retrospectively. Patient charts were analysed for demographic and clinical characteristics, routine laboratory results, therapy (cART/PCPT) information including the third drug, time between start of PCPT and cART, corticosteroid use for severe PCP prior to cART, immunological and virological response data for a 48-week interval and incidence of paradoxical IRIS, following FRENCH's case definitions (PMID: 15280772). Results were compared between patients with or without IRIS. Fisher's exact test was used for categorical and Wilcoxon-Mann-Whitney test for numerical variables.

Results: IRIS occurred in 12/97 patients (12.4%); significant findings in this group were: higher re-hospitalization rate (41.7% vs. 4.7%; odds ratio [OR] =14.46; p=0.009) and more frequent need for intensive care treatment (66.7% vs. 30.6%; OR=4.54; p=0.018); in-patient treatment duration was longer (median=48 days vs. 23; p 6 $\log_{10}$/ml was related to IRIS (41.6% vs. 15.0%; OR=4.05; p=0.042). Serum Immunoglobulin G levels (IgG) [mg/dl] were lower (894.0 vs. 1446.5; p=0.023). A protease inhibitor-sparing cART (63.6% vs. 27.4%; OR=4.64; p=0.023) and lack of corticosteroid use prior to cART were significantly associated with IRIS (25.0% vs. 2.4%; OR=13.83; p=0.013). There were no significant differences regarding other parameters including death, CD4 count or time between start of PCPT and cART.

Conclusion: Hospitalization and morbidity parameters underscore the clinical relevance of PCP-related paradoxical IRIS. A viral load of > 6 $\log_{10}$/ml and serum IgG may previously help to assess the individual risk for IRIS. However, this analysis supports the use of protease inhibitors and corticosteroids, in order to reduce the incidence of PCP-IRIS. No adverse respiratory effects due to early cART initiation or steroid use were observed.



796 NATURAL EXPERIMENT OF SYPHILIS TREATMENT WITH DOXYCYCLINE IN HIV-INFECTED PATIENTS

Marilia B. Antonio, Ricardo d. Vasconcelos, Gabriel Trova, Vivian I. Avelino-Silva
Universidad de São Paulo, São Paulo, Brazil

Background: Although doxycycline is considered an alternative to penicillin as treatment option for syphilis, data on serologic response following treatment

with doxycycline among HIV-infected patients is limited (Tsai et.al., Plos One 2014; Salado-Rasmussen et.al., Acta Derm Venereol 2016).
Methods: In this study, we analyzed serologic response to syphilis treatment with doxycycline among HIV-infected patients treated during a period of penicillin shortage, and compared with treatment response among patients treated with penicillin up to 12 months prior or 6 months after the shortage period. Cases with neurosyphilis and those treated with suboptimal doses or with other medications in association with penicillin or doxycycline were excluded.
Results: 61 patients who received treatment with doxycycline from Sep/2014 to Dec/2016 were compared to 60 patients who received treatment with penicillin. Patients treated with doxycycline were slightly older (mean age 49±10 vs 45±9, p=0.0295) and had lower T CD4+ counts (median 544, IQR 403-694 vs 615, IQR 480-864) compared to patients treated with penicillin. Groups were comparable regarding sex, proportions with HIV suppression under treatment, and syphilis stages (Table 1). Serologic response to treatment, defined as a non-reagent VDRL or a 4-fould or higher reduction in VDRL titers measured 6-12 months after treatment, was seem in 67% (95%CI=54-79%) of patients treated with doxycycline and 68% (95%CI=55-80%) of patients treated with penicillin (p=0.895).
Conclusion: We found no statistically significant difference in serologic response to treatment with either doxycycline or penicillin among HIV-infected patients with syphilis. Although serologic response to treatment with either doxycycline or penicillin in our study were lower than reported in published studies, our findings indicate that doxycycline is an acceptable treatment alternative to HIV-infected patients with syphilis.

797 INTRAOCULAR TREPONEMA AND TOXOPLASMA INFECTIONS ASSOCIATED WITH BLINDING CATARACTS

Juliet Otiti-Sengeri, Colebunders Robert, Lois Bayigga, Rose Nabatanzi, Samuel Kyobe, Damalie Nakanjako
Makerere University College of Health Sciences, Kampala, Uganda

Background: Visual loss due to cataracts is a common age-related disorder that has been documented among 11.6% of HIV-infected adults in Uganda. Evidence suggests that cataracts occur earlier among HIV-infected adults than among healthy HIV-negative individuals, and may be associated with non-specific intra-ocular inflammatory disease processes. We investigated the role presence of active infection with six common intra-ocular infections, known to contribute to cataract development, among HIV-infected adults that reported for cataract surgery, at an ophthalmology surgical camp in south-western Uganda.
Methods: Following written informed consent, all HIV-infected adults that received cataract surgery at an ophthalmology surgical camp, had a detailed preoperative medical and ocular assessment. Individuals with a history of ocular trauma and those with any contraindication to cataract surgery were excluded. Aqueous fluid from all HIV-infected adults that received cataract surgery was analyzed using PCR for the six common opportunistic intraocular infections; Treponema Pallidum (TP), toxoplasma gondii (TG), Herpes simplex 1& 2, Varicella zoster virus (VZV), and Cytomegalovirus (CMV). All patients received adequate postoperative follow up and appropriate therapy was given to those with positive results.
Results: Overall, 119 HIV-positive patients received cataract surgery, of whom 70 (59%) were females and 56 (47.1%) were receiving HAART. Mean age was 50 [IQR 43-62) years, and mean CD4 count was 339 (IQR 221-475) cells/µl. Aqueous fluid was positive for Treponema pallidum among 54/119 (45%), positive for toxoplasma gondii among 15/119 (13%), and 50/119 (42%) had no identified pathogen. None was found with positive PCR for CMV, HSVI&II or VZV.
Conclusion: Up to 68% of HIV-infected adults with blinding cataracts had intra-ocular pathogens (Treponema pallidum and Toxoplasma gondii). Early diagnosis and treatment of intra-ocular infections, as well as control of non-specific intra-ocular inflammation could prevent or slow development of blinding cataracts among HIV-infected adults.

798 PRIOR SYPHILIS PROTECTS AGAINST *T. PALLIDUM* DISSEMINATION IN REPEAT INFECTION

Christina Marra, Clare Maxwell, Sharon Sahi, Lauren Tantalo, Shelia Dunaway, Sheila Lukehart
University of Washington, Seattle, WA, USA

Background: In animal models, infection with one strain of *Treponema pallidum* subspecies *pallidum* (Tp) protects against reinfection with the same strain, and may or may not protect against infection with a different strain. We sought to determine if the course of syphilis in humans is influenced by prior syphilis.
Methods: 897 individuals enrolled in a study of cerebrospinal fluid (CSF) abnormalities in syphilis were categorized as never having had prior syphilis or having ≥1 episode of syphilis before entry. On study, 116 individuals re-enrolled with 1 (n=91) or 2 (n=25) additional episodes of syphilis. Data from the most recent episode were considered. Identification of Tp 16S rRNA in CSF was determined by RT-PCR (n=897), and identification of tp0574 DNA in blood (n=349) by PCR. Associations between categorical variables were assessed using Chi-square or logistic regression.
Results: Most participants were middle aged (median 39 yrs., IQR 32-46), HIV-infected (78%), men (97%). Median serum RPR titer for all episodes was 1:64 (1:16-1:128); 50% were treated for uncomplicated syphilis before the study visit. With additional syphilis episodes (0, 1, or 2 repeat episodes on study), % with primary and latent stages increased and % with secondary decreased (P<0.001). In univariate analysis, odds of detection of Tp in CSF were lower in those with prior syphilis before entry, additional episodes of syphilis on study, treatment for syphilis before study visit, and were higher in those with higher serum RPR titer (Table). In multivariate analysis, the odds of detection of Tp in CSF remained lower in those with prior syphilis and in those with additional episodes of syphilis, even after controlling for treatment and RPR titer (Table). Similarly, in univariate analysis, odds of detection of Tp in blood were lower in those with prior syphilis and those treated before study visit, and were higher in those HIV-infected, with higher serum RPR titer, and with early syphilis (Table). In multivariate analysis, the odds of detecting Tp in blood remained lower in those with prior syphilis, even after taking into account HIV, treatment, RPR, and stage (Table).
Conclusion: Prior syphilis may prevent dissemination of Tp to blood and CSF during subsequent syphilis. This protection may be lower in HIV-infected persons. A dose-response effect of number of syphilis episodes was seen with Tp detection in CSF, but not blood, perhaps because of smaller numbers.

Table

	T. pallidum detected in CSF			*T. pallidum* detected in blood	
	OR	aOR1*	aOR2**	OR	aOR3***
HIV	NS	--	--	3.6 P=0.004	2.4 P=0.10
Syphilis before entry	0.25 P<0.001	--	0.19 P<0.001	0.43 P=0.01	0.20 P<0.001
Additional syphilis episode(s) after entry (each episode)	0.30 P=0.01	0.22 P=0.002	--	NS	--
Treated before study visit	0.11 P<0.001	0.10 P<0.001	0.09 P<0.001	0.07 P<0.001	0.04 P<0.001
Serum RPR ≥1:64	5.1 P<0.001	6.4 P<0.001	5.3 P<0.001	4.4 P<0.001	4.7 P=0.001
Early stage	NS	--	--	3.0 P=0.007	6.0 P=0.001

OR, odds ratio; aOR, adjusted odds ratio
NS, P>0.10
Variables were tested in the multivariate models if P<0.10 in univariate models. Variables were retained in the adjusted models if P<0.10.
*aOR1: model includes additional syphilis episode(s) after entry, treated before study visit, serum RPR ≥1:64.
* aOR2: model includes syphilis before entry, treated before study visit, serum RPR ≥1:64.
**aOR3: model includes HIV, syphilis before entry, treated before study visit, serum RPR ≥1:64, early stage.

799 HIV REPLICATION AS RISK FACTOR FOR 3 OPPORTUNISTIC INFECTIONS

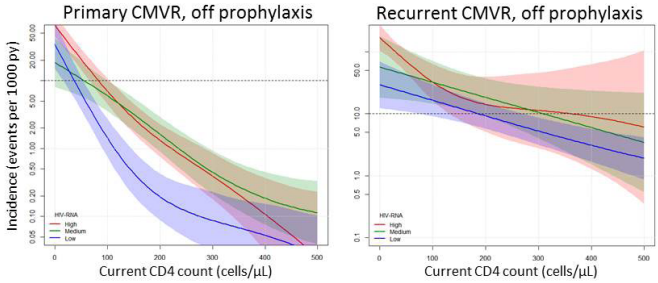
Hansjakob Furrer, *University Hospital of Bern, Bern, Switzerland*

Background: Previous studies have shown that HIV replication is a CD4 independent risk factor for Pneumocystis pneumonia and tuberculosis. We investigated these associations for primary and recurrent events of cytomegalovirus retinitis (CMVR), extrapulmonary cryptococcosis (CRC) and disseminated Mycobacterium avium disease (MAC), and evaluated whether current guidelines for indication of primary and secondary prophylaxis need to be adapted for patients with suppressed HI-viremia.
Methods: We estimated the incidence of primary and recurrent events of CMVR, CRC and MAC in patients off primary or secondary prophylaxis in the COHERE database. We used a Poisson generalized additive model with CD4 modelled by a restricted cubic spline and HIV-RNA stratified as low (10'000c/mL).
Results: There were 634 primary MAC events during 859'058 py of follow-up in 131,003 patients, with 81 recurrences during 8'033 py. For CMVR there were 195 primary (74 recurrent) events during 264'532 (6'358) py of follow-up; CRC having 394 (73) events over 861'753 (5'461) py. The figure shows example estimated

incidence rates for primary and recurrent CMVR events with 95% confidence intervals (CI), for each of the different plasma HIV-RNA strata. In all the analyses except for secondary events of cryptococcosis, the lowest incidence in patients with low CD4 counts was found when viral load was suppressed. Point estimates of incidence of secondary events off prophylaxis in patients with suppressed viral load crossed the 10/1000py threshold at a CD4 count of 87 (MAC), 186 (CMVR) and 172/µL (CRC) while the 95% CI of incidences were wide due to the low number of events of these rare OIs.

Conclusion: HIV replication is a major risk factor for primary and recurrent events of MAC and CMVR and primary CRC, but not for recurrent CRC in low CD4 strata, where IRIS events may play a role. Our data support current guidelines for stopping secondary prophylaxes in patients with suppressed HIV replication. Patients with unsuppressed HIV load may need continuation of maintenance treatment above currently recommended CD4 thresholds.

Figure: Primary and recurrent CMVR in patients off prophylaxis for CD4 level stratified by RNA strata (low = blue, medium = green, high = red)



800 HERPES ZOSTER AND ZOSTER VACCINE RATES AMONG HIV-INFECTED AND UNINFECTED IN THE VACS

Kellie L. Hawkins[1], Kirsha S. Gordon[2], Myron Levin[3], Adriana Weinberg[3], Catherine Battaglia[3], Maria Rodriguez-Barradas[4], Sheldon T. Brown[5], David Rimland[6], Amy C. Justice[2], Janet Tate[2], Kristine M. Erlandson[3]

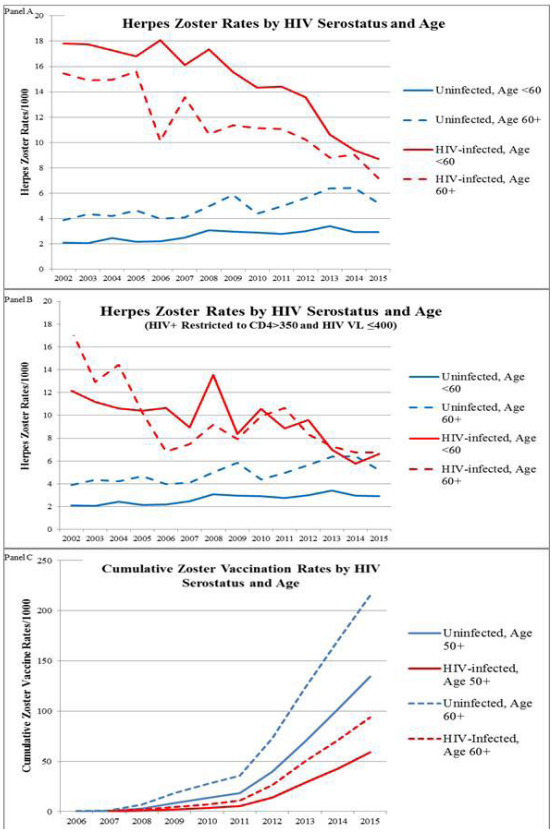
[1]Denver Health Medical Center, Denver, CO, USA, [2]Yale University, New Haven, CT, USA, [3]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [4]Baylor College of Medicine, Houston, TX, USA, [5]James J. Peters VA Medical Center, Bronx, NY, USA, [6]Atlanta VA Medical Center, Decatur, GA, USA

Background: Herpes zoster (HZ) is a major cause of morbidity in aging adults. Despite historically higher rates among HIV-infected individuals, comparative studies of HZ by serostatus since the advent of combination antiretroviral therapy (cART) and the zoster vaccine (ZV) are lacking. Further, while ZV is recommended for uninfected individuals age ≥60 years and studies have shown safety and immunogenicity in HIV-infected with CD4 >200 cells/µL, no vaccine guidelines have been established for HIV-infected individuals.

Methods: Rates of first-episode HZ and ZV receipt were recorded among HIV-infected and uninfected adults in the Veterans Aging Cohort Study annually from 2002-2015 and stratified by HIV serostatus and age. HZ events were captured using ICD9 codes and ZV using procedural codes and pharmacy data. Results were further stratified by age thresholds, CD4 category, and virologically suppressed/unsuppressed HIV-1 RNA (cut off ≤400 copies/mL).

Results: Of 45,177 HIV-infected and 103,040 uninfected adults, mean baseline age was 48 and 49 years, respectively; 46% of the cohort was >50 years and 97% were male. From 2002 to 2015, rates of HZ increased among uninfected adults (2.3 to 4.1/1000) and decreased among the HIV-infected group (17.6 to 8.1/1000), but remained higher than uninfected (8.1 vs 4.1/1000, p<0.001), particularly among HIV-infected adults <60 years (8.7/1000) (Figure 1, Panel A). Among HIV-infected, HZ rates were higher with lower CD4 counts (CD4 <200 cells/µL: 18.0/1000; CD4 201-350: 14.4/1000; CD4 351-500: 7.5/1000; CD4 >500: 6.8/1000) and unsuppressed vs suppressed HIV-1 RNA (21.8 vs 7.1/1000). When restricted to virologically suppressed participants with CD4 >50 cells/µL, HZ rates were similar among HIV-infected adults age <60 and age ≥ 60 (6.6 vs 6.7/1000) (Figure 1, Panel B). By 2015, cumulative receipt of ZV for uninfected was double that of HIV-infected: among age ≥ 50 years (134.3 vs. 58.9/1000) and among those ≥ 60 years (215.1 vs. 93.7/1000) (Figure 1, Panel C).

Conclusion: With cART, HZ rates among older HIV-infected adults have markedly decreased, but remain 50% higher than uninfected in this cohort. Lower rates of ZV combined with high rates of HZ, particularly among HIV-infected adults with CD4 count >200 but <350 cells/µL (regardless of age) support the need for updated, formal ZV guidelines, and consideration for expanded use at ages <60.



801 CMV VIREMIA AND DISEASE IN PATIENTS WITH ADVANCED HIV INFECTION: A PROSPECTIVE STUDY

Adaia Albasanz[1], Juliana Esperalba[1], Ariadna Torrella[2], Bibiana Planas[2], Candela Fernández[1], Antonio Segura[1], Adrià Curran[1], Jordi Navarro[1], Esteban Ribera[1], Joaquin Burgos[1], Rein Willekens[2], Mario Martin[2], **Vicenç Falcó**[1]

[1]Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, [2]Vall d'Hebron Research Institute, Barcelona, Spain

Background: The prevalence of CMV viremia is 30% in patients with < 100 CD4 T-lymphocytes. We hypothesize that antiretroviral treatment (HAART) that ensures a correct immune recovery, rather than anti-CMV specific treatment, is the best strategy to clear CMV viremia in patients without end-stage organ disease (EOD). We aim to study the recovery of specific immune response against CMV after the initiation of HAART since it might be a better predictor of CMV-EOD than CMV viremia.

Methods: Prospective, observational on-going study of all patients with HIV infection with < 100 CD4 T-lymphocytes registered from September 2015. Variables: HIV viral load (VL), CD4 T lymphocytes and CMV VL were determined at baseline, 4,12,24 and 48 weeks. The specific immune response against CMV was determined at baseline and at 48 weeks (QuantiFERON-CMV®). Therapeutic strategy: Antiretroviral therapy was initiated in all patients. CMV specific therapy was initiated only in patients with CMV-EOD. Here we present the results of a pre-planned interim analysis to check the safety of this strategy. Statistical analysis: Wilcoxon signed-rank sum was used to assess the evolution over time of CMV-specific immune response.

Results: Forty-two patients have been included at the moment of the interim analysis, 26 (61.9%) men and 16 (38.1%) women with mean (SD) age 44.2 (10.8) years. The median (IQR) baseline CD4 lymphocytes was 30.0 (12.5-60.0) cel/mm^3 with a median HIV VL of 420,000.0 (159,5-1,170,500) copies/ mL. Thirteen (31%) had detectable CMV viremia at baseline with a median CMV VL of 40,503 (13,307-73,413) copies/ mL. At 12 weeks after TAR initiation only 1 (3.6%) patient had detectable CMV viremia. At 24 and 48 weeks the CMV VL was negative in all patients. We only registered 1 case of CMV-EOD (stomatitis)

during the follow-up. Two patients were loss to follow-up whereas 5 patients died, none of them related to CMV infection. Twenty-nine (69.0%) patients had a positive CMV-specific immune response at baseline and 16 (88.9%) patients at the end of the study. We observed a significant increase of the CMV-specific IFN-γ response among the 20 patients who have already completed the study (p=0.029)

Conclusion: The prevalence of CMV viremia in patients with advanced HIV infection is high. However, the incidence of CMV-EOD is low due to the presence of specific immunological response to CMV, which improves after starting HAART. These findings suggest that CMV specific treatment might not be necessary in these patients.

Time (weeks)	Week 0 (n=42)	Week 4 (n=36)	Week 12 (n=28)	Week 24 (n=26)	Week 48 (n=20)
HIV INFECTION					
CD4+ T cell count (cells/mm3) [Median (IQR)]	30.0 (12.50-60.0)	100.0 (50.0-202.5)	105.5 (80.0-257.5)	115.0 (100.0-230.0)	170.0 (127.5-287.5)
HIV RNA (copies/mL) [Median (IQR)]	420,000.0 (159,500.0-1,170,500.0)	380.0 (126.0-3,580.0)	203.5 (24.0-688.2)	75.0 (24.0-335.0)	36.5 (24.0-121.2)
Undetectable viral load (<50 copies/mL) [n (%)]	2 (4.8)	5 (13.9)	8 (28.6)	11 (42.3)	11 (55.0)
CMV infection					
Positive CMV PCR [n (%)]	13 (30.9)	13 (36.1)	1 (3.6)	0 (0.0)	0 (0.0)
PCR CMV+ (cop/mL) [Median (IQR)]	40,503.0 (13,307.0-73,413.0)	3,956.0 (1,097.0-38,398.0)	2,178 (-)	- (-)	- (-)
CMV-Specific Immunological Response (QuantiFERON CMV ®)					
Reactive (Cut-Off > 0.2 IU/mL) [n (%)]	29 (69.0)				16 (80.0)
CMV-specific IFN-γ response [median (IQR)]	3.210 (1.250-6.260)				7.965 (4.945-39.715)

802 BLASTOCYSTIS INFECTIONS IN HIV POSITIVE AND NEGATIVE ADULTS IN GHANA

Veronica Di Cristanziano[1], Federica Berrilli[2], Rossella D'Alfonso[2], Fred S. Sarfo[3], Lavinia Fabeni[4], Elena Knops[1], Eva Heger[1], Albert Dompreh[5], Rolf Kaiser[1], Torsten Feldt[6], **Kirsten Eberhardt**[7]

[1]University of Cologne, Cologne, Germany, [2]University of Rome Tor Vergata, Rome, Italy, [3]Kwame Nkrumah University of Science and Technology, Kumasi, Ghana, [4]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, [5]Komfo Anokye Teaching Hospital, Kumasi, Ghana, [6]Heinrich Heine University Düsseldorf, Düsseldorf, Germany, [7]Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany

Background: Sub-Saharan Africa is endemic for intestinal parasites and distinguished for the largest burden of HIV cases. Blastocystis is one of the most common intestinal protists infecting humans but its role in human disease is still under debate. We investigated the prevalence of Blastocystis infection in HIV positive and negative people living in Ghana and its association with immune status and other risk factors.

Methods: 122 HIV positive patients with CD4+ T count <200 cells/µl (n=54) and >200 cells/µl (n=68) presenting to the HIV outpatient Department of the Komfo Anokye Teaching Hospital in Kumasi, Ghana, and 70 HIV negative blood donors from the same hospital were included in the present study. Demographic and clinical data were collected. For Blastocystis detection the small subunit (SSU) rRNA amplification was carried out. A phylogenetic analysis on Blastocystis Sanger sequences was performed to determine sample subtype. Samples from symptomatic subjects were screened for the presence of common pathogens by xTAG GPP (Luminex Molecular Diagnostics) and FTD Viral gastroenteritis (Fast-Track Diagnostics).

Results: The overall prevalence of Blastocystis in 192 adults was 11.5% (n=22) with a lower prevalence in HIV positive individuals than in HIV negative persons (6.6% vs. 20.0%, p=0.008). Within HIV positive participants, the prevalence of Blastocystis was lower in those individuals with CD4+ T cell count of <200 cells/µl than in patients with higher CD4+ T cell count (1.9% vs. 10.3%, p=0.076). In HIV negative persons, Blastocystis was associated with lower CD4+ T cell counts and a higher BMI (p=0.025 and p=0.011 respectively). Presence of Blastocystis was correlated with higher CD4+ T counts in HIV positive persons (p=0.035). Remarkably, only 4 subjects with Blastocystis infection were affected from gastrointestinal symptoms and all of those were detected positive for other enteric pathogens. Phylogenetic analysis revealed that Blastocystis subtype 1 was the most prevalent strain.

Conclusion: It is largely reported that PLHIV in Africa are highly affected from parasite infections and that co-infections may adversely impact on their immune status, accelerating progress to AIDS and worsening gastrointestinal manifestations. On the contrary, in this study, the presence of Blastocystis was associated with a better immune status jointly with a healthy weight. This data is in accordance with the recent suggestions that Blastocystis may represent a component of the healthy gut microbioma.

803 INCREASED RISK OF HYPERTENSION IN PREGNANCY AMONG WOMEN ON NEVIRAPINE-BASED REGIMENS

Rebecca Zash[1], Paige L. Williams[2], Denise Jacobson[2], Modiegi Diseko[3], Gloria Mayondi[3], Judith Mabuta[3], Katherine Johnson[1], Mompati O. Mmalane[3], Max Essex[2], Shahin Lockman[4], Joseph Makhema[3], Chipo Petlo[5], Roger L. Shapiro[2]

[1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]Harvard University, Cambridge, MA, USA, [3]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [4]Brigham and Women's Hospital, Boston, MA, USA, [5]Ministry of Health, Gaborone, Botswana

Background: Non-pregnant women on nevirapine(NVP)-based antiretroviral therapy (ART) have increased risk of incident hypertension. We evaluated the risk of hypertension in pregnancy by ART regimen in Botswana.

Methods: Data were collected from all live and stillbirths <=24 weeks gestational age (GA) at 8 hospitals throughout Botswana (~45% of nationwide births). We recorded maternal demographics, medical history, HIV and ART history, and blood pressures and weights during antenatal care. Women were included if they started ART prior to pregnancy, with either zidovudine/lamivudine (ZDV/3TC) or tenofovir/emtricitabine (TDF/FTC) combined with NVP, lopinavir-ritonavir (LPV/r) or efavirenz (EFV). Using log binomial regression, we compared risk of any hypertension (SBP >=140 or DBP >=90), severe hypertension (SBP >=160 or DBP >=110), gestational hypertension (onset of hypertension >=20 weeks GA) and early gestational hypertension (onset of gestational hypertension <34 weeks GA) by maternal ART regimen at conception, adjusting for potential confounders (maternal age, occupation, parity, weight and alcohol/tobacco use).

Results: From Aug 2014-Aug 2016, 5087 women on NVP, LPV-r or EFV-based ART from conception delivered singletons at a surveillance maternity. Of these, 4915 (97%) had at least 1 blood pressure recorded in pregnancy including 2128 (43%) on NVP-based ART and 2797 (57%) on non-NVP based ART. Overall 1090 (22%) had hypertension, 106 (2.2%) had severe hypertension, 691 (14%) had gestational hypertension and 438 (9%) had early gestational hypertension. In adjusted analyses, women on NVP-based regimens were more likely to have hypertension (30% vs. 16%), severe hypertension (3.3% vs. 1.2%), gestational hypertension (18% vs.10%) and early gestational hypertension (12% vs. 7%) compared with women on non-NVP based ART (Table 1). There was no difference in outcomes when NVP was combined with ZDV/3TC vs. TDF/FTC except for severe hypertension which was more common in ZDV/3TC/NVP (6% vs. 2%). There were 48 stillbirths (7.8%) among hypertensive women on NVP, 25 stillbirths (5.6%) among hypertensive women on non-NVP containing ART, and 88 (2.3%) stillbirths among non-hypertensive women. Although hypertensive women on NVP accounted for only 13% of the population, they had 30% of the stillbirths.

Conclusion: HIV-infected women on NVP-based ART have increased risk of developing gestational, severe and early hypertension in pregnancy, which may explain their increased risk for stillbirth.

	Any Hypertension		Severe Hypertension		Gestational Hypertension		Early Gestational Hypertension	
	N (%)	aRR (95% CI)	N (%)	aRR (95% CI)	N (%)	aRR (95% CI)	N (%)	aRR (95% CI)
NVP-based vs. non-NVP-based ART								
Non-NVP based ART (N=2797)	457 (16%)	ref	35 (1.2%)	ref	282 (10%)	ref	191 (7%)	ref
NVP-based ART (N=2128)	634 (30%)	1.61 (1.44, 1.80)	71 (3.3%)	1.57 (1.02, 2.41)	384 (18%)	1.61 (1.39, 1.89)	247 (12%)	1.56 (1.29, 1.90)
Individual ART regimen								
TDF/FTC/EFV (N=2393)	386 (16%)	ref	29 (1.2%)	ref	283 (10%)	ref	164 (7%)	ref
TDF/FTC/ LPV-r (N=230)	41 (18%)	1.10 (0.82, 1.47)	3 (1.3%)	1.06 (0.33, 3.37)	25 (11%)	1.11 (0.74, 1.66)	15 (7%)	0.93 (0.55, 1.58)
ZDV/3TC/ LPV-r (N=164)	29 (18%)	1.11 (0.76, 1.57)	3 (1.8%)	1.09 (0.27, 4.38)	19 (12%)	1.23 (0.78, 1.93)	12 (7%)	0.98 (0.53, 1.82)
TDF/FTC/NVP (N=1360)	225 (29%)	1.62 (1.39, 1.87)	25 (1.8%)	1.51 (0.90, 2.65)	131 (17%)	1.62 (1.31, 2.00)	82 (11%)	1.42 (1.09, 1.87)
ZDV/3TC/NVP (N=768)	409 (30%)	1.64 (1.44, 1.87)	46 (6.0%)	1.63 (1.00, 2.66)	233 (18%)	1.67 (1.39, 2.00)	165 (12%)	1.62 (1.30, 2.02)

804 DOES CHANGING ART IN EARLY PREGNANCY FOR FETAL RISKS DESTABILIZE VIRAL SUPPRESSION?

Violaine Peyronnet[1], Josiane Warszawski[2], **Jeanne Sibiude**[2], Catherine Dollfus[3], Christine Rouzioux[4], Jérôme Le Chenadec[2], Albert Faye[2], Roland Tubiana[5], Laurent Mandelbrot[2]

[1]Hôpital Louis-Mourier, Colombes, France, [2]INSERM, Le Kremlin-Bicetre, France, [3]Assistance Publique – Hôpitaux de Paris, Paris, France, [4]Paris Descartes University, Paris, France, [5]Paris Center Hospital Group, Paris, France

Background: As increasing numbers of women with HIV are on becoming pregnant on antiretroviral therapy, and fewer infants are infected, there is concern about the possible risks for fetuses and infants exposed to ARV in utero. In case of potential toxicities or in the absence of good safety data, one option is to switch the maternal ART regimen as early as possible in pregnancy. Our aim was to study the frequency and reasons of such treatment changes and to determine whether they led to poorer virological outcomes.

Methods: All pregnancies in women with HIV1 enrolled in the national multicenter prospective French Perinatal cohort (EPF) were included if delivery occurred between 01/2005 and 12/2015 at 14 gestational weeks or more and the mother was on antiretroviral therapy (ART) at conception with a plasma viral load < 50 copies/ml. The reasons for switching the antiretroviral regimen (suppression or change of at least one drug) were analyzed in view of treatment guidelines at the time of the pregnancy, and defined as "for medical strategy" after excluding changes for side effects. Virological and pregnancy outcomes were studied by survival analysis censored at the time of ART switch and by logistic regression adjusted for a propensity score established for each patient according to baseline characteristics.

Results: Of 10365 pregnancies with an outcome > 14 weeks' gestation, nearly half (N = 4983) were on antiretroviral therapy at conception, and of these 1019 (9.8%) had a treatment switch in the first trimester of pregnancy. For 66.4% of these switches, the reason was a medical strategy to follow treatment guidelines. The proportion of switches was statistically higher when initial treatment was contraindicated (ORa: 21.9 [13.3-36.1]) or was regarded as an alternative (OR adjusted: 2.2 95% CI [1.3-3.7]), as compared to recommended first-line options. Treatment switches for medical strategy did not lead to poorer virological control, compared to pregnancies without such switches (19.3% vs. 16.2%, HRa: 1.0 [0.7-1.3]).

Conclusion: Changing antiretroviral therapy early in pregnancy with the goal of improving fetal and pregnancy outcomes did not appear to have a destabilizing effect on viral suppression. However, the impact may differ according to the specific regimens and patient characteristics. Multidisciplinary preconceptional care must be provided to women with HIV, as well as further research on recent antiretroviral drugs to document their safety and risks.

Table: Associations between treatment switch for medical strategy in the first trimester and the course of pregnancy in patients with viral suppression at conception. Univariate and multivariate analysis by Cox model and logistic regression (EPF-CO1, 2005-2015)

	Treatment switch in 1st trimester of pregnancy				Multivariate analysis		
	No (N=1409)		Yes (N=411)		ORa[a]/HRa[b]	IC 95%	p
	n	%	n	%			
Loss of virological control (yes versus no)							
VL>50 copies/mL during pregnancy	227	16.2	79	19.3	1.0[a]	[0.7-1.3]	0.8
VL>50 copies/mL at delivery	61	4.7	25	6.5	1.1[a]	[0.6-2.0]	0.7
Treatment change after 13 weeks' gestation							
Yes versus no	206	14.6	95	23.1	0.9[a]	[0.6-1.2]	0.5
Delivery outcomes (yes versus no)							
Cesarean section	681	48.8	182	44.5	0.8[b]	[0.6-1.1]	0.2
AZT intrapartum infusion	1052	75.5	299	73.3	0.8[b]	[0.6-1.1]	0.1
Poor pregnancy outcomes (yes versus no)							
Stillbirth, pregnancy termination or neonatal death	40	2.9	8	1.9	0.7[c]	[0.3-1.7]	0.4
Preterm delivery[d]	177	14.5	49	15.3	1.1[c]	[0.8-1.6]	0.6
Neonatal outcomes (yes versus no)							
Mortality before 1 year	6	0.4	0	0	.	.	.
HIV transmission	0	0	0	0	.	.	.

[a] *adjustment on propensity score (PS)*
[b] *adjustment on PS, Body Mass Index, gestational weeks*
[c] *adjustment on PS, gestational week*
[d] *<37 weeks' gestation*

805 COMPARISON OF FOUR CLASSICAL PI- AND RALTEGRAVIR-BASED REGIMENS DURING PREGNANCY

Jeanne Sibiude[1], Olivia Dialla[2], Roland Tubiana[3], Stephane Blanche[4], Catherine Dollfus[5], Pierre Frange[4], Jérôme Le Chenadec[2], Laurent Mandelbrot[1], Josiane Warszawski[2]

[1]Hôpital Louis-Mourier, Colombes, France, [2]INSERM, Le Kremlin-Bicetre, France, [3]Pitié-Salpêtrière Hospital, Paris, France, [4]Necker Hospital, Paris, France, [5]Hôpital Armand-Trousseau, Paris, France

Background: Antiretroviral therapy (ART) is recommended for all HIV-infected pregnant women as prevention of mother-to-child transmission. A large proportion of women now start pregnancy while already on ART, and more information is needed concerning tolerance of drugs received throughout pregnancy. We sought to compare 3 first-line recommended regimens in France (all of them including one ritonavir-boosted protease inhibitor and two NRTIs), and raltegravir-based ART which has become recently an option for pregnancy.

Methods: All HIV-infected pregnant women included in the national French Perinatal Cohort between 2005 and 2015, receiving at conception a 3-drug regimen containing lopinavir/r, atazanavir/r, darunavir/r or raltegravir associated with 2 NRTIs (xTC+ ZDV, ABC or TDF). Immuno-virological, pregnancy and neonatal outcomes were compared, in intent-to-treat, according to treatment group using univariable and multivariable logistic regressions adjusting for NRTIs, maternal age, and geographical origin.

Results: Among 3125 patients who were on ART at conception, we excluded 1017 patients with non-PI and non-integrase inhibitor based ART, 239 patients with 2-drug or 4-drug regimens and 272 patients with other drugs than those of interest. Overall, 1597 women responded to selection criteria, among which 45% (N=715) were receiving at conception a lopinavir-based regimen, 33% (N=536) atazanavir-based, 18% (N=288) a darunavir-based, and 4% (N=58) a raltegravir-based regimen. Change in ART during pregnancy was more frequent for atazanavir- and raltegravir- than for lopinavir-based regimens (AOR=1.4 [95%CI 1.0-1.8 and AOR=2.4 [1.4-4.3] respectively), but less frequent for darunavir-based regimens (AOR=0.6 [0.4-0.9]). In this population, only one child was HIV-infected. Immuno-virological outcomes, pregnancy and neonatal outcomes did not differ significantly among treatment groups (Table). Power was > 80% to detect a 2-fold increase in hospitalization, gestational diabetes, and preterm birth when comparing darunavir and atazanavir to lopinavir.

Conclusion: Efficacy and tolerance during pregnancy were similar across the 3 groups of PI-based and raltegravir-based regimens. Notably, more recent drugs such as darunavir and raltegravir do not seem to be less safe than lopinavir and atazanavir which have been more largely described in pregnancy. Long term safety for children remains unknown.

Table: Comparison of women treated on conception with 3-drugs classical regimen based on 2 NRTIs and a third agent, in the French Perinatal Cohort (ANRS-EPF-CO1; 2005-15)

Outcomes	Lopinavir Ref group N=715		Atazanavir N=536			Darunavir N=288			Raltegavir N=58			
	%	%	AOR	[95% CI]	%	AOR	[95% CI]	%	AOR	[95% CI]	p
HIV status at delivery												
CD4 < 200/mm3	**5.7**	**4.5**	0.9	[0.5-1.7]	**6.6**	1.4	[0.7-2.8]	**0.0**	NA		0.41
Viral Load > 50 cp/mL	**13.2**	**11.2**	0.9	[0.6-1.3]	**16.6**	1.4	[0.9-2.2]	**3.8**	0.3	[0.1-1.2]	0.06
Pregnancy												
Hospitalization	**29.5**	**28.2**	0.9	[0.7-1.2]	**28.5**	0.9	[0.7-1.3]	**27.3**	0.8	[0.4-1.6]	0.85
Preeclampsia	**2.3**	**2.5**	1.2	[0.5-2.7]	**1.1**	0.5	[0.1-1.8]	**3.6**	1.6	[0.3-7.9]	0.51
Gestational Diabetes	**8.4**	**10.5**	1.2	[0.8-1.9]	**6.4**	0.7	[0.4-1.4]	**12.7**	1.5	[0.6-3.5]	0.27
Preterm Birth	**14.4**	**14.2**	1.0	[0.7-1.5]	**12.8**	0.9	[0.6-1.5]	**12.3**	0.9	[0.4-2.0]	0.96
Neonatal												
Birth Defect	**3.8**	**2.0**	0.6	[0.3-1.4]	**1.8**	0.6	[0.2-1.9]	**4.2**	1.4	[0.3-6.3]	0.56
Birthweight < 3rd ctile	**4.4**	**3.1**	0.8	[0.4-1.6]	**4.4**	1.1	[0.5-2.6]	**2.1**	0.5	[0.1-3.7]	0.69
Birth length < 3rd ctile	**5.6**	**4.3**	0.8	[0.4-1.4]	**5.5**	1.0	[0.5-1.9]	**6.8**	1.2	[0.4-4.2]	
HIV infection	**0**	**0**	NA		**0.3**	NA		**0**	NA		NA

AOR : adjusted odds ratio, adjusted for maternal age, geographical origin and NRTIs (zidovudine, abacavir, tenofovir).

806 RALTEGRAVIR IN PREGNANCY: PATTERNS OF USE AND BIRTH OUTCOMES IN THE UK AND IRELAND

Rebecca Sconza, Virginia Rasi, Helen Peters, Mario Cortina-Borja, Claire Thorne
UCL Great Ormond Street Institute of Child Health, London, UK

Background: Raltegravir (RAL) is an HIV-1 integrase inhibitor known to rapidly reduce HIV RNA viral load (VL). RAL is often used in pregnancy to reduce risk of mother-to-child transmission, particularly for women presenting and/or diagnosed late in pregnancy.

Methods: The National Study of HIV in Pregnancy and Childhood (NSHPC) conducts active surveillance of pregnancies in women living with HIV in the UK and Ireland. We describe trends in RAL use and outcomes among pregnancies resulting in a live- or stillbirth in 2008-16.

Results: RAL was used in 709 (7%) of 10,144 reported pregnancies in 2008-16. RAL use increased steadily over time from 0.5% (13/2605) of pregnancies in 2008-09 to 14.4% (252/1747) in 2015-16 (p<0.001). Of RAL-exposed pregnancies, use at conception increased from 15% (2/13) in 2008-09 to 30% (76/252) in 2015-16. Of 265 pregnancies with late ART start in pregnancy due to late antenatal booking (>27 weeks), 68 (26%) received RAL overall, reaching 52% (15/29) in 2015-16. Of 709 pregnancies on RAL, 161 (23%) conceived on RAL (Group A), 137 (19%) conceived on ART but initiated RAL antenatally (Group B), and 411 (58%) initiated ART and RAL in pregnancy (Group C) (Table). Six pregnancies ended in stillbirth and there were 728 live-born infants (50 twins). Two-thirds (468/695) were in African-born women, 28% (195/709) in women with antenatal HIV diagnosis, and 4% (26/709) in women with perinatally-acquired HIV. In 44 RAL-exposed pregnancies, HIV diagnosis occurred in pregnancy and booking for antenatal care and initiation of ART were late; in these cases, RAL was started at a median 34 gestational weeks (IQR 32-37) and 56% (23/41) had VL >50 copies/ml at delivery (≤30 days). Twenty-one (3.1%) of 678 singleton RAL-exposed liveborn infants had a reported congenital abnormality, with a similar rate seen in unexposed infants (2.7%); 4.0% (7/174) of infants exposed in the first trimester had an abnormality versus 2.7% (13/490) of those exposed in second/third trimester (14 missing RAL start date) (p=0.36).

Conclusion: RAL use is steadily increasing in pregnancy in UK/Ireland, particularly from before conception, but the group of pregnant women on RAL is heterogeneous. Half of pregnancies with late (third trimester) ART initiation received RAL in 2015-16, consistent with recommendations for RAL usage in pregnancy. Data on congenital abnormalities in RAL-exposed pregnancies are reassuring, but more work is needed to assess overall safety.

Table. Characteristics and outcomes of pregnancies receiving raltegravir by treatment group, 2008-2016

	Group A n = 161	Group B n = 137	Group C n = 411	p-value*
Maternal age in years [Median (IQR)] (N=708)	34 (30-38)	35 (30-38)	32 (28-36)	<0.001
Gestational weeks at booking [Median (IQR)] (N=664)	11 (9-14)	12 (10-15)	14 (11-22)	<0.001
Gestational weeks at raltegravir start [Median (IQR)] (N=533)	N/A	31 (24-35)	30 (21-35)	0.164
CD4 <200 at last measurement in pregnancy [n (%)] (N=680)	9 (5.8)	13 (10.2)	76 (19.1)	<0.001
Viral load >50 copies/ml ≤30 days prior to delivery [n (%)] (N=555)	13 (12.0)	33 (30.6)	118 (34.8)	<0.001
Preterm delivery (<37 weeks) [n (%)] (N=709)	28 (17.4)	22 (16.1)	46 (11.2)	0.095

* p-values were obtained using Kruskal-Wallis tests for medians and chi-squared tests for proportions

807 DolPHIN-1: DOLUTEGRAVIR VS EFAVIRENZ WHEN INITIATING TREATMENT IN LATE PREGNANCY

Catriona Waitt[1], Stephen I. Walimbwa[2], Catherine Orrell[3], Mohammed Lamorde[2], Christie Heiberg[3], Ushma Mehta[4], Julian P. Kaboggoza[2], Julie Anne Coombs[3], Josaphat Byagumisha[2], Alieu Amara[1], Thoko Malaba[4], Laura Else[1], Landon Myer[4], **Saye Khoo**[1]
[1]University of Liverpool, Liverpool, UK, [2]Infectious Disease Institute, Kampala, Uganda, [3]Desmond Tutu HIV Foundation, Cape Town, South Africa, [4]University of Cape Town, Cape Town, South Africa

Background: Initiation of ART in the 3rd trimester of pregnancy is associated with adverse outcomes and increased vertical transmission of HIV. DolPHIN-1 (NCT02245022) is a randomised trial of EFV or DTG plus 2NRTIs in pregnant women initiating ART between 28-36w of gestation in Uganda and South Africa. This scheduled interim review was undertaken after the first 16 mothers delivered. The primary endpoint was pharmacokinetics (PK) of DTG; secondary endpoints included VL responses, safety and tolerability of DTG, and placental/breast milk transfer of DTG.

Methods: Eligible, consenting mothers were randomised 1:1 to EFV or DTG arms. To comply with national guidelines, EFV-containing ART was initiated on the day of referral. Subjects randomized to DTG were switched from EFV within 7 days. Demographic, serial clinical and laboratory data and birth outcome data were collected. VL responses were collected at baseline, 14d and 28d, as well as post-partum. All infants were exclusively breastfed. Intensive PK sampling (0-24h) was performed at 14d on DTG, and 2w post-partum.

Results: Of the 16 subjects who delivered, 8 each received DTG or EFV. Median baseline VL was log 4.15 (range 2.43-6.07) copies/mL and similar between arms. PK data in 3rd trimester are shown (Table 1). The proportion of VL reported as less than 50 copies or undetectable at 2 weeks and at 4 weeks of therapy was 5/8 and 4/8 in mothers on DTG, and 1/5 and 2/7 in mothers on EFV, respectively. At 2 weeks post-partum 5/6 and 4/7 mothers on DTG, and EFV respectively had VL less than 50 copies. Two mothers in the DTG arm were withdrawn for virological failure; the first had no detectable drug in plasma and was non-adherent, the second had evidence of 3 class drug resistance (RT and protease mutations); no women were withdrawn from the EFV arm. Both regimens were well-tolerated. A total of 4 SAE's were reported: DTG arm: 1 G3 elevation in liver function tests (possibly drug related, concomitant herbal use recorded) with stillbirth in the same mother (tight cord around the neck, deemed unrelated to study drug); EFV arm: 1 G3 hypertension, 1 baby with polydactyly.

Conclusion: This planned interim assessment suggests DTG appears to be well-tolerated and effective when initiated in late pregnancy. PK findings are consistent with other studies and suggest that dosing of DTG at 50mg once-daily appears appropriate in third trimester. The study continues, with a definitive efficacy study (DolPHIN-2) in development.

Table 1: Third trimester exposures of DTG

Study	N	Gest age (w) Med (range)	AUC GM µg.h/mL (IQR)	Cmax GM µg/mL (IQR)	C24 GM µg/mL (IQR)	Cl/F (L/h) GM (IQR)	Tmax (h) Med (range)	T½ (h) (range)
Dolphin-1	7	29.5 (28-35)	39.4 (25.8-48.9)	2.65 (1.96-3.37)	0.78 (0.46-1.13)	1.27 (1.02-1.94)	3 (2-4)	11.0 (9.9-12.9)

GM (geometric mean), Med (median)
1 DTG subject had undetectable DTG concentrations

808 DIPSTICKS PROTEINURIA TO PREDICT RENAL DYSFUNCTION IN HIV-INFECTED PREGNANT WOMEN

Mwangelwa Mubiana-Mbewe[1], Bridget Mugisa[2], Bernadette Ngeno[3], Paul R. Young[3], Jillian L. Kadota[4], Benjamin H. Chi[5], **Charles B. Holmes**[6], Michael Vinikoor[7]
[1]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, [2]CDC, Lusaka, Zambia, [3]CDC, Atlanta, GA, USA, [4]Center for Infectious Disease Research in Zambia, Lusaka, Zambia, [5]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [6]Johns Hopkins University, Baltimore, MD, USA, [7]University of Alabama at Birmingham, Birmingham, AL, USA

Background: The Zambian national HIV guidelines recommend urinalysis to detect proteinuria as a baseline screening test for renal insufficiency among HIV-infected pregnant women initiating tenofovir-based first-line antiretroviral therapy (ART). To date, few data are available to evaluate the sensitivity of urine dipsticks for renal dysfunction.

Methods: We compared urine dipsticks proteinuria with eGFR among HIV-infected pregnant women starting ART in antenatal care settings in urban Zambia. Analyzing data from a prospective cohort in 3 Lusaka sites, we estimated glomerular filtration rate (eGFR) using the MDRD equation and used the lowest 10th percentile as a proxy for renal dysfunction.. We determined the sensitivity and specificity of 2+ proteinuria and 1+ proteinuria for eGFR in the lowest 10th percentile.
Results: From March to August 2017, 215 HIV-infected pregnant women were enrolled and had data for urine dipstick protein and serum creatinine. Median values for age was 27 years (IQR: 24-33), gestational age was 18 weeks (IQR: 15-22), CD4 count was 305 cells/μL (IQR: 191-418), and haemoglobin was 11.0 g/dL (IQR: 10.1-11.8). Elevated blood pressure (i.e., 140/90mmHg) was noted in 12 women (5.6%). Urine dipstick protein 1+ was seen in 16 women (7.4%) and only 5 women (2.3%) had 2+ proteinuria. Having 2+ proteinuria had 0% sensitivity (97.5%CI: 0.0, 16.1) and 97.4% specificty (95%CI: 94.1, 99.2) for detection of reduced eGFR, while having 1+ proteinuria had 9.5% sensitivity (95%CI:11.7, 30.4) and 92.8% specificity (95%CI: 88.2, 96.0).
Conclusion: In contrast to non-pregnant HIV infected adults in similar settings, we found that impaired renal function was rare among HIV+ pregnant Zambian women, and urine dipsticks proteinuria had <10% sensitivity for detecting reduced eGFR making it inappropriate as a screening test for reduced eGFR. This data is the first in our setting to describe renal function in HIV infected pregnant women and has potential to inform guidelines on renal monitoring in women prescribed tenofovir.

809 CONCENTRATIONS OF TFV-DP DURING PREGNANCY AMONG WOMEN USING PrEP

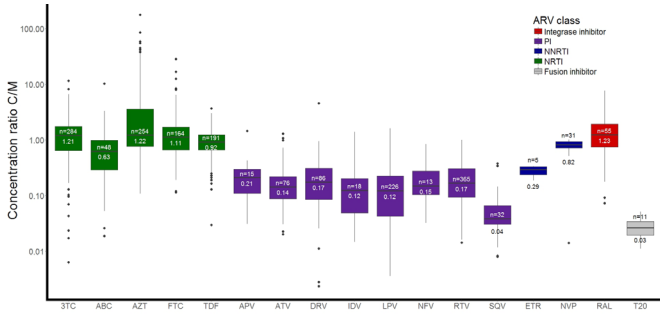
Maria Pyra[1], Peter L. Anderson[2], Kenneth K. Mugwanya[1], Jessica E. Haberer[3], Renee Heffron[1], Stephen Asiimwe[4], Elly T. Katabira[5], Nelly R. Mugo[1], Elizabeth A. Bukusi[1], Connie L. Celum[1], Jared Baeten[1]
[1]University of Washington, Seattle, WA, USA, [2]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Kabwohe Clinical Research Center, Kabwohe, Uganda, [5]Makerere University, Kampala, Uganda

Background: The perinatal period is a time of high HIV risk for some women. PrEP may offer HIV protection, but pregnancy could alter PrEP pharmacokinetics. We examined differences in tenofovir-diphosphate (TFV-DP) concentrations during pregnancy among HIV-uninfected women on daily oral PrEP.
Methods: Concentrations of TFV-DP were analyzed from dried blood spot samples collected from 31 pregnant and 32 non-pregnant women using PrEP in an open-label study in East Africa. The lower limit of quantification (LLQ) was 31.3 fmol/punch, using an LC-MS/MS assay. PrEP adherence was assessed by electronic monitoring (MEMS caps) as the number of days opened in the prior month. The primary analysis was a comparison of TFV-DP concentrations between pregnant and non-pregnant women; a GEE model compared each trimester, adjusted for adherence, baseline age, and BMI. Additional analyses compared concentrations in a subset of 12 women with samples before and during pregnancy; generalized linear mixed effects models were used, adjusted for adherence.
Results: TFV-DP concentrations were lower during pregnancy than during non-pregnant periods, after controlling for adherence: overall, average TFV-DP concentration 637 fmol/punch in non-pregnant women versus 450 fmol/punch in pregnant women (n=102 samples). Adjusting for adherence and baseline characteristics, differences were largest in the 2nd and 3rd trimesters: -52 fmol/punch in 1st trimester (p=0.59), -187 fmol/punch in 2nd trimester (p=0.04), and -179 fmol/punch in 3rd trimester (p=0.07). Results were larger in magnitude and significant when restricted to 83 samples with detectable TFV-DP: -104 fmol/punch in 1st trimester (p=0.27), -278 fmol/punch in 2nd trimester (p=0.004), and -260 fmol/punch in 3rd trimester (p=0.01). Among 12 women with samples before and during pregnancy, TFV-DP concentrations were 289 fmol/punch (95% CI -439 to -139, p=0.005) lower on average during compared to before pregnancy, adjusted for adherence.
Conclusion: Similar to studies of plasma tenofovir concentrations among HIV-infected women on ART, we found evidence that TFV-DP levels during pregnancy are ~70% of non-pregnant levels, even after adjusting for adherence. The difference could be due to changes in clearance, volume of distribution, or adherence effects not fully accounted for by MEMS measurement. Additional studies are needed to understand these mechanisms and whether lower TFV-DP concentrations during pregnancy affect PrEP efficacy.

810 EX VIVO COTYLEDON PERFUSION FAIRLY PREDICTS IN VIVO ARV HUMAN PLACENTAL TRANSFER

Vincent Madelain[1], Minh Le[2], Agnes Bourgeois Moine[2], Sophie Matheron[2], Diane Descamps[2], Laurent Mandelbrot[2], **Gilles Peytavin**[2]
[1]INSERM, Paris, France, [2]AP–HP, Paris, France

Background: Assessing ARV placental transfer in HIV infected pregnant women is important for prevention of fetal infection, as well as potential toxicities. Clinical data are classically obtained by measuring cord blood (F) to mother (M) plasma concentrations (Cpl) ratio at delivery. However, only scarce studies were reported for most ARV. Methods such as the ex vivo dual perfusion of placental cotyledon model are proposed. We aimed to characterize placental transfer patterns of commonly used ARV in a large cohort, and the predictive value of clearance index (CLI) reported in literature from ex vivo experiments.
Methods: In vivo data were obtained from routine therapeutic drug monitoring in Paris hospitals during the 10 last years, where ARV Cpl at delivery were documented for paired M and F samples, collected within 3 hours of each other. Most mothers were adherent to recommended ARV combinations and few fetal transmissions occurred. M and F and amniotic fluid (AF) Cpl were determined by UPLC-MS/MS. Median and 10-90 percentiles were presented for each ARV, and correlation with raw and corrected CLI were tested using Spearman's method.
Results: A total of 540 couples with M and F Cpl were included in the analysis, allowing to calculate 1876 F/M ratios encompassing 20 ARV medications and 179 AF/M ratios. Non Reverse Transcriptase Inhibitors (NRTI) had high F/M ratios above 1 except for abacavir. The F/M ratio appeared to be dependent on the M Cpl, suggesting simple diffusion. On the contrary, Protease Inhibitors (PI) showed far lower F/M ratios than NRTI, below 0.5 for all of them and only 0.04 for saquinavir. Considering NNRTI, the F/M ratio for etravirine was near to those for PI's whereas nevirapine had a similar ratio to NRTI. Raltegravir also had a high ratio of 1.23, also dependent on M Cpl. The AF/M ratios suggested an accumulation of NRTI (except tenofovir), raltegravir and raltegravir glucuronide in AF. Raw CLI were significantly, but moderately, correlated with F/M ratios, (rho=0.59; p= 0.029). Correcting CLI with the Hutson formula (CPT 2011; 90:67–76) markedly improved the correlation (rho=0.81; p= 0.001).
Conclusion: This study confirmed the heterogeneity of drug diffusion to fetus among the different classes of ARV, with high in utero exposure to NRTI and raltegravir, and lower exposure to PI. Although it was not completely predictive, the ex vivo perfusion model effectively explored maternal-to-fetal transfer prior to human administration.



811 CABERGOLINE FOR LACTATION SUPPRESSION AMONG HIV+ AND HIV- WOMEN

Sarah Humphrey, Maeve Baechler, Melissa Schiff, **Jane Hitti**
University of Washington, Seattle, WA, USA

Background: HIV+ women who are counseled not to breastfeed may benefit from pharmacologic lactation suppression. Single-dose cabergoline is highly effective yet infrequently prescribed due to concern for potential effects on maternal blood pressure (BP). We evaluated the effects of cabergoline on maternal BP and pulse immediately postpartum among women with HIV or obstetric indications for lactation suppression such as fetal/neonatal demise.
Methods: We conducted a retrospective cohort study of 224 post-partum women with HIV or obstetric indications for lactation suppression who delivered

at the University of Washington between 1/1/2013-12/31/2016. Women who received 1mg cabergoline within 48 hours post-partum (N=28 HIV+, 43 HIV-) were compared to unexposed women (N=32 HIV+, 121 HIV-) who delivered before cabergoline was available on formulary. Women with hypertension and multiple gestations were excluded. Pulse, systolic and diastolic BP were assessed at 4-hour intervals up to 24-hours after cabergoline and compared to unexposed women using delivery as the reference point. Mean BP and pulse for the two groups were compared using linear regression to estimate mean change (β)and 95% confidence intervals (CI), adjusting for age, lactation suppression, indication and weeks' gestation at delivery.

Results: Among all 60 HIV+ women, 50 (83%) were diagnosed prior to pregnancy and 59 (98%) had HIV RNA <40 prior to delivery. ARV regimen type (PI, NNRTI, II) did not differ between cabergoline-exposed and unexposed women. Among the 28 HIV+ cabergoline-exposed women, 15 (54%) reported effective lactation suppression postpartum, 13 (46%) did not comment and 1 (3%) had breast engorgement/leaking; none reported adverse effects. Among HIV+ and HIV- women combined, cabergoline-exposed women had lower mean systolic BPs at all 4-hour time intervals ranging from -6.9mm Hg (95% CI -11.1 to -2.8) at 0-4 hours to -10.9 mm Hg (95% CI -18.2 to -3.6) at >20-24 hours compared to unexposed women. Diastolic BP was decreased on average –8.1mmHg (95% CI -13.9 to -2.4) at 20-24 hours only, with no significant differences found in maternal pulse between cabergoline-exposed and unexposed groups.

Conclusion: Cabergoline has a modest lowering effect mainly on systolic blood pressure, which was statistically significant but unlikely to be clinically important given no change in maternal pulse. Cabergoline could be considered for more routine use among HIV+ and HIV- women with indications for lactation suppression.

Table. Post-partum blood pressure and pulse for women with indications for lactation suppression who did and did not receive cabergoline at the University of Washington between January 2013 and July 2016.

Hours post cabergoline or post-partum	Received Cabergoline N=71		No Cabergoline N=153		Adjusted β (95% Confidence Interval)
	No (%)	Mean (SD)	No (%)	Mean (SD)	
Systolic Blood Pressure					
>0-4	51 (71.8)	104.8 (13.2)	152 (99.3)	111.7 (12.6)	**-6.9 (-11.1 to -2.8)**
>4-8	41 (57.7)	100.3 (11.7)	138 (90.2)	108.8 (13.9)	**-9.8 (-14.6 to -5.0)**
>12-16	24 (33.8)	103.8 (12.8)	72 (47.0)	109.4 (11.8)	**-8.4(-14.0 to -2.8)**
>20-24	17 (23.9)	101.4 (11.2)	72 (47.0)	111.8 (13.4)	**-10.9 (-18.2 to -3.6)**
Diastolic Blood Pressure					
>0-4	51 (71.8)	61.5 (10.5)	152 (99.3)	60.7 (8.2)	-0.1 (-2.9 to 2.7)
>4-8	41 (57.7)	60.3 (9.5)	138 (90.2)	61.6 (9.7)	-3.1 (-6.6 to 0.5)
>12-16	24 (33.8)	60.3 (8.0)	72 (47.0)	62.3 (9.7)	-3.4 (-8.1 to 1.3)
>20-24	17 (23.9)	60.6 (8.6)	72 (47.0)	66.3 (11.1)	**-8.1 (-13.9 to -2.4)**
Pulse					
>0-4	51 (71.8)	80.5 (14.2)	152 (99.3)	80.3 (13.9)	1.2 (-3.2 to 5.8)
>4-8	41 (57.7)	82.0 (12.1)	138 (90.2)	77.4 (13.5)	3.1 (-1.7 to 7.9)
>12-16	24 (33.8)	78.7 (11.8)	72 (47.0)	81.0 (13.0)	-2.7 (-9.4 to 3.9)
>20-24	17 (23.9)	80.7 (9.1)	71 (46.4)	80.0 (12.1)	0.3 (-6.3 to 6.9)

*Adjusted for indication, maternal age, gestational age.

812 PREDICTORS OF VIROLOGIC FAILURE IN POSTPARTUM WOMEN ON ART IN PROMISE 1077HS

Risa M. Hoffman[1], Meredith G. Warshaw[2], K. Rivet Amico[3], Jose H. Pilotto[4], Gaerolwe Masheto[5], Jullapong Achalapong[6], Elizabeth S. Machado[7], Kulkanya Chokephaibulkit[8], Geraldo Duarte[9], Anne Coletti[10], Renee Browning[11], Nahida Chakhtoura[12], Karin L. Klingman[11], Judith S. Currier[1]
[1]University of California Los Angeles, Los Angeles, CA, USA, [2]Harvard University, Boston, MA, USA, [3]University of Michigan, Ann Arbor, MI, USA, [4]Oswaldo Cruz Foundation - Fiocruz, Rio de Janeiro, Brazil, [5]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [6]Chiang Rai Prachanukroh Hospital, Chiang Rai, Thailand, [7]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [8]Mahidol University, Bangkok, Thailand, [9]Universidad de São Paulo, São Paulo, Brazil, [10]FHI 360, Durham, NC, USA, [11]NIAID, Bethesda, MD, USA, [12]National Institute of Child Health and Human Development, Bethesda, MD, USA

Background: Antiretroviral (ART) adherence can be challenging for postpartum women and may result in virologic failure (VF). We examined predictors of VF and viral re-suppression in postpartum women randomized to continue ART in PROMISE 1077HS.

Methods: Asymptomatic HIV+, non-breastfeeding women with pre-ART CD4 cell counts 400 cells/mm^3 who started ART during pregnancy were randomized up to 42 days after delivery to continue or discontinue treatment. Women were enrolled from 12/2011-11/2014. The preferred regimen was LPV/RTV with TDF/FTC. Viral load and self-reported adherence were collected every 12 weeks. VF was defined as 2 consecutive viral loads >1,000 copies/mL after 24 weeks on ART. Viral re-suppression was defined as 2 consecutive viral loads 1,000 copies/mL after VF. For this analysis, self-reported adherence was dichotomized as missing versus not missing ART doses in the prior 4 weeks. Predictors of VF and re-suppression were examined using Cox proportional hazards univariable and multivariable regression, with adherence as a time-varying covariate. Other predictors were values at baseline.

Results: Among the 802 women randomized to continue ART, median age at entry was 27 years (IQR 23-32) and median CD4 696 cells/mm^3 (IQR 576-865). Participants were enrolled from South America/Caribbean (39%), Africa (28%), Asia (25%), and the United States (8%). Of 175 women with VF, 139 had resistance data available. Of these, 17/139 (12%) failed with resistance to their current regimen. There was an estimated 0.12 probability of VF by week 48, 0.20 by week 96, and 0.25 by week 144. In univariable regressions, self-report of any missed ART doses in the prior 4 weeks, younger age, region, and shorter duration of pre-entry ART were predictive of VF. In the final multivariable model for VF, significant predictors included missed ART doses within the prior 4 weeks, younger age, shorter duration of pre-entry ART, and region (South America/Caribbean) (Table). Among the 175 (22%) women with VF, the probability of re-suppression was 0.37 by 48 weeks, 0.48 by 96 weeks, and 0.57 by 144 weeks. There were no statistically significant predictors of re-suppression.

Conclusion: A simple 4-week ART recall question predicted first VF among women in PROMISE 1077HS. Postpartum women who have VF are high risk for continued viremia, and further research should explore strategies that can successfully support ART adherence for this vulnerable population.

Table: Univariable and Multivariable analyses for virologic failure among women who continued ART in PROMISE 1077HS (N=802)

	Univariable			Multivariable Model		
Variable	Hazard Ratio	(Lower CL*, Upper CL)	p-value	Hazard Ratio	(Lower CL, Upper CL)	p-value
Missed meds in last 4 weeks*	2.55	(1.89, 3.43)	<0.001	2.05	(1.48, 2.84)	<0.001
Age at entry	0.96	(0.93, 0.98)	0.001	0.97	(0.94, 0.99)	0.01
Pre-entry ART duration (months)	0.92	(0.85, 1.00)	0.05	0.91	(0.83, 0.99)	0.02
Region Botswana	1.07	(0.66, 1.74)	0.78	1.06	(0.65, 1.73)	0.81
Region Brazil/Haiti/Argentina/Peru	2.06	(1.36, 3.10)	<0.001	1.69	(1.10, 2.60)	0.02
Region United States	1.60	(0.87, 2.93)	0.13	1.50	(0.81, 2.80)	0.20
Region Thailand/China (reference)	--			--		
Baseline health**	0.98	(0.83, 1.15)	0.78			
ART including PI***	1.22	(0.83, 1.81)	0.31			

*CL: Confidence Limit; *Time-varying co-variate
**Using a self-rated health scale (1=excellent, 5=poor)
***PI: Protease Inhibitor-based ART

813 DISPARITIES IN ANTENATAL VIROLOGIC FAILURE AMONG WOMEN RECEIVING OPTION B+ IN KENYA

Keshet Ronen[1], Brian Khasimwa[2], Bhavna Chohan[3], Daniel Matemo[2], Jennifer Unger[1], Alison L. Drake[1], **John Kinuthia**[2], Grace John-Stewart[1]
[1]University of Washington, Seattle, WA, USA, [2]Kenyatta National Hospital, Nairobi, Kenya, [3]Kenya Medical Research Institute, Nairobi, Kenya

Background: Option B+ prevention of mother-to-child transmission (PMTCT) regimens rely on maternal adherence to ART. It is important to determine rates and correlates of virologic failure in women receiving Option B+. This study evaluates the prevalence and correlates of virologic failure in a cohort of pregnant HIV-infected women receiving ART in public maternal child health (MCH) clinics in Kenya.

Methods: We conducted a cross-sectional analysis of enrollment data from participants in a trial evaluating mHealth strategies to improve ART adherence (Mobile WAChX, NCT02400671). Participants were age ≥14, HIV-infected, pregnant and had daily access to a mobile phone. Participants were recruited from 6 public MCH clinics in Nairobi and Nyanza region. Self-report questionnaires, clinic record abstraction and plasma for viral load (VL) testing were collected. Virologic failure was defined as VL ≥1000 copies/ml among women with ≥6 months on ART. ART adherence behavior skills were assessed using a modified Lifewindows IMB tool and depression using the PHQ9. Correlates of failure were assessed by χ^2 test and univariable logistic regression with clustered standard errors by site.

Results: Of 825 participants enrolled, 451 (56%) had been on ART ≥6 months, of whom all but one had VL data (n=450). Of these, 58 (13%) had virologic failure, 115 (26%) reported ≥mild depression (PHQ9 score ≥5), 433 (96%) had disclosed their HIV status to someone, median adherence behavior skills score was 81%, and median age was 28.5. Prevalence of virologic failure was associated with clinic site (range 1%-27%, p<0.0001), continuous age (OR per

year increase 0.98, 95%CI 0.97-0.99), HIV status disclosure (OR 0.31, 95%CI 0.11-0.83) and ART adherence skills score (OR 0.70 per 10% increase, 95%CI 0.53-0.93); we observed a trend for depression (OR 2.14, 95% CI 0.91-5.02). Marital status, self-reported adherence, history of side effects, social support, history of intimate partner violence or distance to clinic were not associated with virologic failure.

Conclusion: Virologic failure during pregnancy varied widely by MCH clinic, raising concerns about disparities in programmatic implementation of Option B+ in Kenya. Additional support for women who are young, have not disclosed, report difficulty with adherence behavioral skills, and/or with depression may be important to optimize Option B+ efficacy.

814 ART ADHERENCE AMONG PREGNANT AND NON-PREGNANT WOMEN IN SOUTH AFRICA AND UGANDA

Lynn T. Matthews[1], Catherine Orrell[2], Bosco M. Bwana[3], Stephen Asiimwe[4], Gideon Amanyire[3], Nicholas Musinguzi[3], Anna Cross[2], Kathleen Bell[1], Alexander C. Tsai[1], Christina Psaros[1], David R. Bangsberg[5], Jessica E. Haberer[1]

[1]Massachusetts General Hospital, Boston, MA, USA, [2]University of Cape Town, Cape Town, South Africa, [3]Mbarara University of Science and Technology, Mbarara, Uganda, [4]Kabwohe Clinical Research Center, Kabwohe, Uganda, [5]Oregon Health and Sciences University, Portland, OR, USA

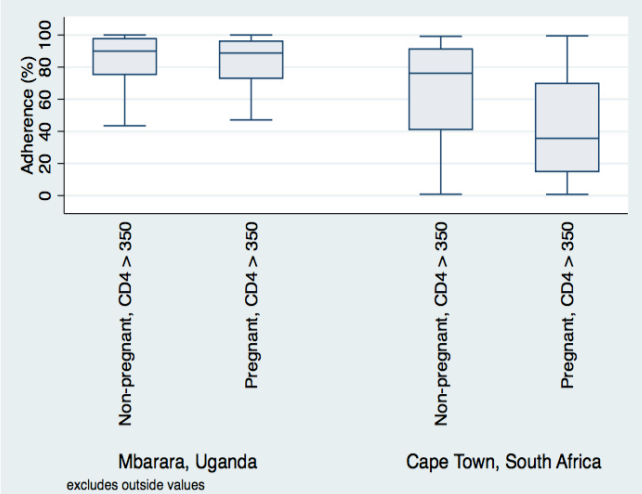
Background: With the advent of Option B+, women living with HIV (WLWH) are offered more streamlined care, but data suggest ongoing challenges to ART adherence and retention in care. We conducted research to understand patterns and correlates of ART adherence among WLWH accessing public sector clinics offering Option B+ as standard of care in Uganda (UG) and South Africa (SA).

Methods: We prospectively observed pregnant and non-pregnant women initiating ART with CD4>350 cells/ml during 2015-2017 in southwestern, UG and Cape Town, SA. Women were seen at 0, 6, and 12 months for socio-behavioral questionnaires and HIV RNA levels. Adherence to ART was monitored in real-time (Wisepill). Those lost to follow-up were considered non-adherent/virally unsuppressed; data were censored at death/disenrollment. Predictors of ART adherence were assessed by multivariable linear regression in site-specific models.

Results: Among 439 enrolled women, 205 pregnant and 234 non-pregnant women had median age 26 (IQR 23-29) vs. 31 (IQR 24-41), CD4 554 (IQR 430-683) vs. 436 (IQR 396-472), with 54 (27%) vs. 68 (36%) reporting a partner living with HIV, and 85 (43%) vs. 96 (51%) reporting serostatus disclosure to partner, respectively. In UG, median adherence to ART for pregnant and non-pregnant women was similar (90% [IQR 75-98] vs. 89% [IQR 73-96], p=0.17), but lower among pregnant women in SA (36% [IQR 15-70] vs. 76% [IQR 41-91], p<0.001). For women in UG, adherence was independently associated with older age (b=1.1 [0.30, 1.9]), employment (b=14.5 [5.3, 23.8]), depression (b=26.2 [14.3, 38.1], and alcohol use (b=-15.5 [-29.2, -1.7]). Substance use (b=-19.8 [-35.2, -4.4]) was the only independent predictor of adherence among non-pregnant women in SA. For pregnant women in SA, adherence was independently associated with marriage (b=24.0 [0.4, 47.5]), depression (b=-31.5 [-53.4, -9.5]), gestational age (b=-1.2 [-2.4, -0.1] per week), and non-disclosure to partner (b=-8.4 [-28,11]). In UG, 96 (90%) and 100 (86%) pregnant and non-pregnant women were virally suppressed at 12 months. In SA, viral suppression was achieved by 36 (58%) of pregnant and 91 (91%) of non-pregnant women.

Conclusion: Effective methods to promote mental health and support within partnerships, while mitigating alcohol and substance use for WLWH accessing care during pregnancy are crucial for the health of women, their children, and their families, particularly in urban South Africa.

Figure 1. Box and whisker plots for percent adherence to ART by Wisepill. Data are presented by site and clustered into pregnant versus not pregnant women.



815 EARLY CLINICAL EVENTS AFTER ART INITIATION IN PREGNANCY INFLUENCE VIRAL LOAD OUTCOMES

Jasantha Odayar[1], Elaine J. Abrams[2], Allison Zerbe[2], Tamsin K. Phillips[1], Landon Myer[1]

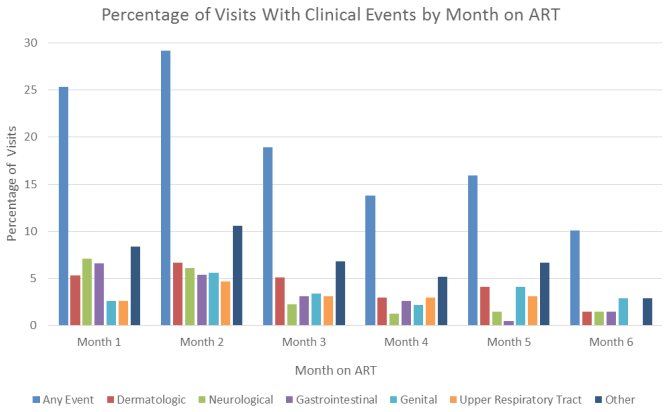
[1]University of Cape Town, Cape Town, South Africa, [2]ICAP at Columbia University, New York, NY, USA

Background: There is growing concern around adherence and virologic outcomes following antiretroviral therapy (ART) initiation in pregnancy. Incident clinical events after ART initiation, including side effects, new symptoms and 'minor' complaints of pregnancy, may influence short-term ART outcomes, but data are few.

Methods: Consecutive women initiating TDF+FTC+EFV in routine antenatal care in Cape Town, South Africa were followed with viral load (VL) monitoring through 12 months postpartum. Data on clinical events during the antenatal period were abstracted from routine records. For each woman, the first episode of a sign, symptom or diagnosis (including side effects, pregnancy disorders and other illnesses) was included. Poisson methods were used to assess the association between clinical events and VL at delivery and through 12 months postpartum.

Results: In 553 women enrolled (median age 28 years; median CD4 count 349 cells/μL; median pre-ART VL 4.0 log[10] copies/ml; median gestation 20 weeks; 258 person-years observation; 1819 clinic visits), 48% (n=263) had at least one clinical event (23%, 14% and 11% had 1, 2 and ≥3 events, respectively). There were 512 clinical events recorded in the cohort, with peak incidence in the first 8 weeks after ART initiation (Figure). Clinical events were significantly more likely at CD4 counts <100 and 100-200 than >200 cells/μL (IRR 1.94, 95% CI 1.21–3.13; and 1.38, 95% CI 1.04–1.83, respectively). Overall, 18% of clinical events were dermatologic, 15% neurological, 14% gastrointestinal, 14% genital, and 12% upper respiratory tract. At delivery (median ART duration 120 days) 72% women had viral suppression (VS) (VL<50 copies/mL). Adjusting for age, enrolment VL, and ART duration, delivery VS was marginally less likely in women experiencing a clinical event antenatally (IRR 0.97, 95% CI 0.90–1.04). This association was amplified in women on ART ≥16 weeks at delivery (IRR 0.93, 95% CI 0.86–0.99) and women who experienced ≥3 clinical events before delivery (IRR 0.93, 95% CI 0.78–1.10). Only 7% of all clinical events resulted in referral to a higher level of care; this was not associated with VS at delivery. There were no associations between clinical events in pregnancy and virologic outcomes in the postpartum period.

Conclusion: Incident clinical events after ART initiation occur commonly during pregnancy and appear associated with viral suppression in the short term; these may warrant specific attention in patient counselling and support interventions.



816 WITHDRAWN

817 QUANTIFYING VISIT ADHERENCE IN PREGNANT WOMEN INITIATING ART IN SWAZILAND

Nontokozo Langwenya[1], Harriet Nuwagaba-Biribonwoha[2], William J. Reidy[2], Averie B. Gachuhi[2], Simangele Mthetwa[3], Velephi Okello[3], Landon Myer[1], Elaine J. Abrams[2]

[1]University of Cape Town, Cape Town, South Africa, [2]ICAP at Columbia University, New York, NY, USA, [3]Ministry of Health, Mbabane, Swaziland

Background: Several studies have reported poor retention among HIV+ pregnant women initiating antiretroviral treatment (ART) under Option B+, particularly at the start of treatment. However, there is limited data on visit attendance patterns among women on ART. We evaluated three measures of ART visit adherence based on the expected follow-up (FU) dates under the Option B+ 'treat-all' approach and Option A, CD4/clinical- eligibility based ART.

Methods: At 12 health facilities in Swaziland, routine patient-level data of all HIV+ pregnant women not on ART making their first antenatal care (ANC) visit was abstracted as part of an implementation science study comparing maternal retention outcomes under Options A and B+. Among patients who initiated ART and had >=2 FU visits, we performed a descriptive analysis of missed visits (>28 days after expected FU), visit constancy (>=1 visit per each 3-month period) and gaps in care (>6 months without a clinic visit) from ART initiation. Associations between these outcomes and demographic and clinical characteristics at ANC entry were examined using cox proportional hazard models.

Results: We analysed 1417 women; mean age=25.6 years (SD=5.53), median CD4=349 cells/μL (IQR=242-483), median gestation=19 weeks (IQR=15-24), at first ANC visit; with 11,595 FU visits. Of 1417 women, 84% (n=1190) had >= 2 FU visits, 90 % (n=446) under A vs 81% (n=789) B+, with a median observation time of 14.1 months on ART (IQR=9.1-17.3). More than a half (57%, n=680) had a missed visit, 40% (n=706) did not have a clinic visit in each 3-month period since ART initiation and 29% (n=346) experienced a gap in care >6 months. Among women with a missed visit, 64% did not achieve visit constancy and 48% had >6 month gap in care. In a cox proportional hazard analysis, the risk of experiencing a missed visit was independently associated with age and gestation at ANC entry; each one-year increase in age from 15 years decreased risk by 3% (aHR=0.97; CI=0.96-0.99) and one-week increase in gestation from 4 weeks gestation increased risk by 2% (aHR=1.02, CI=1.01-1.04). Measures of visit adherence did not significantly differ by Option B+.

Conclusion: Given that non-adherence to clinic visit schedules may increase the risk of mother-to-child transmission, this high level of non-adherence to clinic visits is concerning. Younger age groups and late presenters may require targeted retention counselling and support services.

818 TEXT MESSAGING FOR RETENTION IN PMTCT: A STEPPED-WEDGE CLUSTER-RANDOMIZED TRIAL

Thomas A. Odeny[1], James P. Hughes[2], Elizabeth A. Bukusi[3], Eliud Akama[2], Elvin Geng[4], King Holmes[2], R. Scott McClelland[2]

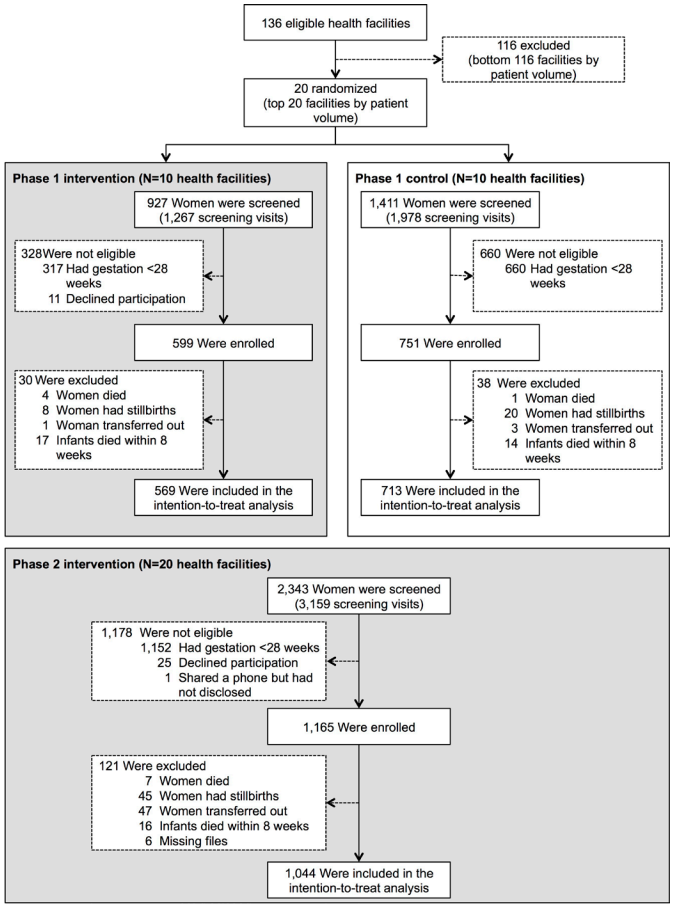
[1]Kenya Medical Research Institute, Kisumu, Kenya, [2]University of Washington, Seattle, WA, USA, [3]Kenya Medical Research Institute, Nairobi, Kenya, [4]University of California San Francisco, San Francisco, CA, USA

Background: Timely diagnosis of infant HIV infection is the sine qua non of successful antiretroviral therapy initiation, yet about 50% of mother-infant pairs are lost to follow-up during the postpartum period. In a randomized controlled trial, we found the TextIT intervention (a two-way theory-based text messaging system) to be efficacious for improving infant HIV testing rates and maternal postpartum retention in prevention of mother-to-child HIV transmission (PMTCT) programs. Using an implementation science approach, we aimed to evaluate real-world effectiveness of the intervention in western Kenya.

Methods: In a pragmatic, cluster randomized, stepped-wedge trial with two time periods of observation, we randomly allocated 10 clinics to begin implementing the intervention immediately, and 10 clinics to begin implementing 6 months later. Inclusion criteria were minimal to approximate real world conditions. We used modified Poisson regression with robust variance estimation to estimate the relative risk and 95% confidence intervals (CI). Generalized estimating equations were applied on individual-level data to account for clustering by site.

Results: Between February 2015 and December 2016, 4,681 women were assessed for study participation (6,404 screening visits) and 2,129 who were less than 28 weeks pregnant were excluded. Of 2,326 infants analyzed, 1,466 of 1,613 (90.9%) in the intervention group and 609 of 713 (85.4%) in the control group met the primary outcome of HIV virologic testing performed before eight weeks after birth (adjusted relative risk [aRR] 1.03; 95% CI 0.97-1.10; P=0.3). Of 2,472 women analyzed, 1,548 (90%) of 1,725 in the intervention group and 571 (76%) of 747 in the control group met the primary outcome of retention in care during the first eight weeks after delivery (aRR 1.12; 95% CI 0.97–1.30; p=0.1).

Conclusion: A greater proportion of infants in the intervention group received HIV testing compared with the control group, but the difference was small, and not statistically significant. There was also a non-significant increase in maternal postpartum retention in the intervention periods. Despite the lack of a significant effect of the intervention, key lessons emerged, both for strengthening PMTCT and for implementation research in general. Perhaps most important, improving the implementation of usual care was sufficient to substantially improve infant HIV testing rates.



819 DOES QI IMPROVE PMTCT PROCESSES IN RURAL SOUTH AFRICA? A STEPPED WEDGE CLUSTER RCT

H. Manisha N. Yapa[1], Jan-Walter De Neve[2], Terusha Chetty[3], Carina Herbst[4], Frank Post[5], David A. Cooper[1], Awachana Jiamsakul[1], Pascal Geldsetzer[6], Guy Harling[7], Philippa Matthews[4], Frank Tanser[4], Kobus Herbst[4], Dickman Gareta[4], Deenan Pillay[4], Till Bärnighausen[2]
[1]Kirby Institute, Sydney, NSW, Australia, [2]Heidelberg University, Heidelberg, Germany, [3]University of KwaZulu-Natal, Durban, South Africa, [4]Africa Health Research Institute, Mtubatuba, South Africa, [5]King's College Hospital NHS Foundation Trust, London, UK, [6]Harvard University, Cambridge, MA, USA, [7]University College London, London, UK

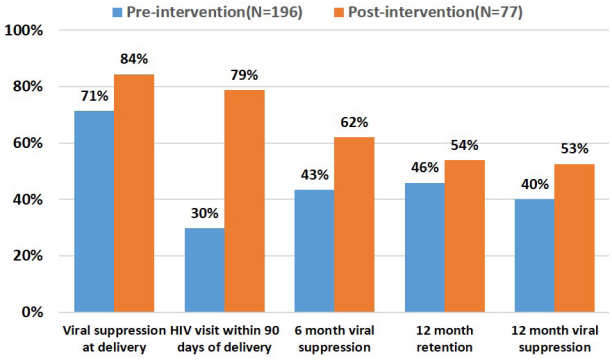
Background: Health systems imperfections continue to lead to preventable HIV vertical transmission in many countries. In sub-Saharan Africa ~4% women are newly infected during the pregnancy or breastfeeding (PBF) period, accounting for ~37% PBF women with viral loads (VL) >1000 copies/mL. VL and repeat HIV testing are key processes in ensuring prevention of mother-to-child transmission (PMTCT) success and maternal health. We test the effectiveness of quality improvement (QI) in increasing VL and repeat HIV testing in PMTCT in rural South Africa.
Methods: The MONARCH stepped-wedge randomised trial (NCT02626351) of a QI intervention was conducted at seven primary health care clinics in a rural community of northern KwaZulu-Natal, South Africa, from July 2015-January 2017. All women aged ≥18 years who delivered during the study were eligible for enrollment. We performed intent-to-treat analyses using Poisson mixed effects hierarchical models, with time fixed effects and clinic random effects. Extracted from routine antenatal medical records, our two pre-registered primary endpoints were: (i) proportion of HIV-positive pregnant women with an up-to-date (within the past 90 days) VL test; (ii) proportion of HIV-negative pregnant women with an up-to-date repeat HIV test.
Results: We report preliminary results. Of 2162 study participants, 54% were exposed to the intervention. Median age was 25 years (interquartile range [IQR] 21-30); median gestational age at first booking was 19 weeks (IQR 15-24); median parity was 1 (IQR 0-2). Overall HIV prevalence was 47% (95% confidence interval [CI] 45-50%): prevalence was highest amongst 30-34 year-olds (70%, 95%CI 65-75%). The proportion of HIV-positive pregnant women (n=1026) receiving VL tests and HIV-negative pregnant women (n=1136) receiving repeat HIV tests increased over calendar time. The QI intervention significantly increased VL testing (risk ratio (RR) 1.26, 95%CI 1.06-1.49, p=0.01), but did not increase repeat HIV testing (RR 1.13, 95%CI 0.96-1.33, p=0.13).
Conclusion: QI led to improvement in VL testing in PMTCT in this rural community in South Africa. This intervention holds promise for improving HIV VL control during pregnancy, helping eliminate mother-to-child HIV transmission and improve maternal health, by strengthening essential antenatal and HIV clinical processes. Future research should identify mechanisms of action to explain differential effects on endpoints.

820 IMPROVED POSTPARTUM HIV OUTCOMES AFTER CARE COORDINATION TEAM INTERVENTION

Anandi N. Sheth[1], Stephanie Hackett[2], Christina M. Meade[1], Jennifer M. Davis[1], Joy Ford[2], Jeronia Blue[2], Lisa Curtin[2], Andres Camacho-Gonzalez[1], Ann Chahroudi[1], Rana Chakraborty[1], Melody P. Palmore[1], Martina L. Badell[1]
[1]Emory University, Atlanta, GA, USA, [2]Grady Health System, Atlanta, GA, USA

Background: While increased health care engagement and antiretroviral therapy (ART) adherence may occur during pregnancy, HIV-infected women are at risk for loss to follow-up and ART discontinuation after delivery. Prompt HIV care after delivery has been associated with improved short- and long-term HIV outcomes. However, targeted interventions to improve such outcomes are lacking.
Methods: In Sept 2015, we assembled a care coordination team of obstetric, adult, and pediatric HIV clinicians, a nurse, and a social worker, to develop monthly care plans for HIV-infected pregnant women seen in a large, safety-net, public hospital in Atlanta. We conducted a retrospective analysis of data collected from women who delivered at ≥24 weeks gestation from Jan 2011-Aug 2017. Using multivariable logistic regression models, we compared the following HIV outcomes pre- vs. post-intervention implementation: viral suppression (VS; HIV RNA <200 copies/mL) at delivery, attendance of an HIV care visit within 90 days of delivery, 12-month retention in care (two HIV care visits or viral load measurements at least 90 days apart) and 6- and 12-month VS.
Results: 196 and 77 women delivered pre- and post-intervention, respectively. Age, race, HIV transmission category, duration of HIV diagnosis, number of previous births, timing/ number of prenatal care visits, pre-pregnancy ART use, and CD4 count/ VS at pregnancy diagnosis were not significantly different in the pre- and post-intervention groups. VS at delivery, HIV care visit attendance within 90 days of delivery and VS at 6 months after delivery all significantly improved in the post-intervention group (Figure 1); HIV care visits occurred on average 146 vs. 73 days after delivery in the pre- vs. post-intervention groups (p<0.0001). Increases noted in 12-month retention and VS were not statistically significant. After adjusting for relevant demographic, HIV, and pregnancy factors, delivery after intervention implementation strongly predicted VS at delivery (OR 2.2, 95%CI 1.0-4.8), HIV care visit attendance within 90 days of delivery (OR 8.2, 95%CI 4.0-16.9), and 6-month VS (OR 3.1, 95%CI 1.6-6.2).
Conclusion: In this population of postpartum HIV-infected women at high risk for disengagement in care, a team-based, care coordination intervention significantly improved short-term HIV outcomes. Timely transition from obstetric to HIV care after delivery in the post-intervention group highlights the potential benefits of care coordination teams to improve long-term outcomes.

Figure 1. Outcomes in HIV-infected women delivering pre- (blue) vs. post- (orange) care coordination intervention implementation, Atlanta, 2011-2017



821 MATERNAL VIRAL LOAD SUPPRESSION AND VERTICAL TRANSMISSION IN MALAWI'S PMTCT PROGRAM

Ernest Nkhoma[1], Monique van Lettow[2], Beth A. Tippett Barr[3], Joep J. van Oosterhout[2], Eunice Mwandira[1], Lloyd Chilikutali[1], Annie Kanyemba[1], Zinenani T. Truwah[1], Andrew F. Auld[4], Megan Landes[2]
[1]Management Sciences for Health, Lilongwe, Malawi, [2]Dignitas International, Zomba, Malawi, [3]CDC, Atlanta, GA, USA, [4]CDC Malawi, Lilongwe, Malawi

Background: In 2011, Malawi implemented Option B+, a universal test and treat strategy for the prevention of maternal to child transmission of HIV (PMTCT), which resulted in marked increases in ART uptake by pregnant and breastfeeding women. We describe viral load (VL) suppression in a nationally representative cohort of HIV-positive women at 4-26 weeks post-partum, along with factors associated with VL suppression and the association between VL suppression and early vertical transmission.
Methods: Known HIV-positive mothers were enrolled at 4-26 weeks post-partum in a cross-sectional sub-study of the national evaluation of Malawi's PMTCT program. Mothers were consented and screened for HIV while attending under-5 clinics in 13 health facilities across 8 districts; HIV-exposed infants received HIV-1 DNA testing. Data collected at the time of enrollment included socio-demographic and PMTCT indicators. Maternal VL testing was conducted from plasma samples using Abbott RealTime HIV-1 Assay.
Results: Among 1154 HIV-positive women on ART; 573 (49.7%) had started ART prior to- and 569 (49.3%) during their last pregnancy. Twelve (1%) had started ART post-partum. At 4-26 weeks of age, 34 (2.9%) infants were HIV-infected. VL data were available for 1124 women; 136 (12.1%) had a VL >1000 copies (i.e., unsuppressed VL). In multivariable analysis, suboptimal adherence (missing >2 days of ART in the past month) was associated with unsuppressed VL (n=35/134 vs 89/886; adjusted odds ratio (aOR) 4.3; 95% confidence interval (CI) 2.5-7.4). Women with unsuppressed VL load were over 16 times more likely to transmit HIV to their infants (n=19/136 vs 14/988; aOR 16.7; 95% CI 6.6-41.8). Maternal age <19 years (n=4/74 vs. 11/535; aOR 6.6; 95% 1.1-39.8) and non-exclusive breastfeeding (n=6/88 vs 27/1064; aOR 4.0; 95% CI 1.2-13.8) were also associated with vertical transmission.

Conclusion: Malawi has nearly reached the target of 90% viral suppression in those on ART among this nationally representative cohort of women in Option B+. A relevant proportion of women with unsuppressed VL are at strongly increased risk of vertical transmission. Further characterization of this group of women and providing tailored support measures will be important to achieve elimination of MTCT.

822 INFANT HIV-FREE SURVIVAL IN THE ERA OF "OPTION B+" SERVICES IN RURAL ZAMBIA

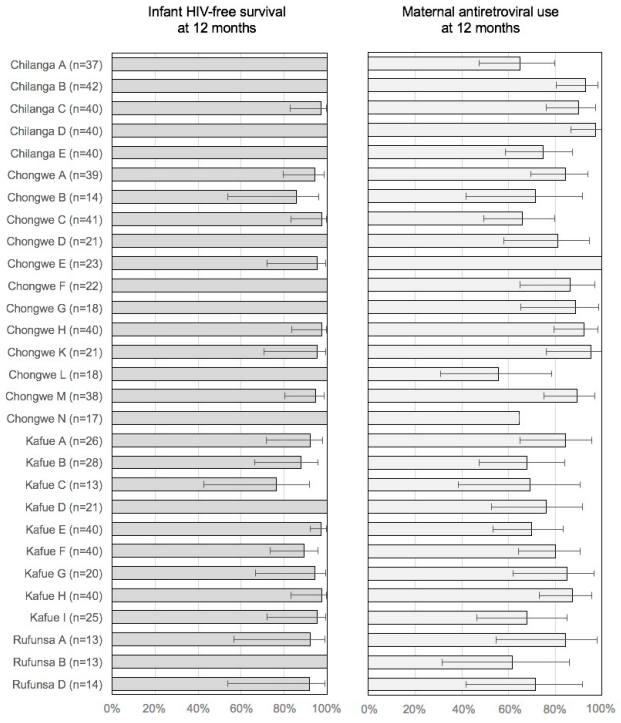
Benjamin H. Chi[1], Wilbroad Mutale[2], Jennifer Winston[1], Winifreda Phiri[1], Joan T. Price[1], Charles Y. Msiska[3], Helen Ayles[4], Jeffrey S. Stringer[1]
[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]University of Zambia, Lusaka, Zambia, [3]Government of Zambia Ministry of Health, Lusaka, Zambia, [4]Zambart, Lusaka, Zambia

Background: Lifelong antiretroviral therapy (ART) is now recommended for all HIV-infected pregnant and breastfeeding women (i.e., "Option B+"); however, few have described overall infant outcomes in this new era of prevention of mother-to-child HIV transmission (PMTCT). This is a particular gap in rural Africa, where disease burden is high and access to health services often limited.

Methods: As part of a broader assessment of PMTCT program impact, we enrolled a prospective cohort study in four predominantly rural districts in Zambia's Lusaka Province. The study coincided with the nationwide scale-up of Option B+ for PMTCT. HIV-infected mothers and their HIV-exposed newborns (≤30 days old) were recruited and followed at 6 weeks, 6 months, and 12 months of life. Information was collected about infant health status and maternal ART use; infant specimens were tested via HIV DNA PCR. In Kaplan-Meier analyses, we estimated the overall infant HIV-free survival at 12 months and stratified by district, community, and maternal ART use. We also investigated the relationship between community-level 12-month maternal ART use and infant HIV-free survival via linear regression.

Results: From Jun-2014 to Nov-2015, we enrolled 827 mother-infant pairs in 33 communities. At 12 months, 23 (2.8%) participating infants had died and 22 (3.0%) were HIV-infected. 36 (4.3%) were lost to follow-up. Overall, infant HIV-free survival was 99.0% (95%CI: 98.0–99.5%) at 6 weeks, 97.5% (95%CI: 96.1–98.4%) at 6 months, and 96.3% (95%CI: 94.8–97.4%) at 12 months. Women reporting ART use at enrollment had higher infant HIV-free survival than those who did not (97.4% vs. 89.0%, p=0.01). Differences were noted at the district (p=0.01) and site levels (p=0.01; figure, left panel). At 12 months, 80.5% (95%CI: 77.7–83.2%) of mothers reported ART use, but this proportion varied widely by community (55.6-100%, p=0.001; figure, right panel). In community-level analysis, no relationship was observed between 12-month infant HIV-free survival and maternal ART use (p=0.65).

Conclusion: Estimates for infant HIV-free survival were relatively similar across all communities, despite a range of reported maternal ART use at the community level. These findings are encouraging, but highlight the need for rigorous monitoring and evaluation of PMTCT services at the population level.



823 HIV-POSITIVITY AMONG HIV-EXPOSED INFANTS IN LESOTHO IN THE ERA OF OPTION B+

Tsigereda G. Belachew, Kieran Hartsough, Andrea Schaaf, Mahlompho Ntholeng, Tiffany G. Harris
Columbia University Medical Center, New York, NY, USA

Background: Lesotho's HIV prevalence among pregnant women is 28%. In 2013, Lesotho's Prevention of Mother to Child Transmission (PMTCT) program adopted Option B+ and revitalized the village health worker (VHW) program to strengthen community level PMTCT. The national goal was to test 95% of HIV-exposed infants (HEI) at 2 and 18 months and reduce transmission rates to <5% by 2016.

Methods: We reviewed routinely collected PMTCT data of infants aged <18 months registered for Under 5 services from July 2013-July 2014 in 111 facilities in 4 high HIV burden districts prioritized for the Accelerating Children on Treatment (ACT) initiative. Two districts (Berea, Leribe) used an Enhanced VHW Model in which women and HEI were accompanied to care visits and 2 districts (Maseru, Mafeteng) used a Standard VHW Model (no accompaniment). This analysis examined HEI positivity, 18-month retention, VHW Care Models effects, and progress to PMTCT targets. Statistical analyses utilized generalized linear mixed models with a random effect to account for facility clustering.

Results: A total of 4,354 HEI registered for care were included. Of 3,612 HEI registered by 2 months of age, 77% (2,748) received 2-month DNA PCR testing on time; of these, 2.5% (70) tested HIV(+), 88% (2,408) tested HIV(-) and 10% (270) had no recorded result. By 18 months of age, overall 2.9% (128/4,354) were HIV(+) [including those who tested HIV(+) prior to 18 months], 27% (1,158) were discharged as HIV(-), while 70% (3,068) did not have a final HIV status, of whom 76% had at least 1 prior HIV(-) test. At both 2 and 18 months, males were less likely to test HIV(+) compared to females (1.9% vs 3.2%, 2.4% vs 3.7%; both p=0.04). HEI in the Enhanced VHW Model were less likely to have an HIV(+) (2.2% vs 3.5%) and missing status (66% vs 74%) at 18 months compared to those in the Standard VHW Model (both p=0.001). HIV(+) infants in the Enhanced VHW Model were less likely to be retained on treatment at 18 months than those in the Standard VHW Model (26% vs 48%, p=0.05).

Conclusion: Overall, HIV positivity among HEI was <5%; however, most HEI were missing a final HIV status at 18 months. Opportunities were missed to provide HIV testing, retain HEI until final status was confirmed at 18 months, and retain HIV(+) infants on treatment. Strengthening interventions, including the Enhanced VHW Model, to identify, link and retain HEI in care are critical to achieve elimination of mother to child transmission.

824 HIGH HIV BURDEN AMONG CHILDREN IN LESOTHO: FINDINGS FROM A POPULATION BASED SURVEY

Koen Frederix[1], Stefania Davia[2], Keletso Ntene-Sealiete[3], Stephen M. Arpadi[4], Stephen McCracken[2], Kyaw Thin[3], Hetal Patel[2], Mosilinyane Letsie[3], Andrea Low[4]
[1]ICAP at Columbia University–Lesotho, Maseru, Lesotho, [2]CDC, Atlanta, GA, USA, [3]Ministry of Health, Maseru, Lesotho, [4]ICAP at Columbia University, New York, NY, USA

Background: Lesotho has the second highest HIV prevalence in the world. In 2013 the country became one of the first African countries to implement Option B+ nationwide. However Lesotho does not have reliable data on HIV prevalence in children, previously relying on estimates modeled from program data. The 2016 Lesotho Population-based HIV Impact Assessment (LePHIA) aimed, among other objectives, to determine HIV prevalence among children 0-14 years in order to assess the efficacy of the prevention of mother to child transmission (PMTCT) program and guide future policy.
Methods: A nationally representative sample of children under 15 years underwent household-based, two-stage rapid HIV testing from November 2016-May 2017. Children <18 months with a reactive screening test were tested for HIV infection using DNA PCR. Parents or legal guardians provided information on children's clinical history. Children aged 10-14 years also answered a questionnaire which included socio-demographic and behavioral questions. National weighted pediatric prevalence was estimated accounting for complex survey design, with Jackknife replication to calculate 95% confidence intervals (CI). We used bivariate statistics to compare characteristics across demographic groups.
Results: A total of 3,966 children were tested for HIV, and 1,601 10-14 year olds completed interviews. Overall, HIV prevalence was 2.1% (95% CI: 1.5-2.6%), corresponding to roughly 13,300 children living with HIV. Prevalence varied across districts, with the highest prevalence in Mokhotlong (4.8%, 95% CI: 2.2-7.3%), and the lowest in Berea (0.5%; 95%CI: 0-1.2%). Prevalence in 10-14 year olds (3.2%; 95% CI: 2.1%, 4.2%) was significantly greater compared to 0-4 year olds (1.0%; 95% CI: 0.5%, 1.6%). Sexual activity was reported in 9.3% (95%CI: 7.3-11.3%) of 10-14 year olds but there was no association with HIV infection. Overall HIV prevalence in females and males was 2.6% (95% CI: 1.8% – 3.3%) and 1.5% (95% CI: 1.0% – 2.1%), respectively.
Conclusion: Substantial progress has been made in the reduction of vertical transmission in Lesotho. But despite the early roll-out of Option B+ in Lesotho, pediatric HIV prevalence remains high, with girls disproportionately affected. Further research is required to understand the greater prevalence among girls, barriers to PMTCT and the possible contribution of horizontal transmission in older children.

Table1: HIV prevalence by age in children 0-14 years, % [95% CI]

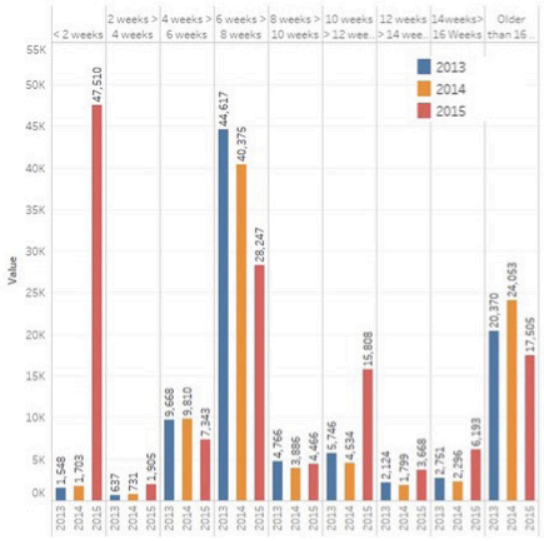
Prevalence	Males		Females		Total	
Age	% HIV positive	Number	% HIV positive	Number	% HIV positive	Number
0-17 months	0.6 [0, 1.7]	157	1.0 [0, 2.5]	158	0.8 [0, 1.7]	315
18-59 months	0.6 [0, 1.3]	423	1.6 [0.5, 2.8]	401	1.1 [0.4, 1.8]	824
5-9 years	0.9 [0.1, 1.6]	663	2.9 [1.7, 4.1]	676	1.9 [1.2, 2.6]	1,339
10-14 years	3.1 [1.7, 4.4]	760	3.3 [1.8, 4.8]	728	3.2 [2.1, 4.2]	1,488
Total 0-4 years	0.6 [0, 1.2]	580	1.5 [0.5, 2.4]	559	1.0 [0.5, 1.6]	1,139
Total 0-14 years	1.5 [1.0, 2.1]	2,003	2.6 [1.8, 3.3]	1,963	2.1 [1.5, 2.6]	3,966

825 IMPACT OF BIRTH TESTING ON EARLY INFANT DIAGNOSIS IN KWAZULU-NATAL, SOUTH AFRICA

Shayla Smith[1], Louise Kuhn[1], Moherndran Archary[2], Pravi Moodley[2], Phillip LaRussa[1], Kerusha Govender[2]
[1]Columbia University Medical Center, New York, NY, USA, [2]University of KwaZulu-Natal, Durban, South Africa

Background: In 2015, early infant diagnosis (EID) guidelines in South Africa shifted to recommending birth HIV PCR testing and a follow up test at 10 weeks of age. Prior to this, initial PCR testing was recommended at 6 weeks of age. Here we examine parameters of EID performance in the KwaZulu-Natal Province before and after this change.
Methods: Data on all HIV diagnostic PCR tests conducted by the National Health Laboratory Service for the province between Jan 2013 and April 2016 were assembled. Tests undertaken on birth cohorts of children born in 2013, 2014 and 2015 were analyzed. Laboratory barcodes allowed identification of repeat tests on the same child. We evaluated coverage, positivity rates, age at testing and frequency of repeat tests across birth cohorts.
Results: The total number of PCR tests and (total number of unique children PCR-tested) increased from 92,226 (78,453) in birth cohort 2013 and 89227 (75,667) birth cohort 2014 to 132,645 (112,533) in birth cohort 2015. The number of unique children PCR-tested <6 weeks of age increased from 67,681 in 2013 and 61,851 in 2014 to 103,298 in birth cohort 2015. Based on numbers of registered births and an assumed 40% HIV prevalence in the Province, these numbers were 79.4% and 73.9% of the estimated HIV-exposed births in 2013 and 2014, respectively, and exceeded the estimated number of HIV-exposed births in 2015. The proportion of positive tests decreased from 3.08% in 2013 and 2014 to 1.81% in 2015. In birth cohorts 2013 and 2014, 62.1% and 61.8%, respectively, of tests <16 weeks were done in children 6 to 8 weeks of age. In birth cohort 2015, 41.3% of tests <16 weeks were done earlier at less than 2 weeks of age. The percentage of children with a positive result who had at least one follow up test increased from 11.5% and 13.1% in birth cohorts 2013 and 2014 to 24.8% in 2015. The percentage of non-positive infants who received at least one follow up test did not appreciably change from 15.0% and 14.4% in 2013 and 2014 to 14.7% in 2015.
Conclusion: Shifts to recommending birth testing has led to greater coverage of HIV-exposed infants and earlier PCR testing. This allows for earlier identification of HIV-infected infants who urgent ART initiation. Although follow-up testing rates may be under-estimated in this data source, repeat testing rates remained consistently low. More effort is needed to ensure infants tested at birth continue to be engaged in care and undergo follow-up testing.

Figure: Number of HIV PCR tests by age of child when tested within birth cohorts 2013, 2014, 2015 in KwaZulu-Natal, South Africa.



826 AGE AT HIV DIAGNOSIS WITHIN SOUTH AFRICA'S EARLY INFANT DIAGNOSIS PROGRAM, 2010-2015

Ahmad Haeri Mazanderani[1], William B. MacLeod[2], Jacob Bor[2], Gayle G. Sherman[3]
[1]National Institute for Communicable Diseases, Johannesburg, South Africa, [2]Boston University, Boston, MA, USA, [3]University of the Witwatersrand, Johannesburg, South Africa

Background: Among infants aged <2 months, South Africa's National Health Laboratory Service's (NHLS) data warehouse has provided effective monitoring of early infant diagnosis (EID) within the national prevention of mother-to-child transmission (PMTCT) program demonstrating improved EID coverage (54%->85%) alongside decreasing early MTCT rates (4.3%-1.5%) between 2010-2015. However, only a third of all positive HIV PCR results occurred in <2 month olds. For older infants, the number of positive HIV PCR tests could not be used to quantify the number of HIV-infected children since the absence of a unique patient identifier precluded de-duplication. Older infants may test PCR positive due to late presentation for testing, postnatal infection or failure to link to care. We describe age at HIV diagnosis in South Africa's EID program for the first time.
Methods: HIV PCR data from 2010-2015, including patient demographics, year of testing and PCR result, were extracted from the NHLS' data warehouse. A patient linking-algorithm using probabilistic matching of date of birth, names, file number and facility was applied to assign multiple tests to a single patient. 'Age at HIV diagnosis' was defined as age at first positive PCR; 'early diagnosis'

as infants aged <3 months, 'late diagnosis' as infants aged ≥3 months. Within 'late diagnosis,' 'late presenters' had no PCR test <3 months of age.
Results: Between 2010-2015, 83 318 (3.5%) of 2 372 064 HIV PCR tests performed were positive. After de-duplication, 71 878 (4.3%) infants were diagnosed with HIV out of 1 674 535 infants tested. Among HIV infected infants, 26 808 (37.3%) and 35 393 (49.2%) tested positive aged <2 and <3 months respectively. Among the 36 485 infants who tested positive ≥3 months of age only 4 513 (12.4%) had a previous negative result at <3 months, indicative of postnatal transmission. The majority of late diagnosis, 31 972 (44.5%), was due to late presenters. Between 2010-2015, the annual number of late presenters decreased from 8 352 to 4 080 (53.8%-37.4% of positives) and confirmed postnatal infections increased from 175 to 862 infants (1.1%-7.9% of positives).
Conclusion: Late presentation for first PCR test declined over time yet, despite high EID coverage, accounted for more than a third of infections in 2015 suggesting poor access to care among HIV-infected mother-infant pairs. Late presenters likely represent different modes of transmission and threaten efforts to eliminate MTCT.

Table 1. HIV PCR Positive Infants by Year of Diagnosis

EID Outcome	Year of Diagnosis 2010	2011	2012	2013	2014	2015	Total
IU (% Pos)	214 (1.4%)	131 (1.0%)	143 (1.2%)	145 (1.4%)	241 (2.3%)	1 444 (13.2%)	2 318 (3.2%)
IU/IP/ePN (% Pos)	6 787 (43.7%)	6 109 (48.0%)	5 785 (48.7%)	5 095 (48.4%)	4 919 (47.7%)	4 380 (40.2%)	33 075 (46.0%)
<3m Pos (% Pos)	7 001 (45.1%)	6 240 (49.0%)	5 928 (49.9%)	5 240 (49.8%)	5 160 (50.0%)	5 824 (53.4%)	35 393 (49.2%)
PN (% Pos)	185 (1.2%)	574 (4.5%)	757 (6.4%)	996 (9.5%)	997 (9.7%)	1 004 (9.2%)	4 513 (6.3%)
Late Presenter (% Pos)	8 352 (53.8%)	5 910 (46.4%)	5 192 (43.7%)	4 285 (40.7%)	4 153 (40.3%)	4 080 (37.4%)	31 972 (44.5%)
=3m Pos (% Pos)	8 537 (54.9%)	6 484 (51.0%)	5 949 (50.1%)	5 281 (50.2%)	5 150 (50.0%)	5 084 (46.6%)	36 485 (50.8%)
Positive (% Total)	15 538 (7.4%)	12 724 (5.1%)	11 877 (4.5%)	10 521 (3.8%)	10 310 (3.4%)	10 908 (2.9%)	71 878 (4.3%)
Negative (% Total)	194 294 (92.6%)	234 488 (94.9%)	253 182 (95.5%)	263 901 (96.2%)	289 999 (96.6%)	366 793 (97.1%)	1 602 657 (95.7%)
Total Tested	**209 832**	**247 212**	**265 059**	**274 422**	**300 309**	**377 701**	**1 674 535**

EID, early infant diagnosis; IU, intrauterine; IP, intrapartum; ePN, early postnatal; PN, postnatal; Late presenter = first PCR test =3m of age; Pos, positive

827 MATERNAL ANTI-HIV-1 NAB RESPONSE ASSOCIATES WITH TRANSMISSION AND INFANT MORBIDITY

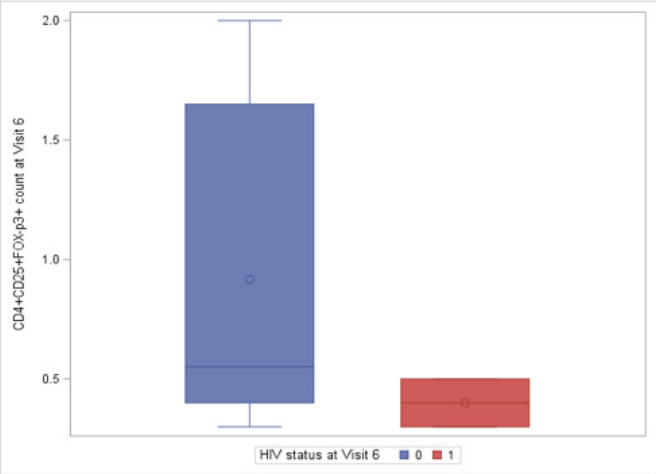
Melissa Ghulam-Smith[1], Alex Olson[1], Laura F. White[1], Charles Chasela[2], Sascha Ellington[3], Athena Kourtis[3], Denise Jamieson[3], Gerald Tegha[4], Charles van der Horst[5], Manish Sagar[1]
[1]Boston University, Boston, MA, USA, [2]University of the Witwatersrand, Johannesburg, South Africa, [3]CDC, Atlanta, GA, USA, [4]University of North Carolina Project–Malawi, Lilongwe, Malawi, [5]University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: In sub-Saharan Africa, mother-to-child transmission (MTCT) of HIV-1 through breast milk may be prevented by passive immunization with neutralizing antibodies (nAbs). Currently, there are conflicting results about the ability of nAbs to halt MTCT and their impact on infant outcomes.
Methods: Breast milk and plasma collected prior to transmission from mother-infant pairs (MIPs) (n = 21) was compared to matched samples from 2 different non-transmitting mother (NTM) and HIV-exposed uninfected (HEU) infant pairs (n = 42). Matching was based on maternal CD4 and virus level, and duration of time from birth to sample collection. Neutralization was assessed against both a pool of full-length envelopes (envs) isolated from maternal plasma using area under the curve and a global panel of reference envs (n=11) using a breadth-potency (BP) score, consisting of the average of log normalized % neutralization. Groups were compared using generalized estimating equations, Wilcoxon rank sum tests, and Kaplan Meier statistics.
Results: HEU infants, compared to those that eventually acquired infection, did not possess higher nAb responses against both the heterologous envs (p = 0.46) or their mothers' viral variants (p = 0.45). Transmitting mothers (TM) plasma as compared to NTM, however, had a unique neutralization fingerprint (p = 0.03) and higher pre-transmission plasma nAb activity against heterologous envs (p = 0.03). TM as compared to NTM also had higher neutralization responses against autologous strains although this difference was not statistically significant (p = 0.39). Infants born to mothers with greater pre-transmission neutralizing breadth and potency had a 3.4-fold greater likelihood of having a grade 4 serious adverse event or death over follow-up (p = 0.03). A subset of maternal breast milk (n = 10) demonstrated neutralization BP scores that were on average 3-fold lower than maternal plasma but significantly correlated with both infant plasma IgG (r = 0.82, p = 0.006) with a trend towards correlation with maternal plasma (r = 0.61, p = 0.07).
Conclusion: These results imply that pre-existing anti-HIV-1 nAb activity present in exposed infants does not prevent breast milk HIV transmission. Pre-existing high maternal neutralizing breadth and potency associated with both a higher frequency of breast milk transmission and subsequent infant morbidity. These results have implications for vaccine and passive immunization strategies for infected mothers targeted at preventing MTCT.

828 ROLE OF REGULATORY T CELLS IN MOTHER TO CHILD TRANSMISSION OF HIV

Peter A. Kessler, Surinder P. Gill, Chris C. Ibegbu
Emory University, Atlanta, GA, USA

Background: Mother-to-child transmission of HIV-1 occurs in a minority of HIV-infected mother-infant pairs, even without any interventions. The mechanisms that protect the majority of HIV-exposed infants from infection are unclear. T regulatory cells (Treg) have important immunomodulatory functions, but their role in the fetus as well as in mother-to-child transmission of HIV is under-studied.
Methods: We studied available cryopreserved peripheral blood mononuclear cells from HIV-exposed infants from the Breastfeeding, Antiretrovirals and Nutrition (BAN) Study cohort in Malawi: 64 infants were HIV-uninfected and 28 infants were HIV-infected at birth. We quantified the frequency of Treg cells (CD4+CD25+FoxP3+), and activated CD4+ and CD8+ T cells (CD38+HLADR+) by flow cytometry at birth, 6 weeks and 6, 9 and 12 months of age. Descriptive statistics were performed to describe the distributions of these lymphocyte markers according to HIV infection status; and Student's t tests and Wilcoxon-Rank Sum tests to perform comparisons between HIV- infected and uninfected infants.
Results: T cell activation increased rapidly in the first 6 weeks of life, more pronounced on CD8+ T cells; a further increase in activation was observed at the time of weaning from breastfeeding at 6 months of age. In contrast, the frequency of Treg was stable over the first 6 weeks of life (median, 0.5%), slightly decreased between 6 weeks and 6 months (median at 6 months, 0.3%) and then slightly increased between 6 months (time of weaning) and 12 months of age (median, 0.45%). HIV-infected infants had significantly higher frequencies of activated T cells than uninfected infants (P<0.01), as expected. At the time of birth, HIV-exposed uninfected infants had higher levels of Treg, compared to infants infected in utero (Figure, P=0.03). Among infants with negative HIV tests at birth, Treg % tended to be higher in those who were HIV-infected by 6 months of life, compared with those who remained uninfected (median, 1.25% vs. 0.55%).
Conclusion: This study provides evidence that Treg may play a role in preventing mother-to-child transmission of HIV, and perhaps even delaying detection of HIV infection in the infant, likely by suppressing immune activation in the fetus and infant. Better characterization of the role of Treg in fetal and neonatal immunity may provide a valuable complementary approach to achieve eradication of mother-to-child transmission of HIV.



829 BIRTH DEFECTS AMONG OFFSPRING OF HIV-INFECTED & UNINFECTED WOMEN IN KAMPALA, UGANDA

Philippa Musoke[1], Daniel M. Mumpe[1], Ayoub Kakande[2], Jolly Nankunda[3], Diana Valencia[4], Joyce Namale[1], Evelyn Nabunya[3], Josaphat Byagumisha[5], Doreen Birabwa-Male[3], Monica Nolan[1], Dhelia Williamson[4], Linda Barlow-Mosha[1]
[1]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, [2]Makerere University, Kampala, Uganda, [3]Mulago National Referral Hospital, Kampala, Uganda, [4]CDC, Atlanta, GA, USA, [5]Makerere University College of Health Sciences, Kampala, Uganda

Background: Universal antiretroviral treatment (ART) is being scaled up for all HIV-infected women; however, the risk for birth defects (BD) related to HIV and ART exposure during pregnancy is not well documented. We compared the prevalence of birth defects in offspring of HIV-infected women (on and off ART) and HIV negative women enrolled in the hospital-based birth defect surveillance (BDS) project in Kampala, Uganda.
Methods: Hospital-based BDS was implemented at Mulago Hospital in Kampala. All informative live births (LB), stillbirths (SB) and abortions were included. Maternal history, HIV status and ART regimens were documented based on medical records and interviews. Eligible births were examined by midwives for selected major structural external birth defects. The prevalence of birth defects and 95% confidence intervals (95% CI) were calculated for HIV-infected (on and off ART) and HIV negative women. Data collected from August 2015 through May 2017 are presented. Association of BDs with ART was determined by logistic regression.
Results: A total of 43,293 births were included with 38,527 (89.0%) delivered by HIV negative, 4,634 (10.7%) HIV-infected women and 132(0.3%) of unknown HIV status. 4,407 (95.1%) HIV-infected women were on ART with 3,403 (77.2%) on TDF/3TC/EFV, 403 (9.1%) on AZT/3TC+NVP, 320 (7.3%) on TDF/3TC/NVP, and 281(6.4%) on other regimens. 475(1.1%) birth defects of interest were identified: 431(1.1%) to HIV negative women and 44(0.9%) to HIV-infected women, with an OR of 0.8(0.6-1.1), p value= 0.31. 41/44 (93%) women with birth defect-affected pregnancies were on ART. Birth defect prevalence in offspring of infected women on ART [41(0.9%)] vs those not on ART [3(1.3%)] was similar [OR 0.6(0.2-2.1) p=0.55]. Prevalence of BD/1,000 births in offspring of those women who initiated ART prior to conception and during the 1st trimester (10.4) was similar to those who initiated ART later (7.3) [OR 1.4 (0.7-2.8) p= 0.3] and did not differ across ART regimens [X2(3) = 4.1, p=0.25]. Overall, common birth defects (n) included talipes equinovarus (51), hypospadias (48), neural tube defects (36), and total limb reduction (24).
Conclusion: The prevalence of birth defects in offspring of HIV-infected women was similar to those who were uninfected. There was no difference in BD by ART, timing of initiation or specific ART regimen. These findings are reassuring but these data only had adequate numbers to examine all birth defects combined and not individual defects or categories.

830 PRECONCEPTIONAL ART AND SPONTANEOUS PRETERM BIRTH IN AN URBAN ZAMBIAN COHORT

Joan T. Price[1], Bellington Vwalika[2], Jennifer Winston[1], Margaret P. Kasaro[1], Humphrey Mwape[1], Benjamin H. Chi[1], Elizabeth M. Stringer[1], Bethany Freeman[1], Courtney Gravett[3], Katelyn J. Rittenhouse[1], Lungowe Njobvu[1], Julie A. Nelson[1], Angela Kashuba[1], Jeffrey S. Stringer[1]
[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]University of Zambia, Lusaka, Zambia, [3]Global Alliance to Prevent Prematurity and Stillbirth, Seattle, WA, USA

Background: HIV and its treatment are associated with preterm birth (PTB) and other adverse birth outcomes. The underlying mechanism(s) may be related to timing of antiretroviral therapy (ART) relative to conception, specific drug exposures, or both.
Methods: The Zambia Preterm Birth Prevention Study is ongoing at the University Teaching Hospital in Lusaka. Participants receive early ultrasound dating, lab testing, midtrimester cervical length measurement, serial fetal growth monitoring, and careful phenotyping of each adverse birth outcome. For the present analysis, we defined PTB as delivery prior to 37 gestational weeks and differentiated between spontaneous and indicated PTB phenotypes. We confirmed timing of ART exposure among HIV+ women by testing drug concentrations at first antenatal visit with liquid chromatography/mass spectrometry.
Results: Between Aug-2015 and Aug-2017, we enrolled 1,425 pregnant women, of whom 929 have delivered. Median maternal age was 27 years (IQR: 23,32); median BMI was 23.9 kg/m2 (IQR: 21.4,27.4); 34% were nulliparous; 30% had ≥1 prior PTB; 2.3% had short cervix (<2.5cm); and 23% were HIV+. Of 946 infants born to date (17 sets of twins), 153 (16%) were small for gestational age (<10%ile) and 27 (2.9%) were stillborn. Of 129 (14%) PTBs, 70 (54%) were spontaneous (i.e., spontaneous labor or membrane rupture prior to labor), 27 (21%) were indicated (i.e., provider-initiated), and 32 (25%) could not be clearly classified. Among 216 HIV+ parturients, 121 (56%) were on preconceptional ART (predominantly TDF/XTC/EFV) and 108 (50%) had viral load <40 copies/mL at first antenatal visit. Factors associated with PTB in multivariable Poisson regression were: short cervix (ARR 2.18, 95% CI 1.16–4.12), twin gestation (ARR 5.01, 95% CI 3.22–7.81), prior PTB (ARR 2.31, 95% CI 1.48 – 3.62), and preconceptional ART (ARR 1.62, 95% CI 1.03–2.55). In a sensitivity analysis limited to the spontaneous PTB phenotype, the risk associated with preconceptional ART was amplified (ARR 1.93, 95% CI 1.03–3.61). Preconceptional ART was not statistically associated with asymmetric fetal growth restriction at 32 weeks, small for gestational age at birth, or stillbirth.
Conclusion: In this African cohort established specifically to study PTB and where the predominant ART exposure is TDF/XTC/EFV, women continuing preconceptional ART are at higher risk of PTB than HIV-negative women and those initiating ART in pregnancy. The risk of preconceptional ART did not extend to other adverse birth outcomes.

Table: Factors Associated with Preterm Birth in an Urban Obstetrical Cohort (Lusaka, Zambia)

	N*	Events	%	Unadjusted RR (95% CI)	Adjusted† aRR (95% CI)
Maternal Age					
< 20	57	4	7%	0.5 (0.2 - 1.3)	0.9 (0.3 - 2.4)
20-34	716	102	14%	ref	ref
≥ 35	121	22	18%	1.3 (0.8 - 1.9)	1.0 (0.6 - 1.6)
Maternal BMI at Entry					
< 18.5	46	8	17%	1.1 (0.6 - 2.1)	1.0 (0.5 - 1.9)
18.5 - 30	697	103	15%	ref	ref
> 30	173	18	10%	0.7 (0.4 - 1.1)	0.5 (0.3 - 1.0)
Prior Preterm Birth					
Nulliparous	290	33	11%	1.1 (0.7 - 1.7)	1.4 (0.8 - 2.4)
Parous, no prior	307	32	10%	ref	ref
Prior preterm	256	58	15%	1.5 (0.9 - 2.5)	2.3 (1.5 - 3.6)
Gestation					
Singleton	891	113	13%	ref	ref
Twins	25	16	64%	5.1 (3.6 - 7.1)	5.0 (3.2 - 7.8)
Cervical Length (at 20-24 weeks)					
≥ 2.5 cm	828	106	13%	ref	ref
< 2.5 cm	20	10	50%	3.9 (2.4 - 6.3)	2.4 (1.4 - 4.4)
ART Exposure					
HIV (-)	635	82	13%	ref	ref
HIV (+) preconceptional ART	121	24	20%	1.5 (1.0 - 2.3)	1.6 (1.0 - 2.6)
HIV (+) no preconceptional	76	12	16%	1.2 (0.7 - 2.1)	1.0 (0.6 - 1.7)

* Ns may not sum to 929 in all cases owing to incomplete data
† Final model also adjusted for gestational age at enrollment

831 PRENATAL ANTIRETROVIRAL EXPOSURE AND RISK OF LOW BIRTH WEIGHT IN LUSAKA, ZAMBIA

Jennifer Winston[1], Margaret P. Kasaro[1], Marie Stoner[1], Lloyd Mulenga[2], Joan T. Price[1], Elizabeth M. Stringer[1], Benjamin H. Chi[1], Bellington Vwalika[2], Jeffrey S. Stringer[1]

[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]University of Zambia, Lusaka, Zambia

Background: Antiretroviral therapy (ART) is recommended for all HIV-infected pregnant women, but some studies suggest that regimens containing protease inhibitors and/or tenofovir are associated with adverse birth outcomes. We investigated the association between antiretroviral drug exposure and low birthweight (LBW; <2500g) using data from two cohorts from Lusaka, Zambia (2008-2012).

Methods: This analysis pooled data from (1) the MEP Study, which enrolled women who became pregnant while on ART, and (2) the UTH-AIDC cohort, which included women who started ART at a tertiary care hospital either before or during pregnancy. In each cohort, ART initiation was based on clinical stage (WHO 3 and 4) and/or CD4 count (<350 cells/mm^3). Consistent with an evolving standard of care at the time, ART regimens included an NRTI/NtRTI backbone (AZT+3TC, TDF+FTC) plus either an NNRTI (EFV, NVP) or PI (LPV/r). We considered each discrete regimen separately, but also combined those containing TDF backbone to evaluate any association between drug exposure and LBW. We estimated uni- and multivariate risk ratios using log-Poisson models.

Results: Our pooled analysis included 674 HIV-infected pregnant women. Prescribed regimens included TDF+FTC+LPV/r (n=13, 2.1%), TDF+FTC+EFV (n=192, 31%), AZT+3TC+LPV/r (n=28, 4.6%), and AZT+3TC+EFV (n=380, 62%). In univariate models, when compared to those taking AZT+3TC+EFV, women taking TDF+FTC+LPV/r (RR 2.4; 95%CI 1.1–4.9) and TDF+FTC+EFV (RR 1.4; 95%CI 1.0–2.0) had higher risk for LBW infant. AZT+3TC+LPV/r was not associated with LBW. In a multivariable model, this trend remained for TDF+FTC+LPV/r (RR 1.9; 95%CI 0.9–3.8) and TDF+FTC+EFV (RR 1.3; 95%CI 0.9 – 1.9), but was no longer significant. In models comparing regimens with a TDF backbone to those with an AZT backbone, TDF was associated with an elevated risk of LBW in univariate models (RR 1.5; 95%CI 1.0-2.0) and multivariate models (RR 1.4; 95%CI 1.0–2.0).

Conclusion: In this pooled secondary analysis, in utero exposure to TDF was associated with modest elevations in LBW risk. Further research is needed about the safety of TDF-based regimens, given the growing number of HIV-infected pregnant women initiating lifelong ART.

Table: Unadjusted and adjusted risk ratios (RR) for low birth weight <2500 grams among women with prenatal exposure to ART in Lusaka, Zambia

	N	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Cohort			
UTH-AIDC	67	ref	ref
MEP	57	1.08 (0.78, 1.48)	1.38 (0.92, 2.07)
Prior Preterm birth			
Parous, no prior	92	ref	ref
Nulliparous	19	1.21 (0.77, 1.89)	1.34 (0.80, 2.26)
Prior preterm births	20	1.79 (1.18, 2.71)	1.72 (1.10, 2.67)
CD4 count			
>=200	90	ref	ref
<200	34	1.77 (1.26, 2.49)	1.64 (1.02, 2.46)
WHO stage			
1 or 2	99	ref	ref
3 or 4	18	2.19 (1.45, 3.28)	1.99 (1.22, 3.23)
ART regimen			
AZT+3TC+EFV	98	ref	ref
TDF+FTC+LPV/r	5	2.35 (1.14 - 4.85)	1.86 (0.90 - 3.83)
TDF+FTC+EFV	52	1.40 (0.99 - 1.99)	1.35 (0.93 - 1.94)
AZT+3TC+LPV/r	3	1.13 (0.50 - 2.58)	1.01 (0.42 - 2.42)

832 PREGNANCY OUTCOMES IN THE ERA OF UNIVERSAL HAART IN AFRICA (THE POISE STUDY)

Sufia Dadabhai[1], Luis Gadama[2], Rachel Chamanga[2], Rachel Kawalazira[2], Chaplain Katumbi[2], Dingase E. Dula[2], Isaac Singini[3], Leslie Degnan[2], Melvin C. Kamanga[2], Taha E. Taha[4]

[1]Malawi College of Medicine-Johns Hopkins University Research Project, Blantyre, Malawi, [2]Malawi Coll of Med–Johns Hopkins Univ Rsr Proj, Blantyre, Malawi, [3]University of Cape Town, Cape Town, South Africa, [4]The Johns Hopkins University, Baltimore, MD, USA

Background: In the era of universal HAART, concerns remain that triple-therapy may increase adverse pregnancy outcomes. We compared preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA) in infants born to ART-experienced women to HIV-uninfected women in Blantyre, Malawi, where first-line ART includes tenofovir, lamivudine, and efavirenz.

Methods: We enrolled HIV-infected and uninfected women and their infants at delivery into a one-year prospective study at five health-facilities in Blantyre, Malawi. Eligibility included confirmed HIV status, consent, singleton births, CD4>350 cells/mL3, and no stage 3/4 HIV. We documented sociodemographic data, clinical and reproductive history, birth weight and gestational age. LBW was defined as birth weight <2.5 kg, PTB was defined as gestational age <37 completed weeks gestation (Ballard Score), and SGA was defined as <10th percentile of birth weight of a standard population (Very SGA was defined as <3rd percentile). We applied logistic regression to measure the association between HIV and LBW and PTB. Odds ratios and 95% CIs are presented.

Results: 685 HIV-uninfected and 593 HIV-infected women on ART were enrolled from January 2016 to mid-September 2017. 72.5% of the HIV-infected women were virally suppressed at baseline (<40 copies per/mL). Rates of PTB were 10.1% among HIV-infected women and 9.5% among uninfected women (p=0.71) and rates of LBW were 6.9% among HIV-infected women and 4.9% among HIV-uninfected women (p=0.15). The rates of SGA (and Very SGA) were 17.4% (7.7%) among HIV-infected women and 18.3% (7.2%) among HIV-uninfected women (>0.05). In multivariate analyses (See Table), there was no association between HIV status and PTB after controlling for other factors. There was a moderately statistically significant association between being HIV-infected (and on ART) and LBW (adjusted OR=1.81; p=0.04) after adjusting for potential risk factors (Table). The rate of PTB was 13.0% (36/277) among HIV-infected women who started ART before pregnancy; 6.6% (17/257) among women starting ART during first or second trimester; and 12.1% (7/58) among women starting ART in third trimester.

Conclusion: The adverse pregnancy outcomes of PTB and SGA were not different between healthy HIV-infected women and HIV-uninfected women. It appears that near-universal ART can eliminate mother-to-child transmission of HIV without substantially impacting other pregnancy outcomes.

Table: Association of HIV and Other Risk Factors with Adverse Pregnancy Outcomes, Blantyre, Malawi

Baseline Characteristics		Preterm Birth		Low Birth Weight	
		Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
HIV Status (reference = HIV-, n=685)	HIV+ (n=593)	1.07 (0.74, 1.56)	1.08 (0.72, 1.63)	1.42 (0.89, 2.28)	1.81 (1.03, 3.16)
Maternal age	Per year of age	0.99 (0.97, 1.03)	1.02 (0.98, 1.06)	0.99 (0.95, 1.03)	1.00 (0.95, 1.06)
Gravidity (reference=1, n=2670	Pregnancy (>1) (n=1011)	0.74 (049, 1.14)	0.64 (0.38, 1.09)	0.50 (0.30, 0.83)	0.38 (0.19, 0.75)
Body Mass Index at delivery (kg/m2) (reference = 18.5-24.9, n=838)	<18.5 (n=34)	2.49 (1.09, 5.67)	2.47 (1.07, 5.69)	1.97 (0.67, 5.81)	2.12 (0.69, 6.47)
	≥25 (n=406)	0.53 (0.33, 0.84)	0.53 (0.33, 0.85)	0.69 (0.39, 1.19)	0.71 (0.39, 1.31)
Estimated work load during pregnancy (reference = In house only, n=1021)	In house + outdoor (n=72)	0.80 (0.34, 1.89)	0.98 (0.41, 2.36)	0.66 (0.20, 2.16)	0.89 (0.27, 2.98)
	Moderate to heavy (n=184)	0.73 (0.41, 1.29)	0.64 (0.35, 1.16)	0.69 (0.33, 1.47)	0.47 (0.19, 1.23)
Electricity at home (reference = Yes, n=622)	No (n=655)	2.22 (1.49, 3.31)	2.21 (1.48, 3.31)	1.93 (1.18, 3.17)	1.68 (0.99, 2.83)
Hemoglobin (reference = ≥10 mmHg, n=945)	<10 mm HG (n=193)	1.01 (0.61, 1.68)	0.84 (0.49, 1.43)	1.22 (0.65, 2.28)	0.98 (0.51, 1.89)

833 HIGH RATES OF ADVERSE BIRTH OUTCOMES IN SYPHILIS & HIV COINFECTED WOMEN IN BOTSWANA

Emily Shava[1], Sikhulile Moyo[1], Modiegi Diseko[1], Rebecca Zash[1], Eldah N. Dintwa[2], Lucy Mupfumi[1], Judith Mabuta[1], Gloria Mayondi[1], Jennifer Y. Chen[1], Shahin Lockman[1], Mompati O. Mmalane[1], Joseph Makhema[1], Roger L. Shapiro[1]

[1]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [2]Botswana Ministry of Health, Gaborone, Botswana

Background: HIV and syphilis infections each cause morbidity to mother and/or infant as well as adverse birth outcomes in Sub-Saharan Africa. Little is known about the impact of HIV and syphilis co-infection in pregnant women and the impact on birth outcomes.

Methods: Data from antenatal and obstetric records were abstracted from women who delivered at multiple government-run maternity wards in Botswana between 2008-2011 (5 sites) and 2014-2016 (8 sites). Antenatal HIV and syphilis test result, and infant birth record were collected in both time

periods, and antimicrobial treatment data were collected in 2014-16. We used logistic regression techniques to describe adverse birth outcomes by HIV status amongst syphilis-infected women. Outcomes were stillbirth, preterm delivery (<37 weeks gestational age), low birth weight (<2500g), and in-hospital neonatal death (<28 days).

Results: Of 76,466 women delivering in the two study periods, 75,770 (99.1%) had HIV test results, and 20,520 (27.1%) were HIV positive. Syphilis test results were available for 67,290 (88.0%) women, and 697 (1.0%) had reactive RPR/VDRL. HIV co-infection was present in 37.7% (95% CI: 34.1 – 41.4) of the 692 women with syphilis who also had an HIV test result. HIV-infected women were more likely to be co-infected with syphilis compared with HIV-uninfected women (OR=1.68; 95%CI 1.44 – 1.96). Between 2008-2011 and 2014-2016, the proportion of women with syphilis remained constant (1.1% vs. 1.0%, p=0.41), while the prevalence of HIV/syphilis co-infection declined from 45% to 27% (p<0.0001). HIV/syphilis co-infected women had more stillbirth, preterm delivery and low birth weight infants compared with HIV mono-infected and syphilis mono-infected women (Table 1). Stillbirth was significantly more common among co-infected women than HIV mono-infected women (OR=1.75; 95%CI 1.03 – 2.97) and low birthweight was significantly more common among co-infected women compared to syphilis mono-infected women (OR=1.85; 95%CI: 1.26 – 2.74).

Conclusion: Syphilis/HIV co-infection during pregnancy has declined in the past decade in Botswana. The mechanism by which HIV and syphilis combine to increase adverse birth outcomes requires further exploration.

Table 1: Adverse Birth Outcomes by Syphilis and HIV status, Botswana, 2008-2011 and 2014-2016

Adverse Birth Outcome	Total N = 76,466	HIV- and Syphilis- N= 48,583	HIV+/Syphilis- N = 17,545	HIV-/Syphilis+ N = 431	HIV+ and Syphilis+ N = 261
Stillbirth	2.6%	1.9%	3.4%	3.7%	5.8%
Preterm Delivery (<37 wks)	23.4%	19.7%	27.4%	25.6%	31.4%
Low Birth Weight (<2500g)	15.1%	12.1%	20.0%	14.6%	24.1%
Neonatal Death	1.4%	1.1%	1.5%	2.7%	1.6%

834 PLACENTAL EVIDENCE OF MATERNAL VASCULAR MALPERFUSION AMONG HIV-INFECTED WOMEN

Rebecca Zash[1], Morgan Jengela[2], Drucilla Roberts[3], Sajini Souda[2], Modiegi Diseko[4], Shally Morgan[4], Gloria Mayondi[4], Mukendi Kayembe[2], Lisa Bebell[3], Mompati O. Mmalane[4], Max Essex[5], Shahin Lockman[6], Joseph Makhema[4], Roger L. Shapiro[5]

[1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]University of Botswana, Gaborone, Botswana, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [5]Harvard University, Cambridge, MA, USA, [6]Brigham and Women's Hospital, Boston, MA, USA

Background: HIV-infected women have increased stillbirth, preterm delivery, and small-for-gestational age (SGA) infants, but the mechanism is unknown.

Methods: We collected a placentas from women who delivered >=24 weeks gestation at a tertiary hospital in Botswana, including a pre-specified number of HIV+ and HIV- women with stillbirth, preterm delivery and SGA outcomes. Placentas were weighed, examined, fixed in paraffin blocks in Botswana and then sectioned/stained at Mass General Hospital and read by a placental pathologist blinded to exposure status. Maternal vascular malperfusion was defined ≥2 of the following: low placental weight for gestational age, histologic presence of decidual arteriopathy with or without atherosis, distal villous hypoplasia, placental infarcts or placental abruption.

Results: From Dec 2015 - Jan 2017, 208 placentas were collected from 101 HIV+ women (92 received antiretroviral treatment [ART]) and 107 HIV- women. These included 18 normal births, 40 stillbirths, 113 preterm births, and 60 SGA; 23 were both preterm and SGA. In women with normal births, placental weight was lower in HIV+ women (median 369g, IQR 357,396) than HIV- women (median 441g, IQR 392,527) (p=0.26). In women with stillbirths, placental weight was lower in HIV+ women (median 194g, IQR 154,245) than HIV- women (median 252g, IQR 189,331) (p=0.04). In women with preterm-SGA, placental weight was lower in HIV+ women (median 249g, IQR 206,309) than HIV- women (median 314g, IQR 272,355) (p=0.09). Maternal vascular malperfusion was more common among HIV+ women with stillbirths than HIV- women with stillbirths (58% vs. 33%, p=0.12), and also more common among HIV+ women with preterm-SGA than HIV- women with preterm-SGA (67% vs. 25%, p=0.15). Placental weight and maternal vascular malperfusion were similar by HIV status among infants who were preterm alone or full-term SGA. Among 11 HIV-infected women on efavirenz (EFV)-based ART with stillbirth, 5 (45%) had maternal vascular malperfusion compared with 17/ 23 (74%) of women on NVP-based ART and 6/14 (43%) on zidovudine monotherapy (from a prior placental stillbirth study in Botswana).

Conclusion: Among women with stillbirth and preterm-SGA, HIV infection was associated with lower placental weight and maternal vascular malperfusion. Whether this finding is due to endothelial dysfunction from chronic HIV-infection or due to effect of specific ART needs further investigation.

	Placental Weight in grams (Median, IQR)		
	Total	HIV -	HIV +
Total	322 [267, 391]	325 [278,393]	317 [257,385]
Normal	395 [359,527]	441 [392,527]	369 [357,396]
Stillbirth	230 [165,312]	252 [189,331]	194 [154,245]
SGA (all)	316 [272,370]	316 [285,365]	316 [250,372]
Full-term SGA	331 [292,378]	316 [290,365]	353 [305,383]
Preterm	323 [278,393]	330 [283,393]	317 [273,396]
Preterm and SGA	285 [239,337]	314 [272,355]	249 [206,309]

835 INFLAMMATION IN HIV-INFECTED PREGNANT WOMEN IS ASSOCIATED WITH PRETERM BIRTH

Rupak Shivakoti[1], Nikhil Gupte[1], Nathella P. Kumar[2], Vandana Kulkarni[1], Usha Balasubramanian[3], Ramesh Bhosale[3], Pradeep Sambarey[3], Aarti Kinikar[3], Renu Bharadwaj[3], Sandesh Patil[3], Sadaf Inamdar[3], Nishi Suryavanshi[1], Subash Babu[4], Robert Bollinger[1], Amita Gupta[1]

[1]Johns Hopkins University, Baltimore, MD, USA, [2]National Institute for Research in TB, Chennai, India, [3]BJGMC Clinical Trials Unit, Pune, India, [4]NIH, Bethesda, MD, USA

Background: Preterm birth (PTB) is the leading cause of childhood morbidity and mortality. PTB rates are high in HIV-infected populations, even when on treatment. Still, only a subset of all births in HIV-infected pregnant women result in PTB, suggesting risk factors other than HIV infection itself are also important. While inflammation is a known risk factor in uninfected populations, the immune pathways involved are not clear and non-invasive immune markers with predictive value are lacking. Our objective was to determine the association of various markers of inflammation with PTB in HIV-infected pregnant women.

Methods: Within a randomized trial of pregnant women receiving Nevirapine (SWEN trial), we nested a case-control study (n=107; 26 cases, 81 controls) to determine the association of maternal inflammation with PTB. Cases were defined as PTB (<37 weeks gestational age (GA)) and controls as term births. Inflammation was assessed using enzyme-linked immunosorbent assay to measure plasma levels of general inflammation markers (acute phase proteins including C-reactive protein (CRP) and alpha 1-acid glycoprotein (AGP)) and markers of microbial translocation (intestinal fatty acid binding protein (I-FABP) to assess intestinal integrity, and soluble CD14 (sCD14) and CD163 (sCD163) to assess monocyte activation). These markers were assessed in visits prior to birth and randomization (21-33 weeks GA). Multivariable logistic regression was used to estimate the adjusted odds of PTB per log2 increase of each marker.

Results: In univariable and multivariable models adjusting for maternal age, BMI, education, parity, history of previous preterm birth, HIV treatment regimen, CD4 T-cell count and viral load (measured during time of inflammation assessment), there was increased odds of PTB per unit increase of Log2 AGP (adjusted odds ratio (aOR): 3.07, 95% confidence interval (CI): 1.67-5.65), Log2 sCD14 (aOR: 1.87, 95% CI: 1.04-3.35), Log2 sCD163 (aOR: 3.30, 95% CI: 1.43-7.62) and Log2 I-FABP (aOR: 1.93, 95% CI: 1.08-3.44) but not Log2 CRP (aOR: 0.90, 95% CI: 0.64-1.25).

Conclusion: In our case-control study, higher levels of markers of intestinal integrity, monocyte activation, and acute phase proteins were associated increased PTB. Our results identify immune markers that could predict PTB in HIV-infected populations and suggest modulating inflammation and microbial translocation may affect PTB.

Table 3: Association of pregnancy inflammation markers with preterm birth

	Univariable model		Multivariable model*	
	Odds ratio (95% CI)	p-value	Adjusted Odds ratio (95% CI)	p-value
Log_2(AGP)	2.29 (1.39-3.76)	0.001	3.07 (1.67-5.65)	<0.001
Log_2(CRP)	0.86 (0.63-1.17)	0.33	0.90 (0.64-1.25)	0.64
Log_2(sCD14)	1.70 (1.01-2.86)	0.04	1.87 (1.04-3.35)	0.04
$Log2_2$(sCD163)	2.32 (1.15-4.69)	0.02	3.30 (1.43-7.62)	0.005
Log_2(I-FABP)	1.85 (1.07-3.22)	0.03	1.93 (1.08-3.44)	0.03

*Multivariable models adjusted for maternal age, BMI, education, parity, history of previous preterm birth, CD4 T-cell count and viral load (at time of inflammation assessment), and maternal HIV treatment during pregnancy.

836 MARKERS OF PRETERM DELIVERY IN HIV+ WOMEN; ROLE OF PROTEASE INHIBITORS AND VITAMIN D

Adriana Weinberg[1], Yanling Huo[2], Deborah Kacanek[2], Kunjal Patel[2], Heather Watts[3], Diane Wara[4], Jelena Klawitter[1], Uwe Christians[1]

[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [2]Harvard University, Cambridge, MA, USA, [3]National Institute of Child Health and Human Development, Bethesda, MD, USA, [4]University of California San Francisco, San Francisco, CA, USA

Background: HIV+ women have increased risk of spontaneous preterm delivery (SPD). We identified plasma biomarkers associated with the risk of SPD in HIV+ women and their correlations with factors that were previously shown to affect the risk of SPD, such as HIV suppression, vitamin D deficiency, and use of PI in pregnancy.

Methods: Plasma was obtained from 103 HIV+ women with SPD (≤35 wg) and 205 controls with term delivery (≥37 wg) matched to cases 2:1 by race and gestational age at blood draw. Women with obstetric risk factors for SPD were excluded. Plasma levels of inflammatory markers TNFα, IFNγ, IL6, IL8, IL1β, IL18, IL17, GCSF, MCP1, IP10, sIL2Rα, sCD14, VEGFA, MCSF, GROα and MMP9; anti-inflammatory IL10, TGFβ and sCTLA4; and eicosanoids were compared between cases and controls using conditional logistic regression, adjusted for HIV-unrelated risk factors of SPD and inflammation. Weighted linear regression was used to evaluate associations of viral suppression, vitamin D deficiency (<20 ng/mL), and PI use in pregnancy with plasma biomarkers correlated with SPD.

Results: Among 308 women (mean age=29y, BMI=31; 58% black, 33% Hispanic), 80% were on PI and 19% were on ARV without PI. At plasma collection, 68% were in the 3rd trimester of pregnancy, 63% had CD4>350 cells/μL and 76% had VL<400 HIV RNA c/mL. Demographic and HIV disease characteristics were similar in the two groups. In adjusted analyses, higher levels of sIL2Rα were significantly associated with increased odds of SPD (aOR=2.97, p=0.01). Higher levels of sCD14, GCSF, PGF2α and 5-HEPE were marginally associated with greater odds of SPD. Women who initiated PI before or during the 1st trimester, but not later in pregnancy, had higher levels of GCSF (Estimated Difference=0.15, p=0.03) and 5-HEPE (Est. Diff.=0.26, p=0.01) compared with women on ARV without PI. Vitamin D deficiency was associated with higher sCD14 (Est. Diff.=0.06, p=0.04), higher PGF2α (Est. Diff 0.16, p=0.02), and lower 5-HEPE (Est. Diff.=-0.25, p=0.002). No associations were found with HIV suppression.

Conclusion: The best plasma predictor of SPD in HIV+ women was sIL2Rα, a marker of T cell activation. Monocyte activation (sCD14; GCSF), PGF2α (uterine prostaglandin; promotes contraction), and 5-HEPE (epoxide; induces regulatory T cells) were also associated with the risk of SPD. Vitamin D deficiency and use of PI in early pregnancy may increase the risk of SPD by modulating monocyte activation and/or the metabolism of eicosanoids, hypotheses that warrant further testing.

837 EFFECT OF ANTITUBERCULOSIS THERAPY ON THE PHARMACOKINETICS OF EFAVIRENZ IN CHILDREN

Awewura Kwara[1], Hongmei Yang[2], Sampson Antwi[3], Anthony Enimil[3], Fizza S. Gillani[4], Anima M. Sarfo[3], Antoinette Ortsin[3], Albert Dompreh[3], Lubbe Wiesner[5], Charles A. Peloquin[1]

[1]University of Florida, Gainesville, FL, USA, [2]University of Rochester, Rochester, NY, USA, [3]Komfo Anokye Teaching Hospital, Kumasi, Ghana, [4]Brown University, Providence, RI, USA, [5]University of Cape Town, Cape Town, South Africa

Background: Efavirenz-containing antiretroviral therapy (ART) is the preferred regimen in children older than 3 years receiving rifampin-containing antituberculosis (anti-TB) therapy. To date, there is limited data on the drug-drug interactions between efavirenz and 4-drug anti-TB therapy in children. We hypothesized that at the population level, efavirenz plasma concentrations in TB/HIV co-infected children who are treated with the maximized weight-based efavirenz dosage during anti-TB treatment will be comparable to concentrations in HIV-infected children receiving ART alone.

Methods: ART-naïve HIV-infected children aged 3 – 14 years old were enrolled and given ART regimen consisting of efavirenz (10-13.9kg – 200 mg; 14-24.9kg – 300mg; 25-39.9kg – 400 mg and > 40Kg – 600 mg) per WHO recommended weight-band dosing, plus zidovudine 180 - 240 mg/m2 and lamivudine 4 mg/kg twice daily. For the TB/HIV co-infected patients, anti-TB treatment using the new WHO recommended TB drug dosages for children was started immediately upon TB diagnosis and ART started within 2 to 8 weeks of TB therapy. Blood samples were collected at times 0, 2, 8, 12 and 24 hours post-dose after 4 weeks of ART in both arms. Efavirenz concentrations in plasma were measured using validated LC/MS/MS assays and pharmacokinetic parameters calculated using noncompartmental analysis. Pharmacokinetic parameters were compared by rank sum test.

Results: Of the 72 patients, 38 (53%) had TB coinfection. Children with TB coinfection compared to those with HIV infection alone were younger, had lower body weight and height but received a higher efavirenz dose (median, 15 mg/kg vs. 13 mg/kg, P = 0.008). TB/HIV co-infected patients had significantly lower efvairenz Cmax, Cmin and AUC0-24h compared to those with HIV alone (see table below). The proportion of children with efavirenz Cmin < 1 μg/mL (considered subtherapeutic) was also higher among those with TB/HIV coinfection than those with TB alone (47.4% vs. 17.6%, P = 0.008).

Conclusion: This is the first study to investigate effect of first-line anti-TB drug regimen using new higher drugs dosages on efavirenz pharmacokinetics in children. Unlike the findings of adults and prior pediatric studies, 4-drug anti-TB therapy in the co-infected children was associated with significant reduction in efavirenz plasma exposure and trough concentrations. The effect of anti-TB treatment on long-term HIV treatment outcome in TB/HIV co-infected children need to be evaluated.

Median (IQR) pharmacokinetic parameter estimates of efavirenz in Ghanaian children with HIV with and without tuberculosis

Parameter	All (N = 72)	HIV (N = 34)	TB/HIV (N = 38)	P value
T_{max} (h)	2.1 (2.0 – 8.0)	2.0 (2.0 – 8.0)	2.1 (2.0 – 8.0)	0.317
C_{max} (μg/mL)	3.4 (2.5 – 4.5)	4.1 (2.9 – 5.1)	3.1 (2.3 – 4.0)	0.031
C_{12h} (μg/mL)	1.8 (1.2 – 2.8)	2.0 (1.5 – 3.4)	1.5 (0.8 – 2.7)	0.068
C_{last} (μg/mL)	1.3 (0.7 – 2.4)	1.7 (1.2 – 3.3)	0.8 (0.6 – 1.6)	0.001
T_{min} (h)	12.0 (0.2 – 12.2)	11.9 (0.2 – 12.1)	12.0 (0.2 – 12.3)	0.671
C_{min} (μg/mL)	1.4 (0.8 – 2.5)	1.6 (1.2 – 2.8)	1.0 (0.6 – 2.3)	0.042
AUC_{0-24h} (μg *hr/mL)	51.0 (32.0 – 68.3)	56.4 (47.3 – 70.4)	40.4 (26.1 – 64.6)	0.017
CL/F (L/hr)	5.9 (3.8 – 8.5)	5.5 (3.4 – 7.6)	6.5 (4.5 – 10.9)	0.085
Vz/F (L)	159 (96 – 245)	164 (100 – 263)	143 (94 – 226)	0.664

838 PHARMACOKINETICS OF 8-HOURLY LOPINAVIR/RITONOVIR IN CHILDREN ON RIFAMPICIN

Helena Rabie[1], Holly Rawizza[2], Peter Zuidewind[1], Jana L. Winckler[1], Heather Zar[3], Annelies Van Rie[4], Jennifer Norman[3], Helen Mcilleron[3]

[1]Stellenbosch University, Tygerberg, South Africa, [2]Brigham and Women's Hospital, Boston, MA, USA, [3]University of Cape Town, Cape Town, South Africa, [4]University of Antwerp, Antwerp, Belgium

Background: In children requiring lopinavir/ritonavir (LPV/r) and rifampicin, doubling the dose of LPV/r-4:1 fails to achieve lopinavir Cmin>1mg/L in 60%. Adding ritonavir to a 1:1 ratio LPV/RTV-1:1 achieves lopinavir exposures comparable to those in children not receiving rifampicin, but this strategy is complex and ritonavir alone is not widely available. Pharmacokinetic modeling predicts that adjusted 8-hourly dosing of LPV/r -4:1 could achieve adequate Cmin in >95% of children receiving rifampicin. This study tests that hypothesis.

Methods: This pharmacokinetic study evaluated lopinavir concentrations among South African children treated with co-formulated LPV/r-4:1 oral solution and rifampicin-based TB treatment. Children where switched from LPV/RTV-1:1 dosing (South African standard of care) to 8-hourly LPV/r-4:1 dosed according to weight, with children in the 3-5.9, 6-9.9, 10-13.9 and 14-19.9kg weight bands receiving approximately 27, 21, 20, and 18mg/kg lopinavir per dose, respectively. Two weeks after starting 8-hourly LPV/r-4:1, 2-10 hours sampling after the morning LPV/r-4:1 dose was performed, where after children were switched back to standard LPV/RTV-1:1. Alanine Aminotransferase (ALT) were performed to assess safety. Rifampicin was dosed according to the WHO guidelines.

Results: Eleven children were enrolled (four female), with median (IQR) age 15.0 (12.8-28.1) months and weight 9.8 (8.4-10.7) kg. LPV doses ranged from 20.0-23.5 mg/kg/8 h. Four children (36%) had Cmin<1mg/L, the median AUC was 48.7mg*h/L (5.6-70.2). Children who received doses below the median (21.5mg/kg) were significantly more likely to have low Cmin values (p=0.006). There was no association between AUC-8h and age, sex, weight, or weight-for-height z-score. AUC-8h and total LPV dose exhibited a positive trend in association (p=0.08). No significant ALT elevation occurred.
Conclusion: In this small cohort 8-hourly LPV/r dosing was safe and appeared to perform better than the current double-dose q12h strategy, but further adjustment of the 8-hourly LPV/r-4:1 dose is needed to optimize this strategy.

839 TUBERCULOSIS DISEASE AND ISONIAZID USE IN SOUTH AFRICAN CHILDREN LIVING WITH HIV

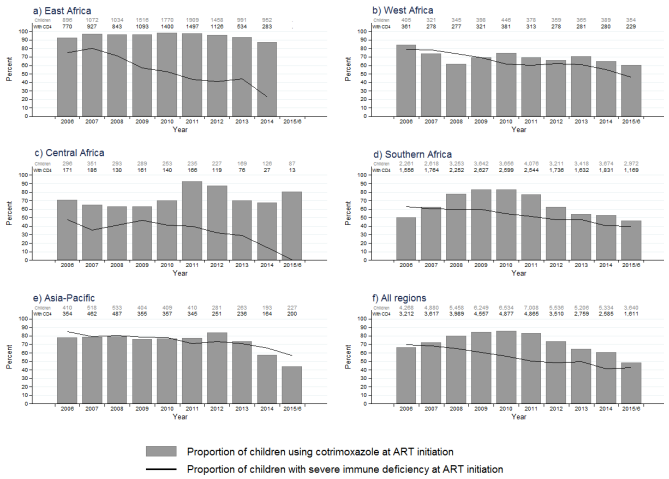
Gloria E. Anyalechi[1], Chloe A. Teasdale[2], Emilia M. Rivadeneira[1], Rommel Bain[1], Gurpreet Kindra[3], Mary Mogashoa[3], Stephen M. Arpadi[2], Elaine J. Abrams[2]
[1]CDC, Atlanta, GA, USA, [2]ICAP at Columbia University, New York, NY, USA, [3]US CDC Pretoria, Pretoria, South Africa

Background: Tuberculosis (TB) is a major cause of morbidity and mortality for children living with HIV (CLHIV). In 2016, South Africa had an estimated 33,000 TB cases in children < 15 years but no data for TB in CLHIV. Although World Health Organization (WHO) and South African guidelines recommend isoniazid preventive therapy (IPT) in HIV, uptake of this effective intervention has been poor. We describe factors associated with TB prevalence among HIV-infected children 0-12 years in a cohort eligible for antiretroviral therapy (ART) in South Africa and examine IPT use among enrolled children.
Methods: From 2012-2014 HIV-infected children receiving care at five facilities in Eastern Cape Province were enrolled into a prospective cohort at ART eligibility based on South African 2010 and 2013 guidelines. Children were defined to have TB at cohort enrollment if a caregiver reported TB or TB was recorded in the medical record 90 days before or after enrollment. IPT as of enrollment was defined for children with an IPT start date recorded in the medical record prior to or on the enrollment date. Factors associated with TB at enrollment were assessed using logistic regression with generalized estimating equation adjusted odds ratios (aOR) and 95% confidence intervals (CI) to account for facility clustering.
Results: Of 397 enrolled children, 106 (26.7%) had TB disease at enrollment including; twenty-four (16.2%) infants < 1 year; 37 (30.8%) children 1-< 5 years; and 45 (34.9%) children 5-12 years. In multivariable analyses, including sex, CD4 count, and history of TB as known risk factors, only older age (5-12 years vs. <1 year) (aOR 3.2 [1.0-9.7]) and weight for age z-score < 2 standard deviations below the mean (aOR 1.7 [1.0-2.8]) were significantly associated with TB at enrollment. Among 362 children with available IPT data, 31 (8.6%) were documented to have ever received IPT. Of 26 (83.9%) children with known IPT start date, 19 (73.1%) received IPT prior to, or on the date of enrollment at a median of 7 days (range: 0-723) before enrollment.
Conclusion: Among these HIV-infected South African children eligible for ART, 27% had TB while less than 10% were documented to have ever received IPT. Children 5-12 years old, and those with moderate malnutrition were more likely to have TB. Preventing, diagnosing, and treating TB must be prioritized for vulnerable populations in South African HIV programs particularly older and malnourished children.

840 TEMPORAL TRENDS IN GLOBAL PEDIATRIC COTRIMOXAZOLE USE AND IMPACT ON MORTALITY

David C. Boettiger[1], Matthew Law[1], Annette H. Sohn[2], Mary-Ann Davies[3], Kara K. Wools-Kaloustian[4], Valériane Leroy[5], Marcel Yotebieng[6], Michael J. Vinikoor[7], Rachel Vreeman[4], Andrew Edmonds[8], Azar Kariminia[1]
[1]Kirby Institute, Sydney, NSW, Australia, [2]TREAT Asia, amfAR, Bangkok, Thailand, [3]University of Cape Town, Cape Town, South Africa, [4]Indiana University, Indianapolis, IN, USA, [5]INSERM, Toulouse, France, [6]The Ohio State University, Columbus, OH, USA, [7]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, [8]University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: Cotrimoxazole (CTX) is recommended for all children recently diagnosed with HIV in order to prevent pneumocystis pneumonia. Although it improves survival in HIV-infected children, the impact of CTX on mortality in those without severe immune deficiency is unclear. We evaluated temporal trends in CTX use at antiretroviral therapy (ART) initiation and mortality rates while on CTX in the absence of severe immune deficiency.
Methods: Pediatric data collected between 1 Jan 2006 and 31 Mar 2016 in the International Epidemiology Databases to Evaluate AIDS global cohort consortium were analyzed from regions that routinely report information on CTX use (East, West, Central, and Southern Africa, Asia-Pacific). All 24 countries included are considered low- or middle-income by World Bank criteria. Severe immune deficiency was defined by the age-specific CD4 thresholds in the 2006 WHO ART guidelines. Logistic regression was used to evaluate factors associated with using CTX at ART initiation. Competing risk regression was used to assess factors associated with mortality. Sensitivity analyses used multiple imputation to account for missing data.
Results: A total of 54,113 children aged 1 month to 15 years were included. Median age at ART initiation was 5.7 years and 51% were female. CTX use increased from 67% in 2006 to a peak of 86% in 2010 and then declined to 49% in 2015/16. The proportion of children with severe immune deficiency dropped from 70% in 2006 to 43% in 2015/16 (figure). In our adjusted analysis, age (odds ratio [OR] 1.2 for <1 year vs. 1 to <5 years, 95% confidence interval [CI] 1.1-1.3), anemia (OR 1.1, 95%CI 1.0-1.2), severe immune deficiency (OR 1.3, 95%CI 1.2-1.3), height-for-age z-score (OR 1.2 for <-3 vs. >-2, 95%CI 1.1-1.2), year of ART initiation (OR 2.8 for 2010 vs. 2006, 95%CI 2.5-3.1 and OR 0.7 for 2015/16 vs. 2006, 95%CI 0.6-0.8) and region (OR 9.0 for East vs. Southern Africa, 95%CI 8.2-9.9) were associated with CTX use. The rate of death in children without severe immune deficiency was 0.5 per 100 person-years and did not differ with CTX use (adjusted hazard ratio 1.0 for non-users versus users, 95%CI 0.8-1.3). Sensitivity analyses yielded similar results.
Conclusion: Recent declines in pediatric CTX use coincide with declines in the proportion of children starting ART with severe immune deficiency. CTX did not improve survival among children without severe immune deficiency although use was not randomized and unmeasured confounders cannot be excluded.



841 PHARMACOKINETICS AND SAFETY OF LOPINAVIR/RITONAVIR SOLUTION IN HIV-INFECTED NEWBORNS

Adrie Bekker[1], Nathan Hanan[2], Mae Cababasay[3], Jiajia Wang[3], Firdose Nakwa[4], Elizabeth Smith[5], Jack Moye[6], Avy Violari[4], Mark Cotton[1], Lubbe Wiesner[7], Jennifer Norman[7], Barend Fourie[1], Edmund V. Capparelli[2], Mark Mirochnick[8]
[1]Stellenbosch University, Cape Town, South Africa, [2]University of California San Diego, La Jolla, CA, USA, [3]Harvard University, Cambridge, MA, USA, [4]University of the Witwatersrand, Johannesburg, South Africa, [5]DAIDS, NIAID, Bethesda, MD, USA, [6]NIH, Bethesda, MD, USA, [7]University of Cape Town, Cape Town, South Africa, [8]Boston University, Boston, MA, USA

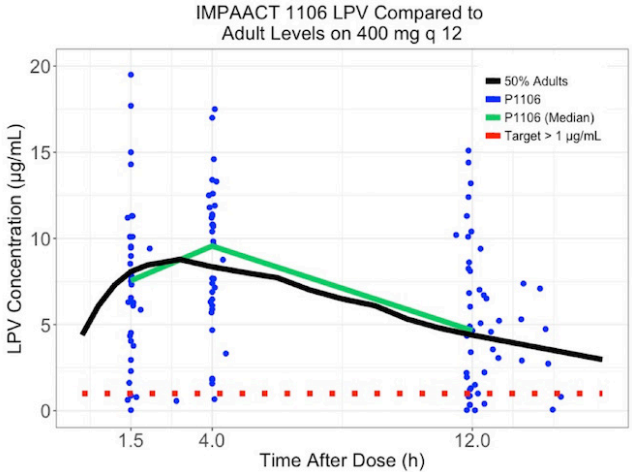
Background: Reports of life-threatening cardiac, metabolic, renal and CNS dysfunction in newborns receiving lopinavir/ritonavir (LPV/r) in the first weeks of life have led to a recommendation that LPV/r should not be used in newborns <2 weeks postnatal and <42 weeks postconceptional age. Due to limited treatment options, however, clinicians may initiate LPV/r in newborns if benefit outweighs risk. Data on pharmacokinetics (PK) and safety of LPV/r in newborns are few.
Methods: IMPAACT P1106 is a multi-arm Phase IV study of PK/safety in newborns on antiretroviral and antituberculosis medicines received for clinical care at two South African sites. HIV-infected newborns in whom LPV/r was

initiated at 1 µg/mL. Safety evaluations included echocardiograms (ECHOs) at baseline and weeks 1 and 6, and electrocardiograms at baseline, day 5, and weeks 1, 2, and 6. Adverse events (AE) were classified as expected (associated with prematurity) or unexpected.

Results: Twenty-five newborns were enrolled;13 (52%) male and 22 (88%) black African. The median (interquartile range (IQR)) birth weight and gestational age were 2130 (1775, 2630) grams and 35 (32, 37) weeks, respectively. The median (IQR) age at enrollment was 45 (35, 61) days old. As of August 2017, 22 newborns contributed to 124 LPV concentrations. Median C0 was 4.7 (IQR 1.5, 7.4) µg/mL, with 1.5 and 4 hour levels approximately 1.5-2 times higher, similar to adults. LPV C0 was above target in 41/50 samples (figure 1). Of the 24 newborns with safety data, 11 had Grade 3/4 unexpected AEs (none treatment related) and four newborns had Grade 3/4 expected AEs. Most AEs were infection related (n=11). One infant died from presumed sepsis on day 2 of LPV/r. Infant ECHOs were normal except for two with mild abnormalities. No abnormal PR or QTc interval prolongation was observed. Median serum osmolality post LPV/r initiation was 289 (IQR 287, 291) mOsm/kg.

Conclusion: No treatment related adverse events were observed in this study of LPV/r safety and PK in newborns and very young infants. LPV concentrations were similar to adult levels, with most C0 >1 µg/mL.

Figure 1. Observed lopinavir concentrations plotted by time after dose



842 EFFECTIVENESS AND SAFETY OF LPV/R PELLETS-BASED ART IN CHILDREN: 48-WEEK ANALYSIS

Isabelle Andrieux-Meyer[1], Olawale Salami[1], Raymond Omollo[1], **Dalton Wamalwa**[2], Elizabeth Maleche Obimbo[2], Adeodata Kekitiinwa[3], Juliet Mwanga-Amumpaire[4], Patrick Oyaro[5], Elizabeth A. Bukusi[6], Moses Waweru[1], Monique Wasunna[1], Janice Lee[1], François Simon[1], Marc Lallemant[1]

[1]Drug for Neglected Diseases Initiative, Geneva, Switzerland, [2]University of Nairobi, Nairobi, Kenya, [3]Baylor College of Medicine Children's Foundation, Kampala, Uganda, [4]Epicentre, Mbarara, Uganda, [5]Kenya Medical Research Institute, Kisumu, Kenya, [6]Kenya Medical Research Institute, Nairobi, Kenya

Background: A palatable, heat-stable, easy-to-administer pellets' formulation of LPV/r has received tentative USFDA approval for use in infants and young children. However, there are few data on its effectiveness and safety in routine care. The LIVING study evaluates the effectiveness, safety, PK and acceptability of LPV/r pellets + ABC/3TC (or AZT/3TC) dispersible tablets, in HIV+ children unable to swallow tablets in Kenya and Uganda.

Methods: An open-label, single-arm, prospective, multi-centre, phase-3b implementation study. Inclusion criteria: ARV naïve, on liquid LPV/r-based or failing NNRTI based ART; Weight ≥3 and <25kg. ART dosing based on WHO weight bands. Children assessed at baseline, 1 month then 3-monthly. Effectiveness was defined as a composite of VL<1000copies/ml, no death and being on study drugs. AEs were graded using DAIDS tables. Stunting was defined as height-for-age <-2SD, wasting as weight for height <-2SD and immunodeficiency following WHO age-specified CD4% cut offs.

Results: As of 31/07/17, 610 patients had been enrolled, of whom 378 and 223 had reached WK24 and WK48 respectively, with a cohort retention of 88.7% (5 deaths). Baseline and WK 48 VL available in 220 children (49% female; 11% ART naïve,84% switched from LPV/r and 5% from NVP based ART). At Baseline, median (IQR) age in months was 20 (8-41) in ARV naïve, 47 (32-66) in LPV/r exposed and 50 (41-67) in NVP exposed, while VL results: Median VL (log_{10} cp/ml) and % with VL<50, <400 and <1000 cp/ml were 5.4 (4.7-5.8), 3.5%, 9.5% and 11.3% respectively in naïve, 2.2 (1.6-3.9), 29.5%, 57.9% and 63.5% in LPV/r exposed and 4.7 (4.3-5.4), 5.3%, 10.6% and 10.6% in the NVP exposed. At WK48, VL parameters were 2.1 (1.3-3.8),43.5%, 65.2% and 70% respectively in naïve,1.6(1.3-2.1), 56%, 80.9% and 85.1% in LPV/r exposed and 1.5(1.3-2.5), 58.3%, 75% and 83.3% in the NVP exposed. At baseline, Immunodeficiency, wasting and stunting were present in 70%, 50% and 35% of naïve respectively, 33%, 17% and 7.8% of LPV/r and in 40%, 20% and 14.3% of NVP exposed, reaching 36.4%, 9% and 5% of naïve, 21.7%, 2% and 3% % of LPV/r exposed and 40%, 0%, and 14.3% of NVP exposed respectively at Wk48. 21 children had 67 AEs grade 3/4, 2 leading to treatment stoppage.

Conclusion: LPV/r pellets were well accepted with minimal safety concerns. Naïve, those failing NVP, as well as those switching from LPV/r liquid were well suppressed at week 48 and had recuperated immunologically and clinically.

HIV RNA VL (log_{10} copies/mL)	Patient type	N	Median	IQR	VL: <1.7 (<50copies/ml)	VL: 1.7 to 2.6 (50 to <400 copies/ml)	VL: 2.6 to 3.0 (400 to <1000 copies/ml)	VL: > 3.0 (>1000 copies/ml)	Data available
Enrollment	Naive	58	5.4	4.8 – 5.8	2 (3.8%)	3 (5.7%)	1 (1.9%)	47 (88.7%)	53
	NNRTI+LPV/r	514	2.2	1.6 – 3.9	142 (29.5%)	137 (28.4%)	27 (5.6%)	177 (36.5%)	483
	NNRTI	38	4.7	4.3 – 5.5	2 (5.3%)	2 (5.3%)	0 (0%)	33 (86.8%)	37
	Overall	610	2.5	1.7 – 4.6	146 (25.5%)	142 (24.8%)	28 (4.9%)	257 (44.8%)	573
6 months	Naive	31	2.0	1.3 – 3.5	11 (35.5%)	7 (22.6%)	2 (6.5%)	11 (35.5%)	31
	NNRTI+LPV/r	322	1.7	1.3 – 2.5	160 (50%)	79 (24.7%)	11 (3.4%)	62 (19.4%)	312
	NNRTI	25	1.8	1.3 – 2.5	11 (45.8%)	7 (29.2%)	2 (8.3%)	4 (16.7%)	24
	Overall	378	1.7	1.3 – 2.6	182 (48.5%)	93 (24.8%)	15 (4%)	77 (20.5%)	367
12 months	Naive	23	2.1	1.3 – 3.8	10 (43.5%)	5 (21.7%)	1 (4.4%)	7 (30.4%)	23
	NNRTI+LPV/r	188	1.6	1.3 – 2.1	105 (55.9%)	47 (25%)	5 (2.7%)	28 (14.9%)	185
	NNRTI	12	1.5	1.3 – 2.5	7 (58.3%)	2 (16.7%)	1 (8.3%)	2 (16.7%)	12
	Overall	223	1.6	1.3 – 2.3	122 (54.7%)	54 (24.2%)	7 (3.1%)	37 (16.6%)	220

843 SAFETY, PK, & EFFICACY OF FTC/TAF IN HIV-INFECTED ADOLESCENTS (12-18 YRS)

Janet Chen[1], Xavier Saez-Llorens[2], Elizabeth Castaño[2], Faeezah Patel[3], Ann Melvin[4], Elizabeth J. McFarland[5], Jaime G. Deville[6], Mark Cotton[7], Chrisna Andersen[8], Heather Maxwell[9], Mingjin Yan[9], Sophia R. Majeed[9], Erin Quirk[9], Hiba Graham[9], Cheryl Pikora[9]

[1]Drexel College of Medicine, Philadelphia, PA, USA, [2]Hospital del Niño, Panama City, Panama, [3]Empilweni Service and Research Unit, Johannesburg, South Africa, [4]Seattle Children's Hospital, Seattle, WA, USA, [5]University of Colorado, Aurora, CO, USA, [6]University of California Los Angeles, Los Angeles, CA, USA, [7]Tygerberg Hospital, Cape Town, South Africa, [8]Be Part Yoluntu Centre, Paarl, South Africa, [9]Gilead Sciences, Inc, Foster City, CA, USA

Background: Fixed-dose combination emtricitabine (FTC)/tenofovir alafenamide (TAF) is approved for adolescents (US, EU) and a recommended first-line NRTI backbone for adolescents (US). Safety and efficacy of TAF in adolescents has been demonstrated in studies of elvitegravir/cobicistat/FTC/TAF, including favorable bone and renal safety. Safety, pharmacokinetics (PK), and efficacy of other FTC/TAF-containing regimens in adolescents have not been reported. We describe safety, PK and efficacy of FTC/TAF in combination with boosted or unboosted third antiretroviral (ARV) agents to adolescents.

Methods: This open-label, 2-part, 48-week (W) trial evaluated switching from 2 NRTIs to FTC/TAF while remaining on various third ARV agents (eg efavirenz or lopinavir/ritonavir). Virologically suppressed adolescents (12 to <18 yrs) weighing ≥35 kg were enrolled and given FTC/TAF 200/10 mg or 200/25 mg, with boosted or unboosted third ARVs, respectively. Adverse events (AE), laboratory tests (eg renal biomarkers) and bone mineral density (BMD) were assessed. Intensive PK was evaluated at W2. Efficacy was evaluated as proportion of adolescents with plasma HIV-1 RNA <50 copies(c)/mL (snapshot algorithm). We report safety, PK and efficacy through W24.

Results: We treated 28 adolescents; median age 14 yrs (range 12-17), median weight 45 kg (range 35-62), 43% female, 43% Black. Median (Q1, Q3) duration of exposure to study drug was 76 (56, 129) wks. Mean study drug adherence was high (93%). Most common AE was viral upper respiratory infection (32%). Two participants had serious, unrelated AEs. Five had AEs related to study drug; none discontinued study drug due to an AE. Mean % change from baseline in BMD at W24 was +3.9% for spine and +2.2% for total body less head (TBLH). Mean change in BMD height-age adjusted Z-score was 0.00 for spine and -0.03

for TBLH. Mean (SD) estimated change in glomerular filtration rate was 2.0 (20.95) mL/min/1.73m^2. No clinically relevant differences in TAF and tenofovir exposures were observed in adolescents v. adults (Table). Most (93%, 26/28) maintained HIV-1 RNA <50 c/mL.

Conclusion: FTC/TAF with boosted or unboosted third agents in HIV-infected adolescents 12 to <18 yrs had high adherence rates and was well tolerated, while demonstrating increased BMD over 24 weeks. Exposure of TAF was similar to adults. High rate of virologic suppression was maintained at W24. Findings support FTC/TAF as a safe and effective NRTI backbone in adolescents.

Table. Plasma TAF and TFV exposure (AUC) after FTC/TAF administration in adolescents and adults

	Regimen[a]	Adolescent[a] AUC_{tau}, ng*h/mL	Adult[b] AUC_{tau}, ng*h/mL	% GLSM Ratio(90% CI)
TAF	FTC/TAF 200/25 mg	201 (41.8)	167 (32.7)	117 (93.7, 147)
	FTC/TAF 200/10 mg	140 (80.9)	101 (60.2)	116 (72.2, 185)
TFV	FTC/TAF 200/25 mg	193 (24.2)	356 (37.2)	56 (49.0, 64.2)
	FTC/TAF 200/10 mg	416 (25.5)	336 (43.1)	128 (113, 145)

GLSM, Geometric least-squares mean

a The dose of TAF was 10 mg with a boosted third agent and 25 mg with an unboosted third agent.

b n=12 for FTC/TAF 200/25 mg; n=13 for FTC/TAF 200/10 mg from intensive PK substudy in current adolescent cohort

c n=161 for FTC/TAF 200/25 mg; n=131 for FTC/TAF 200/10 mg;. ASM microbe: Custodio 2016, poster SUNDAY-407.

Statistical comparisons in adolescents (test) versus adults from the FTC/TAF Phase 3 study (reference) were made using geometric least-squares mean (GLSM) ratios and associated 90% confidence intervals (CI)

844 BICTEGRAVIR/FTC/TAF SINGLE-TABLET-REGIMEN IN ADOLESCENTS: WEEK 24 RESULTS

Aditya Gaur[1], Carina Rodriguez[2], Eric J. McGrath[3], Elizabeth Hellstrom[4], Afaaf Liberty[5], Eva Natukunda[6], Pope Kosalaraksa[7], Kulkanya Chokephaibulkit[8], Amy Coluci[9], Sophia R. Majeed[9], Danielle Porter[9], Pamela Wong[9], Erin Quirk[9], Hiba Graham[9], Cheryl Pikora[9]

[1]St. Jude Children's Research Hospital, Memphis, TN, USA, [2]University of South Florida, Tampa, FL, USA, [3]Children's Hospital of Michigan, Detroit, MI, USA, [4]Be Part Yoluntu Centre, Paarl, South Africa, [5]Chris Hani Baragwanath Hospital, Johannesburg, South Africa, [6]Joint Clinical Research Centre, Kampala, Uganda, [7]Khon Kaen University, Khon Kaen, Thailand, [8]Mahidol University, Bangkok, Thailand, [9]Gilead Sciences, Inc, Foster City, CA, USA

Background: Bictegravir (BIC), a novel, unboosted integrase strand transfer inhibitor (INSTI) with a high genetic barrier to resistance, has been coformulated with emtricitabine and tenofovir alafenamide (BIC/FTC/TAF; B/F/TAF) into a once daily, single-tablet regimen (STR) of small tablet size that can be taken with/without food. We report pharmacokinetics (PK), safety and efficacy from a planned interim analysis of the first clinical trial of B/F/TAF in HIV-infected adolescents.

Methods: Virologically suppressed adolescents (12 to <18 yrs) weighing ≥35 kg with HIV-1 RNA <50 c/mL for ≥6 months before screening and CD4 ≤200 cells/μL received B/F/TAF once daily in a prospective, 48-week (W), single-arm, open-label trial. Steady-state PK parameters in adolescents were compared to those observed in adults treated with B/F/TAF. Adverse events (AE), laboratory tests, and the proportion of subjects with HIV-1 RNA <50 c/mL were assessed through W24.

Results: 24 adolescents enrolled; median age 15 yrs (range 12-17 yrs), median weight 48.9 kg (range 36.1-88.6 kg), 79% female, 52% Black, median CD4 count 708 cells/μL, 88% vertically infected. All (100%) had HIV-1 RNA <50 c/mL at W24 and none met criteria for resistance testing. Mean change in CD4 count from baseline was 44 cells/μL. No clinically relevant differences in drug exposures of B/F/TAF components were observed compared with data from adults (Table). Through a median (Q1, Q3) duration of exposure to study drug of 25.6 (24.7, 26.6) weeks, the most common treatment emergent AE was upper respiratory tract infection (21%, 5 of 24); no other AE occurred in >2 participants. No subject discontinued for AE. All participants reported B/F/TAF size and shape to be acceptable, and mean (SD) adherence to study drug was high (97.1% [7.02]). μ μ

Conclusion: The B/F/TAF STR maintained virologic suppression in all adolescent subjects enrolled and was well-tolerated through 24 weeks. Similar to adults treated with B/F/TAF, therapeutic plasma concentrations of all components of B/F/TAF were achieved. The efficacy and safety in adolescents is consistent with phase 3 B/F/TAF results in adults, which showed high proportions with viral suppression and no resistance. These data support further pediatric studies of B/F/TAF, which may be an important unboosted INSTI option for HIV-infected adolescents and children due to its high barrier to resistance, small tablet size and lack of food requirement.

Table. PK parameters of bictegravir (BIC), emtricitabine (FTC) and tenofovir alafenamide (TAF) after BIC/FTC/TAF Single-Tablet Regimen administration in adolescents and adults

	Parameter	Adolescent[a]	Adult[b]	%GLSM Ratio (90% CI)
BIC	AUC_{tau}, ng*h/mL	109668 (31)	102001 (27)	107 (97,118)
	C_{max}, ng/mL	8087 (30)	6146 (23)	130 (119,143)
	C_{tau}, ng/mL	2327 (49)	2610 (35)	86 (74,100)
FTC	AUC_{tau}, ng*h/mL	13579 (22)	12294 (29)	113 (102,124)
	C_{max}, ng/mL	2689 (34)	2127 (35)	127 (111,145)
	C_{tau}, ng/mL	64 (25)	96 (37)	69 (62,78)
TAF	AUC_{tau}, ng*h/mL	271 (50)	229 (63)	125 (102,153)
	C_{max}, ng/mL	262 (45)	277 (62)	101 (80,128)

Parameters are presented as arithmetic mean (%CV); GLSM: Geometric least-squares mean

[a] n=24 from intensive PK substudy in current adolescent cohort

[b] From pooled intensive PK data from 4 Phase 3 Studies in HIV-infected adults

Statistical comparisons of the PK parameters in adolescents (test) versus adults from Phase 3 studies (reference) were made using geometric least-squares mean (GLSM) ratios and associated 90% confidence intervals (CI).

845 P1101: PHASEI/II STUDY OF RALTEGRAVIR CONTAINING REGIMEN IN HIV-TB COTREATED CHILDREN

Tammy Meyers[1], **Paul Krogstad**[2], Pearl Samson[3], Edward P. Acosta[4], Jack Moye[5], Ellen Townley[6], Sarah Bradford[7], Linda Marillo[8], Laura Hovind[8], Thucuma Sise[6], Hedy Teppler[9], Sylvia Dittmer[10], Lee Fairlie[11], Anneke Hesseling[12], Mark Cotton[13]

[1]The Chinese University of Hong Kong, Hong Kong, Hong Kong, [2]University of California Los Angeles, Los Angeles, CA, USA, [3]Harvard University, Cambridge, MA, USA, [4]University of Alabama at Birmingham, Birmingham, AL, USA, [5]National Institute of Child Health and Human Development, Bethesda, MD, USA, [6]NIAID, Rockville, MD, USA, [7]FHI 360, Durham, NC, USA, [8]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [9]Merck & Co, Inc, Palo Alto, CA, USA, [10]Chris Hani Baragwanath Hospital, Johannesburg, South Africa, [11]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [12]Desmond Tutu TB Centre, Western Cape, South Africa, [13]Stellenbosch University, Cape Town, South Africa

Background: Current antiretroviral (ARV) treatment options for children co-infected with TB and HIV-infection are limited. RIF induces UDP-glucuronosyltransferase activity accelerating the clearance of raltegravir (RAL). In adults, doubling the RAL dose partially overcame this PK interaction with no safety concerns. We sought to determine the optimal and safe dose of RAL when administered with RIF-containing anti-TB therapy in HIV-infected children.

Methods: P1101 is a dose finding study for RAL for HIV-infected children receiving RIF-containing TB therapy for at least one week, with three age cohorts: Cohort 1: 2 to <6 years (closed), Cohort 2: 6 to <12 years of age and Cohort 3: 4 weeks to <2 years, aiming to enroll 12 evaluable children for PK and safety in each cohort. At enrollment children start 3 ARVs, including chewable RAL formulation at 12 mg/kg/dose twice daily (twice the recommended pediatric dose). Intensive RAL PK sampling is done 1 week after ARV therapy is initiated and then a 4th ARV is added. Clinical and lab assessments are routinely completed. RAL is stopped at TB treatment completion and children are followed for additional 3 mos. PK targets are a geometric mean (GM) AUC12h of 14-45 (μM-h) and GM C12h ≥75 nM. Here we report the results from Cohort 1.

Results: Among 12 children, 7 (58%) were male, median age 3 years (IQR 2-5), baseline Log10 RNA median 4.91 (IQR 4.42-5.42), median CD4 count 559 cells/mL (IQR 390-1185), median CD4 percent 15% (IQR 9-24). PK at Week 1 showed GM AUC12h (%CV) of 28.8 mMxh (50%); the GM C12h was 229 nM (76%). 1/12 (8% with 95% CI [0%,34%]) had a grade 3 elevation of ALT at Week 4 deemed possibly related to RAL. RAL/ART were temporarily withheld for 21 days and then restarted, with no subsequent recurrence. While RAL was held temporarily, this child did not achieve virologic success (>1 $\log_{10}$ drop from baseline at Week 8 or HIV RNA ≤400 copies/mL). 11/12 (92%), were virologically suppressed by Week 8, with 95% CI (62%, 100%). For n=12 at Week 8, median $\log_{10}$RNA change from baseline was -3.16 (IQR -3.79, -2.55), median CD4 change from baseline was 101 cells/mL (IQR -70 to 230], median CD4 percent change from baseline was 6.1% (IQR 1.9-9.7).

Conclusion: A 12mg/kg dose twice daily of the oral chewable formulation of RAL safely achieved PK targets in HIV-infected children 2 to <6 years with TB.

846 MILESTONES AND OUTCOMES OF YOUNG ADULTS WITH PERINATAL HIV INFECTION OR EXPOSURE

Elaine J. Abrams[1], Claude A. Mellins[2], Amelia Bucek[3], Curtis Dolezal[2], Jeannette Raymond[2], Andrew Wiznia[4], Cheng-Shiun Leu[2]
[1]ICAP at Columbia University, New York, NY, USA, [2]New York State Psychiatric Institute, New York, NY, USA, [3]Columbia University, New York, NY, USA, [4]Albert Einstein College of Medicine, Bronx, NY, USA

Background: With aging of the population with perinatal HIV infection (PHIV+) in the US, concerns have emerged about transition into adulthood. Using data from CASAH, one of the largest behavioral longitudinal cohort studies on PHIV+ and perinatally HIV-exposed uninfected (PHEU) youth, we examined young adult (YA) milestones, and behavioral and biomedical outcomes.

Methods: Participants were recruited from 4 NYC medical centers in 2003-2008, at ages 9-16yrs and followed every 12-18mos with validated psychiatric and psychosocial interviews and medical chart abstraction. Data from visits conducted in 2014–2017 were analyzed. Descriptive statistics, chi-square and t-tests were used to compare YA milestones, sexual and reproductive health, psychiatric disorders, substance use (SU) and neurocognitive (NC) function between PHEU and PHIV+ YA.

Results: Among 246 participants (149 PHIV+), 53% were female; 69% African American/Black, 50% Latino; mean age 22yrs (SD2.6; range18-28). Participants achieved many YA milestones: 70% graduated high school/GED, 20% were currently in college; 41% were working; only 38% were not in school or working; 48% were in romantic relationships and 5% married/engaged. Also, 92% initiated sex; 62% had vaginal or anal sex in past 3mos; 41% reported condomless sex in past 3mos. There were no HIV status differences in these outcomes. Pregnancy was reported by 39% of females and males, over half reported at least one live birth (PHIV+ > PHEU, p<.05) and 67% reported living with the child. The majority (68%) of PHEU were living with family or friends rent free, whereas PHIV+ YA were significantly more likely to be paying/contributing rent (54%; p<.001), likely due to higher rates of HIV-related public assistance (p<.001). Rates of psychiatric disorder (26%, most prevalent mood and anxiety) and SU disorder (27%, most prevalent alcohol and marijuana) were similar by HIV status. PHIV+ YA performed worse on 2 tests assessing working memory, processing speed and planning. Among the PHIV+, mean CD4 488 cells/mm^3, range, 2-1430, 44% had CD4>500, 15% had CD4<100. For 52% most recent viral load (VL) was <50 copies/mL, while 32% had a VL>1000 copies/mL; 94% were on ART, 63% and 30% taking 2 and 3 drug class regimens respectively. Only 32% were taking 1 pill once daily regimens.

Conclusion: Similar to PHEU, most PHIV+ YA are achieving age appropriate adult milestones, but high rates of psychiatric and substance use disorders, neurocognitive dysfunction and viremia on ART warrant attention.

	Total = 246 N (%[a])	PHIV+ = 149 N (%[a])	PHEU(-) = 97 N (%[a])	P[b]
Female	131 (53%)	82 (55%)	49 (51%)	.488
Age [mean (SD) range]	22.3 (2.6) 18-28	22.8 (2.6) 18-28	21.7 (2.6) 18-28	.002
Employed or in school	152 (62%)	87 (58%)	65 (67%)	.174
Condomless sex (vaginal/anal) in past 3 months	100 (41%)	56 (38%)	44 (46%)	.231
Any pregnancy ended in live birth	49 (20%)	36 (25%)	13 (14%)	.033
Any psychiatric disorder	63 (26%)	37 (26%)	26 (27%)	.872
Any substance use disorder	65 (27%)	35 (25%)	30 (31%)	.284
Neurocognitive function:				
Trails Making test A [mean (SD) range]	25.9 (9.4) 12-66	27.5 (10.2) 12-66	23.4 (7.4) 12-53	.001
Trails making test B [mean (SD) range]	71.7 (39.7) 21-331	73.9 (38.7) 27-331	68.3 (41.0) 21-255	.083[c]
Digit span standard score [mean (SD) range]	8.0 (2.7) 1-17	7.7 (2.8) 1-17	8.6 (2.4) 3-15	.010

[a]Percents are based on those with non-missing data.

[b]P values from comparisons of PHIV+ and PHEU(-) by chi-square tests (for dichotomous/categorical variables) or t-tests (for continuous variables).

[c]Value log-transformed prior to t-test due to skewed distribution.

847 SELF-HARM IN ADOLESCENTS WITH PERINATAL HIV AND HIV-AFFECTED ADOLESCENTS IN ENGLAND

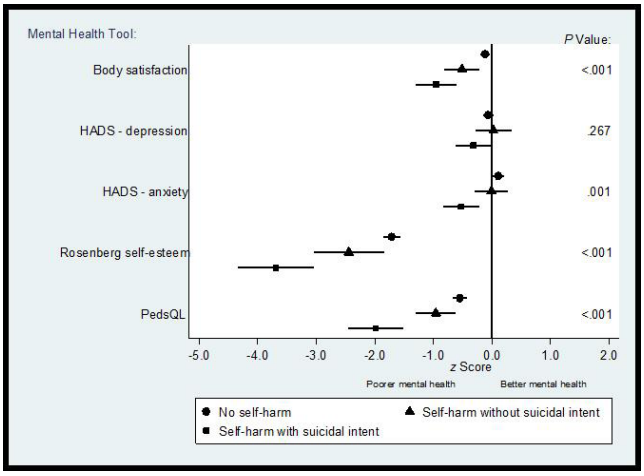
Julie Copelyn[1], Lindsay Thompson[2], Marthe Le Prevost[2], Kate Sturgeon[2], Katie Rowson[2], Susie Brice[2], Ali Judd[2]
[1]UCL Great Ormond Street Institute of Child Health, London, UK, [2]University College London, London, UK

Background: Suicide is the leading cause of death among 15-29 year olds globally, and self-harm is the strongest predictor for subsequent suicide. The prevalence of self-harm among adolescents aged 16-17 years in a large birth cohort in the general population in England was 19%. Adolescents with perinatal HIV (PHIV+) may be at increased risk of poor mental health outcomes, however limited evidence exists on the prevalence of self-harm in this population. We investigated prevalence of self-harm among PHIV+ adolescents and an HIV negative but affected comparator group living in England.

Methods: 303 PHIV+, and 100 HIV- adolescents with a family member with HIV (12-21yrs and 13-23yrs respectively), completed computer-assisted self-interview questions on self-harm, and underwent standardised mental health tests during face-to-face interviews in 2013-15. Z-scores for Rosenberg self-esteem scores were calculated using data from an Irish study of almost 5000 youths aged 13-17. Chi2 compared proportions, and logistic regression identified predictors of self-harm.

Results: Median age of both groups was 17 years (PHIV+: IQR 15, 18, HIV-: IQR 15, 19), and 41% of PHIV+ and 31% of HIV- participants were male. Most participants in both groups were of Black African ethnicity (PHIV+: 86%, HIV-: 73%, p=0.003). Overall 14% (56/403) reported having ever self-harmed, with no difference between PHIV+ and HIV- (12% vs. 19% respectively, p=0.089). Of those who self-harmed, 46% (26/56) reported suicidal intent. After adjustment, predictors of self-harm were female sex (AOR 5.3, 95%CI 1.9, 14.1, p=0.001 vs male), lower self-esteem (AOR 1.2 95%CI 1.1, 1.2, p‹0.001 per 1 unit decrease in Rosenberg score) and ever having alcohol (AOR 3.8, 95%CI 1.8, 7.8, p‹0.001 vs. no alcohol). Mean self-esteem z-scores for PHIV+ and HIV- participants were -1.9 {standard deviation 1.5} and -1.9 {1.6} respectively. Comparing mental health test scores between those with no self-harm, those with self-harm without suicidal intent and those with self-harm with suicidal intent, there was a progressive worsening of z scores across tests, with those reporting no self-harm having the highest z scores (ie better mental health), and those with self-harm with suicidal intent the lowest z scores (Figure).

Conclusion: Self-harm is common among PHIV+ and HIV- affected adolescents in England, but comparable to age matched population data. However, levels of self-esteem in both groups fell well below population normative levels and warrants further attention.



848 MONITORING THE 3RD 90: ARE WE ON TRACK WITH ADOLESCENTS AND YOUTH?

Evelyne Ngugi[1], Agnes Natukunda[2], Tai Ho Chen[1], Kenneth Masamaro[1], Lucy Ng'ang'a[1], Jonathan Mwangi[1], Immaculate Mutisya[1], Abraham Katana[1], Peter W. Young[1]
[1]US CDC Nairobi, Nairobi, Kenya, [2]University of California San Francisco, San Francisco, CA, USA

Background: Kenya has implemented the UNAIDS 90-90-90 strategy; the 3rd 90 target has implications for patient outcomes and secondary HIV prevention. As of June 2017, over one million persons living with HIV were on antiretroviral therapy (ART); with a viral load (VL) uptake of 85% nationally, with consistently lower viral suppression rates among adolescents and youth. We evaluated viral suppression rates among patients aged ≥15 years.

Methods: In a nationally-representative cross-sectional survey conducted from October 2015–September 2016, samples were collected from 2561 persons aged ≥15 years on ART ≥12 months from 50 health facilities in Kenya. HIV-1 RNA quantification was performed on 2497 of the collected DBS samples. Dried blood spots were prepared from whole blood on Whatman 903 DBS filters for analysis using the Abbott m2000rt system. We assessed VL suppression (VL less than 1000 copies/ml) and factors associated with non-suppression using logistic regression. Missing covariates were multiply imputed and analyses weighted to account for complex survey design.
Results: Of 2497 patients with samples analyzed for VL, 744 (29.8%) were men. Median age was 41.3 years (inter-quartile range [IQR] 34.5–49.0) and 596 (23.2%) were youth aged 15-24 years. Median time on ART was 5.3 years (IQR 2.9–7.9); 2474 (99.3%) were on NNRTI-based regimens at ART initiation. Overall viral suppression was 83.5% (95% confidence interval [CI] 78.7–88.3) with no difference between women and men (p=0.952), nor based on ART regimen. (p=0.206). Suppression was lower among adolescents aged 15–19 years (55.6% [95% CI 42.8–68.4]) and highest among persons aged ≥55 years (87.6% [95% CI 80.2–95.1]). Students had lower suppression rates, 53.9% (95% CI 35.5–72.4), compared to employed persons at 88.0% (95% CI 85.3–90.7). In multivariable logistic regression, younger age (15–24 years) was independently associated with non-suppression (adjusted odds ratio (AOR) =2.18, 95% CI 1.29–3.70), as was being a student versus employed (AOR=2.08, 95% CI 1.04–4.13) and non-disclosure to spouse, however, there was no difference in viral suppression by time on ART, baseline CD4, WHO stage, or BMI.
Conclusion: Overall viral suppression among ART patients in Kenya is approaching 90%, but youth and adolescents show substantially lower suppression rates. Identifying and implementing effective interventions to help young people and students achieve viral suppression should be prioritized.

849 STUNTING AND GROWTH OF HIV-INFECTED ADOLESCENTS: HOW TO INTERPRET PROGRAMMATIC DATA?

Julie Jesson[1], Michael Schomaker[2], Karen Malateste[3], Dewi K. Wati[4], Azar Kariminia[5], Mariam Sylla[6], Kouakou Kouadio[7], Shobna Sawry[8], Michael J. Vinikoor[9], Samuel Ayaya[10], Rachel Vreeman[11], Mary-Ann Davies[2], Valériane Leroy[1]
[1]INSERM, Toulouse, France, [2]University of Cape Town, Cape Town, South Africa, [3]INSERM, Bordeaux, France, [4]Sanglah Hospital, Bali, Indonesia, [5]Kirby Institute, Sydney, NSW, Australia, [6]Hôpital Gabriel Touré, Bamako, Mali, [7]CIRBA, Abidjan, Côte d'Ivoire, [8]University of the Witwatersrand, Johannesburg, South Africa, [9]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, [10]Moi University, Eldoret, Kenya, [11]Indiana University, Indianapolis, IN, USA

Background: Among the increasing cohort of HIV-infected adolescents worldwide, little is known about their growth. We aimed to estimate the prevalence of stunting and describe growth of HIV-infected adolescents in the International Epidemiologic Databases to Evaluate AIDS (IeDEA) consortium of programmatic cohorts, where data come from patient cohorts in the course of routine HIV care.
Methods: Data from sub-Saharan Africa, the Asia-Pacific, and the Caribbean and South America collected between 2003 and 2016 were used. All HIV-infected patients with at least one height measurement available while aged 10-19 years were included. If HIV exposure type was not reported, perinatal infection was assumed as having entered care before 15 years of age, and behavioral infection after 15 years. Factors associated with stunting (Height-for-Age Z-score [HAZ] <-2 SD, WHO Child Growth Standards) at age 10, 15 and 18 years were studied using logistic regression. Growth HAZ curves were stratified by sex, and stunting was described at entering or leaving (death or drop-out) care between 10 and 19 years.
Results: Overall, 50,434 adolescents met the inclusion criteria; 59% from Southern Africa, 20% from East Africa. Median age at first visit was 11.2 years (Interquartile Range [IQR] 7.1-16.1), 60% were female, 95% received antiretroviral therapy (ART), and 70% were perinatally infected. Prevalence of stunting at 10, 15 and 18 years was 36% (N=19078), 45% (N=14292) and 27% (N=11332), respectively. Factors associated with stunting included late age at ART initiation (e.g. at 15y: adjusted Odds Ratio [aOR] 10-15y vs 0-5y=2.5 [2.1-3.0]); and low CD4 count at current age (e.g. at 10y: aOR <350 vs >500 cells/mL =1.9 [1.7-2.1]). At 18y, those perinatally infected were more likely stunted than those behaviorally infected (aOR=1.3 [1.0-1.5]). Growth trajectories between 10 and 19 years differed by sex; HAZ decreased between 10 and 15 years old, then increased (Figure 1). Those entering or leaving care between 10 and 15 years were slightly more stunted than those entering or leaving care between 15 and 19 years (entering: 49% vs 22%, leaving: 46% vs 28%).
Conclusion: Stunting is a major concern among HIV-infected adolescents worldwide. Our growth curves were generated from a mixed population, with perinatally infected adolescents often having advanced HIV and stunted, compared to the mostly healthier behaviourally infected. This heterogeneity is relevant for future nutritional programs.

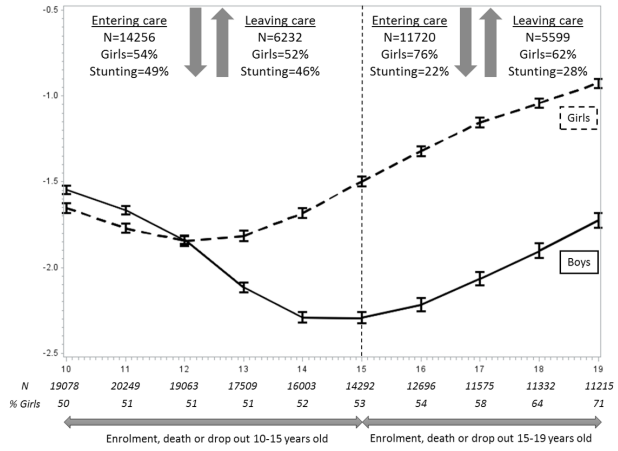


Figure 1: Height-for-age Z-score evolution between 10 and 15 years by sex and stunting at enrolment or last visit before death or drop out.

850 PREVALENCE OF GLOMERULAR DYSFUNCTION AMONG PERINATALLY HIV-INFECTED THAI ADOLESCENTS

Tavitiya Sudjaritruk[1], Suparat Kanjanavanit[2], Linda Aurpibul[3], Tawalchaya Chotecharoentanan[3], Saowalak Sarachai[3], Kamolrawee Sintupat[3], Ratchaneekorn Khampan[3]
[1]Chiang Mai University, Chiang Mai, Thailand, [2]Nakornping Hosp, Chiang Mai, Thailand, [3]Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand

Background: This study aimed to assess the prevalence and associated factors of glomerular dysfunction among perinatally HIV-infected Thai adolescents.
Methods: This is a multicenter, prospective cohort study. We enrolled (1) HIV-infected adolescents (aged 10-25 years) who received antiretroviral treatment (ART) for ≥1 year, and (2) age- and sex-matched healthy controls (ratio 2:1). HIV-infected adolescents were further classified according to their current status of tenofovir disoproxil fumarate use (TDF vs. non-TDF users). Glomerular function parameters, including serum creatinine, and random urine creatinine and protein levels were measured at baseline and 3 months. Estimated glomerular filtration rate (eGFR) and urine protein-to-creatinine ratio (UPCR) were calculated. Glomerular dysfunction was defined as having either (1) impaired eGFR: eGFR<60mL/min/1.73m2 for 2 times, or decline ≥30% from baseline; or (2) proteinuria: UPCR ≥0.2mg/mg for 2 times. Median values are provided with interquartile ranges. Logistic regression analysis was performed to identify associated factors of glomerular dysfunction among our HIV-infected adolescents.
Results: Between December 2016 and June 2017, 140 HIV-infected adolescents and 70 healthy controls were enrolled, half (50%) were female. The median age and body mass index (BMI) were 18 (15-21) years, and 20 (18-22) kg/m2, respectively. Thirty-seven adolescents (18%) were wasted (BMI<5th percentile or <18.5kg/m2 for participants aged<18 or ≥18 years, respectively). Among HIV-infected adolescents, 70 (50%) were TDF users, of whom 35 (50%) were concurrently receiving protease inhibitor (PI)-based regimens. Glomerular dysfunction was identified in 15 TDF users (21%; 95%CI: 13-33%), 6 non-TDF users (9%; 95%CI: 3-18%), and 1 healthy control (1%: 95%CI: 0.1-8%) (P<0.01) (Table1). Among TDF users, the prevalence of glomerular dysfunction was not different between individuals on PI-based vs. non-nucleoside reverse transcriptase inhibitor-based regimens (8 [23%] vs. 7 [20%]; P=0.77). In the multivariable analysis among HIV-infected adolescents, TDF use (adjusted odds ratio[aOR]:4.2; 95%CI: 1.2-15.2), age <18 years (aOR:11.1; 95%CI: 2.3-53.3), and wasting (aOR: 7.2: 95%CI: 1.9-27.3) were significantly associated with glomerular dysfunction.

Conclusion: Glomerular dysfunction is common in our HIV-infected adolescents, particularly among TDF users. Monitoring of glomerular function is important in the routine clinical practice, and should be considered in individuals at risk.

Table 1. Prevalence of glomerular dysfunction, proteinuria and impaired estimated glomerular filtration rate among perinatally HIV-infected and healthy adolescents.

Parameters*	HIV-infected adolescents (n=140)		Healthy adolescents	*P-value*
	TDF users (n=70)	Non-TDF users (n=70)	(n=70)	
Glomerular dysfunction	15 (21.4%)	6 (8.6%)	1 (1.4%)	<0.001
(either impaired eGFR or proteinuria)	95% CI: 12.5-32.9%	95% CI: 3.2-17.7%	95% CI: 0.1-7.7	
Proteinuria	9 (12.9%)	3 (4.3%)	0 (0%)	0.004
(UPCR ≥0.2 mg/mg for 2 times)	95% CI: 6.1-23.0%	95% CI: 0.9-12.0%		
Impaired eGFR	7 (10.0%)	3 (4.4%)	1 (1.4%)	0.07
(eGFR <60 mL/min/1.73m² for 2 times, or decline ≥30% from baseline)	95% CI: 4.1-19.5%	95% CI: 0.9-12.2%	95% CI: 0.1-7.7%	

Abbreviations: eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio, 95% CI, 95% confidence interval.
*Data were presented as number (%).

851 VIROLOGIC RESPONSE TO EFAVIRENZ-BASED FIRST-LINE IN CHILDREN BY PMTCT EXPOSURE STATUS

Lee Fairlie[1], Patience Nyakato[2], Mary-Ann Davies[2], Karl Technau[3], Geoffrey Fatti[4], Helena Rabie[5], Frank Tanser[6], Andrew Boulle[2], Robin Wood[2], Brian Eley[2], Shobna Sawry[1], Janet Giddy[7], Nosisa Sipambo[3], Andreas D. Haas[8], Louise Kuhn[9]
[1]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [2]University of Cape Town, Cape Town, South Africa, [3]University of the Witwatersrand, Johannesburg, South Africa, [4]Kheth'Impilo, Cape Town, South Africa, [5]Stellenbosch University, Cape Town, South Africa, [6]University of KwaZulu-Natal, Durban, South Africa, [7]McCord Hospital, Durban, South Africa, [8]University of Bern, Bern, Switzerland, [9]Columbia University, New York, NY, USA

Background: WHO recommends an efavirenz (EFV)-based first-line regimen for children ≥3 years of age starting antiretroviral therapy (ART), despite the possible risk of resistance with prior exposure to non-nucleoside reverse transcriptase inhibitors for prevention of mother-to-child transmission (PMTCT). We aimed to investigate the association between PMTCT exposure and virologic outcomes in children ≥3 years starting EFV-based ART using routine data from the International epidemiology Databases to Evaluate AIDS (IeDEA).
Methods: We included children aged 3-13 years who initiated EFV-based ART between 2004 and 2014, and had ≥2 viral load (VL) measures from 4-18 months on ART at 10 IeDEA public sector ART programs in South Africa. PMTCT exposure status was recorded by the program at enrolment as exposed, unexposed or unknown. Exact PMTCT regimens were not routinely recorded. We used logistic regression to examine the association between recorded PMTCT exposure and VL >1000 copies/ml (cpm) between 4-18 months on ART adjusting for patient characteristics associated with viral outcomes and calendar year. In additional analyses we assumed PMTCT exposure for those where exposure was unknown as either (1) all exposed to South African PMTCT guidelines at the time of the child's birth or (2) all unexposed.
Results: The median age at ART start of 8,383 children included was 7.5 years; 50% were girls. Recorded PMTCT exposure was as follows: 67% unexposed, 7% exposed and 26% unknown. VL >1000 cpm was experienced by 23% of children. Children with PMTCT exposure had similar risk of VL >1000 cpm compared to unexposed children (adjusted Odds Ratio [aOR]: 0.9; 95% CI:0.66, 1.24), but children with unknown PMTCT exposure were less likely to have VL >1000 cpm (aOR: 0.75; 95% CI:0.64, 0.88) (Table). After assuming children with unknown exposure received PMTCT available according to South African guidelines, PMTCT exposed children were less likely to have VL >1000 cpm compared to unexposed children (aOR:0.74; 95%CI: 0.61, 0.89). When assuming no PMTCT exposure for those with unknown exposure, PMTCT was not associated with VL >1000 cpm. Starting ART in more recent calendar years had a higher risk of VL >1000 cpm (Table).
Conclusion: In our study previous PMTCT exposure was not associated with poorer virologic outcomes in children >3 years starting EFV-based ART. Further research is needed to understand the effect of calendar year on VL outcomes.

	No assumptions made for unknown PMTCT		Children with unknown PMTCT assumed to have received PMTCT available at time of birth		Children with unknown PMTCT assumed to have received no PMTCT	
Patient characterisitics at ART start	**Adjusted OR**	**95% CI**	**Adjusted OR**	**95% CI**	**Adjusted OR**	**95% CI**
PMTCT						
No	1		1		1	
Yes	0.9	0.66, 1.24	0.74	0.61, 0.89	0.97	0.71, 1.34
Unknown	0.75	0.64, 0.88				
Sex						
Male	1		1		1	
Female	0.77	0.66, 0.88	0.77	0.68, 0.88	0.77	0.68, 0.88
Calendar Year of ART start						
< 2008	1		1		1	
2008-2010	1.36	1.13, 1.63	1.41	1.17, 1.70	1.37	1.14, 1.65
2011 and above	1.95	1.62, 2.35	2.12	1.77, 2.55	2.08	1.74, 2.50
WHO Stage						
Stage 1&2	1		1		1	
Stage 3&4	1.13	0.98, 1.31	1.14	0.99, 1.32	1,12	0.99, 1.32
WHO-defined immunosuppression						
No	1		1		1	
Yes	1.32	1.15, 1.52	1.32	1.15, 1.51	1,32	1.15, 1.50
Age at ART start (per year increase)	1.01	0.99, 1.04	1	0.98, 1.02	1	0.99, 1.04

852 VIRAL SUPPRESSION IN HIV-INFECTED CHILD-CAREGIVER DYADS IN WESTERN KENYA

John M. Humphrey[1], Beverly Musick[1], Edith Apondi[2], Becky L. Genberg[3], Adrian Gardner[1], Joseph Hogan[4], Kara K. Wools-Kaloustian[1]
[1]Indiana University, Indianapolis, IN, USA, [2]Moi University, Eldoret, Kenya, [3]Johns Hopkins Hospital, Baltimore, MD, USA, [4]Brown University, Providence, RI, USA

Background: Despite the role of caregivers (CG) in managing children with HIV, viral suppression in child-caregiver dyads in which both individuals are HIV-infected is not well characterized. We explored viral suppression in dyads enrolled in the Academic Model Providing Access to Healthcare (AMPATH) program in Kenya.
Methods: We analyzed medical records of all HIV-infected children < 15 years of age linked to HIV-infected CGs, who both received HIV care at an AMPATH clinic between 1/2015 and 2/2017. To be included in the analysis, children and CGs must have had ≥ 1 viral load (VL) within the study window and at least 6 months after ART initiation. For dyads with > 1 VL within the window, the child and CG VLs in closest temporal proximity to each other were chosen for analysis. The characteristics of children, CGs, and dyads were summarized with descriptive statistics. Odds ratios (OR) were calculated to determine the association of viral non-suppression (defined as VL ≥ 1000 copies/mL) among children and CGs.
Results: Of 7,669 children who received HIV care at AMPATH during the study window, 5,278 met the inclusion criteria. Of these, 2,912 (55%) were linked to a CG, and 2,154 (74%) CGs also met the inclusion criteria (n=2,154 dyads). Overall, 93% of CGs were mothers, median [IQR] age at HIV care enrollment was 32 [27, 36] years, median CD4 count at ART initiation 165 cells/uL [88, 259], and median years since ART initiation 5.9 [3.7, 8.0]. For children, 52% were girls, median age at enrollment was 3 [1.3, 5.3] years, median CD4% 15% [10, 22] (< 5 years at ART initiation), median CD4 count 382 [228, 686] (≥ 5 years at ART initiation), and median years since ART initiation 4.9 [2.6, 6.7]. The median number of days between caregiver and child VLs was 15 [0, 81]; child and CG VLs occurred on the same day in 44% of dyads. CG-child viral suppression was: both suppressed (56%), CG suppressed and child unsuppressed (23%), CG unsuppressed and child suppressed (10%), and both unsuppressed (11%). Children with unsuppressed CGs were 3 times more likely (OR=2.8, 95% CI: 2.3-3.5) than children with suppressed CGs to have unsuppressed VL.
Conclusion: Children with CGs who have unsuppressed VLs are at higher risk of viral non-suppression. Further research is needed to understand the barriers to viral suppression within the context of these family environments and identify interventions to address these barriers. Careful monitoring should be initiated for children who have HIV-infected CGs who are not suppressed.

853 ARE HIV+ MIGRANT CHILDREN IN EUROPE AT INCREASED RISK OF POOR OUTCOMES ON ART?

Malte Kohns[1], Ruth Goodall[2], Luisa Galli[3], Ali Judd[2], Tessa Goetghebuer[4], Antoni Noguera-Julian[5], Laura Rodrigues[1], Henriëtte J. Scherpbier[6], **Intira J. Collins**[2]
[1]London School of Hygiene & Tropical Medicine, London, UK, [2]University College London, London, UK, [3]University of Florence, Florence, Italy, [4]Saint-Pierre University Hospital, Brussels, Belgium, [5]Hospital Sant Joan de Déu Barcelona, Esplugues, Spain, [6]Emma Children's Hospital/Academic Medical Center, Amsterdam, Netherlands

Background: HIV-infected adult migrants in Europe have increased risk of AIDS and poorer response to antiretroviral therapy (ART) compared to domestic-born patients. There are few comparable studies in children.

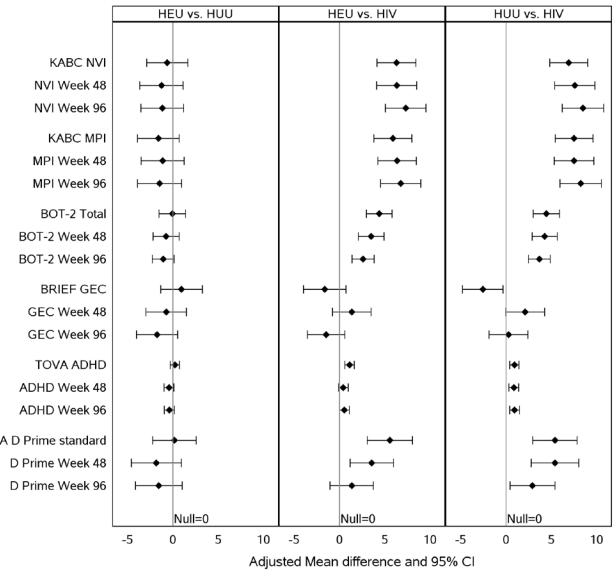
Methods: Children aged under 18-years at initiation of combination ART, in cohorts where ≥5% of children were born abroad (defined as migrants) were included. Follow-up was from ART start to death, last visit in paediatric care or 21st birthday. Hazard of first AIDS event or death among children AIDS-free at ART start was assessed by migrant status, using multivariable Cox models adjusting for sex, mode of transmission, age, weight-for-age z-score, WHO severe immunosuppression for age (based on CD4% or count) and calendar year at ART start. Missing baseline values were imputed. Sensitivity analysis assessed new/recurrent AIDS or death in all children, including those with AIDS at ART start.
Results: Of 2,284 children from 11 European countries, 55% were migrants (of whom 85% were from Africa), the proportion of migrants varied by country, from 5% in Poland to 97% in Sweden. At ART start, migrant children were older than domestic-born (median 8.1[IQR 4.0,11.7] vs 1.8[0.3,7.2] respectively; p<0.001), and more likely to be severely immunocompromised (48.3% vs 42.3%, p=0.013) and TB co-infected (2.2% vs. 0.7%; p=0.003), but fewer had AIDS (14.5% vs. 18.7%; p=0.012). Median follow-up after ART start was 5.4[2.3,8.7] and 7.6[3.1,11.1] years, respectively (p<0.001). Of 1,901 children AIDS-free at ART start, 103 (5.4%) had ≥1 AIDS event and 14 (0.7%) died. The rate of AIDS/death was 1.02 {95% CI 0.85, 1.23}/100 person-years. Cumulative probability of AIDS/death at 5 years after ART start was 6.0% {4.6,7.7} in migrant vs. 5.0% {3.7,6.7} in domestic-born children (p=0.17). After adjustment, the hazard of AIDS/death was not significantly higher among migrant children (adjusted hazard ratio (aHR) 1.45 {0.90,2.33}, p=0.129). In sensitivity analysis including all children, 141 (6.2%) had ≥1 AIDS event and 36 (1.6%) died, cumulative probabilities of AIDS/death at 5 years were 7.1% migrant vs. 7.3% domestic (p=0.75), again with no effect of migrant status (aHR 1.29 (0.88,1.88), p=0.199).
Conclusion: After adjusting for characteristics at ART start there was no increased risk of AIDS/death in migrant compared to domestic-born children in Europe. This may be partly due to the rarity of events or selection bias of long-term survivors among migrant children, or may indicate equality in care.

854 BETTER TREATMENT OUTCOMES FOR RWANDAN CHILDREN AFTER "TREAT ALL"

Stephen M. Arpadi[1], Matthew R. Lamb[1], Isaie Nzeyimana[1], Greet Vandebriel[1], Gloria E. Anyalechi[2], Marcia Wong[1], Rebecca Smith[1], Emilia M. Rivadeneira[2], Eugenie Kayirangwa[3], Samuel S. Malamba[3], Canisious Musoni[3], Emilia Koumans[2], Sabin Nsanzimana[4]
[1]ICAP at Columbia University, New York, NY, USA, [2]CDC, Atlanta, GA, USA, [3]CDC, Kigali, Rwanda, [4]Rwanda Biomedical Centre, Kigali, Rwanda
Background: In 2012, Rwanda expanded criteria for universal ART in HIV-infected children from 18 to 60 months of age regardless of CD4 count or clinical status. We compared antiretroviral therapy (ART) initiation and outcomes, before and after this change.
Methods: We conducted a nationally-representative retrospective study of children 18-60 months enrolled in care between June 2009-December 2011 (Before Treat All cohort [BTA]) and July 2012-April 2015 (Treat All cohort [TA]). Probability proportional to size sampling identified 100 health facilities. We extracted medical records up to 14 months after enrollment for all eligible children. Differences in frequencies of health problems (reported symptoms or opportunistic infection), median and mean outcomes were compared using chi-square, Wilcoxon rank sum, and t-tests. We compared outcomes (loss to follow-up or death) with competing-risk cumulative incidence functions.
Results: There were 374 children enrolled; 227 in the BTA and 147 in the TA. Mean (SD) age (3 years [1]) and WAZ (-2 [2]) at enrollment were similar across cohorts. Among the BTA, 59% initiated ART within one year, vs. 89% in the TA cohort. Median time to ART initiation was 68 days (interquartile range [IQR] 14-494) for the BTA and 9 days (IQR 0-28) for the TA (p<0.001); 9 children (5%) in the BTA had same-day initiation compared to 50 (37%) in the TA (p < 0.001). Prior to ART initiation, 59% of children in the BTA reported at least one health problem compared to 35% in the TA cohort (p < 0.001). Infectious diseases (BTA: 41%, TA: 24%, p = 0.001), diarrhea (BTA: 19%, TA: 10%, p = 0.02), and wasting syndrome (BTA: 5%, TA: 1%, p = 0.02) were more frequent in the BTA compared to the TA. After ART initiation, reported conditions were similar between cohorts. Viral load was done for 13% of the BTA compared to 44% of the TA on ART. Of 56 children on ART for > 6 months in the TA, 84% had a viral load < 1,000 copies/ml. Four children (2%) died prior to ART initiation in the BTA, compared to 1 (1%) in the TA (p=0.4). Overall loss to follow-up was similar between cohorts (BTA: 13%, TA: 8%, p = 0.2) while loss to follow-up before ART initiation was higher in the BTA cohort (8% versus 2%, p = 0.02).
Conclusion: Nearly 90% of Rwandan children 18 to 60 months old started ART within one year of enrollment; most within 1 month, with greater than 90% retention following implementation of 2012 guidelines. The 'Treat All' strategy is also associated with lower morbidity and better retention prior to ART.

855 AFRICAN MULTI-SITE 2-YEAR STUDY OF NEUROCOGNITION IN HIV INFECTED/AFFECTED CHILDREN

Michael J. Boivin[1], **Miriam Chernoff**[2], Barbara Laughton[3], Bonnie Zimmer[4], Celeste Joyce[5], Linda Barlow-Mosha[6], Mutsa Bwakura-Dangarembizi[7], Mmule Ratswana[8], Lee Fairlie[8], Portia Kamthunzi[9], Katie McCarthy[10], Patrick Jean-Philippe[11], Avy Violari[8], Mark Cotton[12], Paul Palumbo[13]
[1]Michigan State University, East Lansing, MI, USA, [2]Harvard University, Cambridge, MA, USA, [3]Stellenbosch University, Cape Town, South Africa, [4]Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, [5]Chris Hani Baragwanath Hospital, Johannesburg, South Africa, [6]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda, [7]Harare City Health Department, Harare, Zimbabwe, [8]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [9]Malawi Department of HIV and AIDS, Lilongwe, Malawi, [10]FHI 360, Durham, NC, USA, [11]NIAID, Bethesda, MD, USA, [12]Stellenbosch University, Tygerberg, South Africa, [13]Dartmouth–Hitchcock Medical Center, Lebanon, NH, USA
Background: We compared cognitive outcomes at weeks 0, 48, and 96 for HIV-infected (HIV), HIV-exposed uninfected (HEU), and HIV-unexposed/uninfected (HUU) cohorts of children at 6 sub-Saharan sites.
Methods: IMPAACT P1060 compared Nevirapine (NVP) versus Lopinavir/Ritonavir (LPVr)-based ARV in children (HIV+) 6 to 35 months of age. They were later enrolled for neurocognitive follow-up at 5 to 11 yrs, evaluating them at 3 annual time points, compared to age-matched HEU and HUU controls. Most HIV children in the NVP arm had been switched to 2nd line cART prior to the present study and 96% were virally suppressed (WHO Stage I=38 (15%); Stage II=58 (24%), Stage III=137 (56%); Stage IV=13 (5%)). They were tested with the Kaufman Assessment Battery for Children, 2nd ed. (KABC-II) cognitive ability, Tests of Variables of Attention (TOVA) attention/impulsivity, Bruininks-Oseretsky Test of Motor Proficiency (BOT-2), and parental Behavior Rating Inventory of Executive Function (BRIEF). Cohorts were compared using linear mixed models adjusted for site, child's age and gender.
Results: 611 (246 HIV+, 183 HEU, 182 HUU) of the 615 enrolled at 6 sites (South Africa [3], Zimbabwe, Malawi, Uganda), were compared across 3 assessment time points (weeks 0, 48, 96). 603 children completed week 48 and 588 completed week 96 visits. Mean age at enrollment was 7.2 years, 47% were male, and 69% were in school. 94% of caregivers were biological mothers (85% for HIV group), 32% completing high school, 22% on social grants, 38% in urban areas, 29% reporting sufficient family income. Cohort comparisons were consistent across time points, with the HIV cohort significantly worse than the HEU and HUU cohorts at all KABC-II, TOVA, BOT-2 global outcomes (P<0.001) (Figure 1, center and right). The HUU and HEU cohorts were comparable (Figure 1, left). On the BRIEF (parent ratings), the HIV cohort performed similarly or better at week 48 & 96, perhaps from biased caregiver perceptions. The magnitude of neurocognitive deficits among cohorts was consistent across the 3 assessments, except for HIV children for the KABC-II planning subtests, where they showed less improvement than the HUU/HEU groups.
Conclusion: Despite 56% being Stage III at diagnosis, HIV children had excellent clinical care and robust virological suppression. Still, the HIV group had poorer neurocognitive function at all 3 assessment points, especially in terms of executive function across time. Such deficits pose a serious risk as these children age into adolescence.



856 CARDIO-ANKLE VASCULAR INDEX AMONG PERINATALLY HIV-INFECTED THAI ADOLESCENTS

Tavitiya Sudjaritruk[1], Linda Aurpibul[2], Suvaporn Anugulreungkit[3], Tawalchaya Chotecharoentanan[2], Siwanart Thamsala[4], Rattika Thummalangka[2], Kittipan Rerkasem[1], Thanyawee Puthanakit[3]
[1]Chiang Mai University, Chiang Mai, Thailand, [2]Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand, [3]Chulalongkorn University, Bangkok, Thailand, [4]HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand

Background: Cardio-ankle vascular index(CAVI) was developed to demonstrate arterial stiffness independent of blood pressure(BP). A previous study in HIV-infected Thai adults(mean age 42 years) showed that the prevalence of arterial stiffness(CAVI≥9m/s) was 38%. Yet, data in HIV-infected adolescents is scarce. This study aimed to assess CAVI in HIV-infected Thai adolescents

Methods: A multicenter, cross-sectional study was conducted. Perinatally HIV-infected adolescents(10-25years) receiving antiretroviral therapy(ART) for ≥1 year, and age- and sex-matched healthy controls(ratio3:1) were enrolled. CAVI(m/s) was measured by the VaSera(VS-1500) device(Fukuda Denshi, Japan) on both arms and legs. An average value of the two sides represents CAVI for each adolescent. CAVI≥9m/s defines arterial stiffness. Risk for metabolic disorder was assessed, and defined as having either body mass index(BMI)≥30 kg/m2, triglyceride(TG)≥150 mg/dL, LDL-C≥130 mg/dL, HDL-C<40 mg/dL, or homeostasis model assessment of insulin resistance(HOMA-IR)>3.16. Linear regression analysis was performed to identify factors associated with CAVI among HIV-infected adolescents.

Results: Of 200 adolescents(150 HIV-infected and 50 healthy) enrolled, half(50%) were male, and median age(IQR) was 18(15-21) years. Among HIV-infected adolescents, 65(43%) currently received protease inhibitor-based regimens, and median ART duration(IQR) was 13(9-14) years. Systemic hypertension(HT) (systolic BP≥130 or diastolic BP≥85 mmHg) was identified in 14(7%) adolescents, and 31(16%) were overweight/obese which were not different between HIV-infected and healthy adolescents(P>0.05). Insulin resistance (HOMA-IR>3.16: 30% vs. 8%; P<0.01) and dyslipidemia (HDL-C<40 mg/dL: 25% vs. 6%, and TG≥150 mg/dL: 26% vs. 8%;P<0.01) were greater in HIV-infected adolescents compared with healthy controls. The median CAVI(IQR) were 5.8(5.2-6.2) and 5.8(5.4-6.3)m/s in HIV-infected and healthy adolescents(P=0.48), respectively. Although there was no adolescent having arterial stiffness (CAVI≥9m/s), those with CAVI ranking ≥95th percentile of our cohort were predominately HIV-infected(n=9), and had ≥1 risk for metabolic disorder(n=8) (Table1). In multivariable analysis, age≥18 years, systemic HT, and ART duration were significantly associated with increased CAVI in HIV-infected adolescents (P<0.05).

Conclusion: Despite low CAVI demonstrated in our HIV-infected adolescents, individuals with risk factors should be monitored for the progression towards significant arterial diseases.

Table 1. Clinical profiles of adolescents with cardio-ankle vascular index ranking at or above 95th percentile of the cohort.

No.	Age (yr)	Sex	HT	Risk for metabolic disorder	HIV-related characteristics				CAVI (m/s)
					ARV regimen	ARV duration (yr)	CD4 count (cells/mm³)	HIV RNA (copies/mL)	
1	21	M	Yes	HDL-C <40	NNRTI	15	523	<20	8.6
2	20	M	Yes	LDL-C ≥130	NNRTI	13	1374	40	7.4
3	25	M	No	BMI >30, TG ≥150, HDL-C <40, HOMA-IR >3.16	NNRTI	14	329	<20	7.4
4	25	M	No	TG ≥150, LDL-C ≥130	PI	13	510	18794	7.2
5	20	M	No	TG ≥150, HDL-C <40	PI	15	459	<20	7.8
6	24	M	No	TG ≥150	PI	18	499	40	7.3
7	20	F	No	TG ≥150	II	15	650	40	7.6
8	20	F	No	LDL-C ≥130	PI	18	738	<20	7.2
9	19	F	No	No	NNRTI	14	645	<20	7.3
10*	15	F	No	No	NA	NA	NA	NA	7.4

Abbreviations: ARV, antiretroviral treatment; BMI, body mass index; CAVI, cardio-ankle vascular index; F, female; HDL-C, high density lipoprotein-cholesterol; HIV, human immunodeficiency virus; HOMA-IR, homeostasis model assessment of insulin resistance; HT, hypertension; II, integrase inhibitor; LDL-C, low density lipoprotein-cholesterol; M, male; NA, not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor, PI, protease inhibitor; TG, triglyceride.
*Healthy, HIV-uninfected adolescent.

857 SUBSTANTIAL GENDER DIFFERENCES IN LONGITUDINAL ARTERIAL STIFFNESS IN CHILDREN ON ART

Steve Innes[1], Mark Cotton[1], Kennedy N. Otwombe[2], Barbara Laughton[1], Philip Herbst[1], Innocent Karangwa[1], Sara H. Browne[3]
[1]Stellenbosch University, Cape Town, South Africa, [2]Perinatal HIV Research Unit, Soweto, South Africa, [3]University of California San Diego, La Jolla, CA, USA

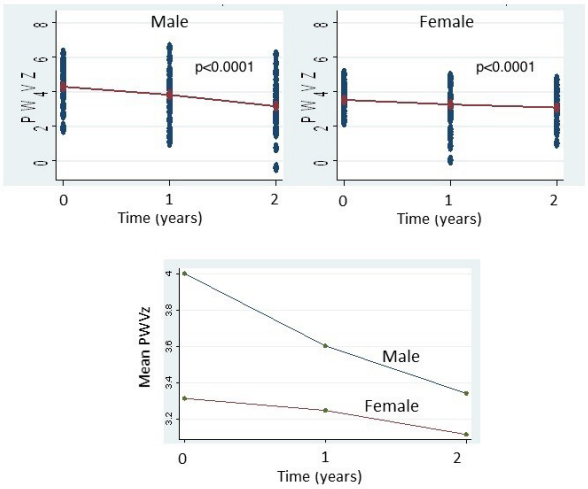
Background: Atherosclerotic vascular disease (AVD) is the major determinant of morbidity and survival in adult HIV+ persons on long-term suppressive antiretroviral therapy (ART), with women affected less severely than men. Whether this gender difference is present before puberty is unknown. HIV-specific mechanisms of AVD pathogenesis are uncertain but there is good evidence that AVD originates in childhood. AVD progression is reflected in pulse wave velocity (PWV), a direct measure of arterial stiffness.

Methods: Prospective PWV over 2 years in a long-standing cohort of well-suppressed HIV+ children (all prepubertal at entry) and an existing well-matched HIV-uninfected control group consisting of HIV-exposed (HEU) and -unexposed (HUU) children from the same communities and socio-economic background. Possible risk factors were modeled using forward stepwise regression: age, gender, serum cotinine (measures tobacco smoke exposure), fasted total cholesterol, HDL, LDL, triglycerides, glucose, blood pressure, extensive anthropometrics including waist circumference, waist-hip ratio, and body mass index. Linear mixed effects model used to compare longitudinal change in PWV in HIV+ and HIV- boys and girls.

Results: 87 HIV+ (median age 7.7 [IQR: 7.6–7.8] years, 46% male) who initiated ART at median 9 (7–12) weeks of age, with cumulative time on ART of median 7.1 (6.7–7.5) years and normal CD4 counts. 53 uninfected (31 HUU; 22 HEU) of median age 8.5 (7.8–8.7) years, 60% male, with similar anthropometric z-scores between groups (p>0.10). PWV z-score for height and gender (PWVz) was abnormally elevated in HIV+ children compared with HIV-unexposed (median 3.9 versus 3.4, p=0.02). In the HIV+ model, arterial stiffness was predicted by fasting glucose (p<0.0001), waist circumference (p<0.0001) and gender, but not by lipids. Among HIV+, PWVz was higher in boys than girls at baseline (median 4.0 versus 3.3, p=0.006), but both slowly improved with accumulating time on suppressive ART (Figure 1). PWVz improved more quickly in boys than girls (mean improvement -0.53 per year in boys versus -0.27 in girls; p<0.0001) but remained higher than girls after 2 years (Figure 1). No change in arterial stiffness was seen in HIV-uninfected over time in either gender.

Conclusion: In prepubertal children on suppressive ART, arterial stiffness is abnormally elevated in both genders, with boys more severely affected. Over 2 years, boys improved more quickly than girls but remain more severely affected.

Figure 1: Prospective pulse wave velocity z-scores (PWVz) in HIV+ children by gender



858 MITOCHONDRIAL DYSFUNCTION IN WELL-SUPPRESSED PERINATALLY HIV-INFECTED CHILDREN ON ART

Jing Shen[1], Renate Strehlau[2], Afaaf Liberty[2], Stephanie Shiau[1], Faeezah Patel[2], Megan Burke[2], Avy Violari[2], Marc D. Foca[1], Stephen M. Arpadi[1], Louise Kuhn[1]
[1]Columbia University, New York, NY, USA, [2]University of the Witwatersrand, Johannesburg, South Africa

Background: Although abnormalities in mitochondrial (mt) biomarkers are reported in HIV-infected children and/or antiretroviral treatment (ART), mt function in children with sustained viral suppression after initiation of ART in early life has not been described. Here we examined multiple markers of mt function in HIV-infected children on ART.

Methods: We selected a cross-sectional sample of 120 HIV-infected children with viral load < 400 copies/mL and 60 age-matched uninfected controls enrolled in a cohort study in Johannesburg, South Africa. Half the HIV-infected children initiated ART <6 months of age, and the others between 6-24 months. Markers of mt function were measured when children were suppressed on lopinavir/ritonavir plus nucleoside reverse transcriptase inhibitors (3TC and D4T or ABC). Complex IV (CIV) and citrate synthase (CS) activity (ODS units) were measured by spectrophotometry, and relative mtDNA content (copies/nDNA) was measured by real-time PCR. The ratio of CIV/CS was categorized as normal (>0.22 [75th quantile]) or impaired (≤0.22). Mt markers were compared by HIV status, age at ART initiation, duration of ART, and anthropometric characteristics.

Results: Median age was 6.8 years, ART duration ranged from 3 to 8 years in HIV-infected children. Compared to uninfected controls, mean CIV (1.40 vs. 1.76) and CS (8.45 vs. 9.29) were significantly reduced in HIV-infected (Table). Infected children also had increased risk of impaired CIV/CS ratio compared to uninfected controls (OR=2.33, 95%CI: 1.09-4.94). We observed a bimodal distribution of mtDNA in both groups and stratified children into those with lower (<12 copies/nDNA) or higher quantity mtDNA (>50 copies/nDNA). MtDNA in HIV-infected children was decreased compared with uninfected children within both lower quantity (3.36 and 4.63) and higher quantity (425 and 849) subsets. In HIV-infected children, CIV was significantly decreased in children who were stunted (height-for-age Z-score <-2) vs. children who were not stunted (1.20 vs. 1.43). CIV and mtDNA increased from 1.18 to 1.50 and 258 to 541, respectively with longer duration on ART (≥5 yrs). Earlier initiation of ART had no significant impact on CIV, CS and mtDNA content compared with later initiation.

Conclusion: Despite early treatment and prolonged viral suppression, mt dysfunction is detectable in HIV-infected children particularly among those with stunting. Whether mt function normalizes with continued time on ART requires further longitudinal studies.

Table. Comparisons of CIV, CS, CIV/CS and mtDNA in HIV-infected and non-infected children in Johannesburg, South Africa

Mitochondrial markers	HIV(-) children	HIV(+) children	p	HIV(+) *ART started 6-24 mo*	HIV(+) *ART started <6 mo*	p
No	**60**	**120**		**60**	**60**	
CIV (ODS units), Mean (SD)	1.76 (0.27)	1.40 (0.37)	<0.0001*	1.43 (0.36)	1.36 (0.39)	0.255*
CS (ODS units), Median	9.29	8.45	0.0475[δ]	8.42	8.69	0.809[δ]
CIV/CS[†]	**No (%)**	**No (%)**		**No (%)**	**No (%)**	
> 0.22	19 (31.7)	21 (17.5)		12 (20.0)	9 (15.0)	
≤ 0.22	41 (68.3)	99 (82.5)		48 (80.0)	51 (85.0)	
OR (95%CI)[‡]	1.00 (ref)	2.33 (1.09-4.94)	0.028	1.00 (ref)	1.31 (0.44-3.90)	0.624
Lower quantity mtDNA (<12 copies/nDNA)	**N = 30**	**N = 55**		**N = 28**	**N = 28**	
Mean (SD)	4.63 (1.87)	3.36 (1.73)	0.0173	3.12 (1.69)	3.66 (1.77)	0.299
Higher quantity mtDNA (>50 copies/nDNA)	**N = 30**	**N = 64**		**N = 32**	**N = 32**	
Mean (SD)	849.22 (2.30)	424.61 (2.39)	0.0004	396.18 (2.40)	451.94 (2.39)	0.543

* Welch's ANOVA test; [δ] Wilcoxon rank-sum test; [†] Categorized by 75% quantile; [‡] Logistic regression model adjusted for age at mt markers test

859 VITAMIN D SUPPLEMENTATION ATTENUATES IMMUNE ACTIVATION IN HIV+ AVIREMIC YOUTH

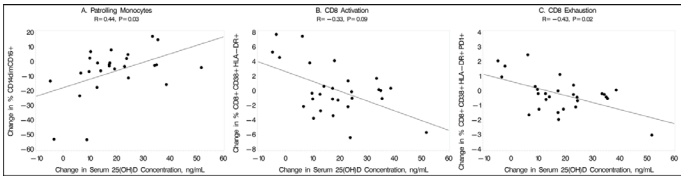
Allison R. Eckard[1], Mary Ann O'Riordan[2], Vin Tangpricha[3], Danielle Labbato[2], Ann Chahroudi[3], Grace A. McComsey[2]
[1]Medical University of South Carolina, Charleston, SC, USA, [2]Case Western Reserve University, Cleveland, OH, USA, [3]Emory University, Atlanta, GA, USA

Background: Heightened immune activation and global immune dysfunction drive HIV disease progression and co-morbidities. Vitamin D has pleiotropic effects on the immune system, but little is known about the long-term effects of supplementation in HIV-infected youth.

Methods: This is a 24-month randomized, active-control, double-blind trial investigating 3 different monthly vitamin D3 doses [18,000 (standard), 60,000 (moderate) or 120,000 (high) IU/month] in 8-26 year old HIV+ youth on antiretroviral therapy with baseline 25-hydroxyvitamin D (25(OH)D) ≤30 ng/mL and HIV-1 RNA <1000 copies/mL. Soluble and cellular markers of immune activation were measured by ELISA and flow cytometry, respectively.

Results: 68 subjects completed the 24-month study period: 66% male, 88% black with median (Q1, Q3) age of 20 (15, 23) years and CD4 count of 654 (430, 894) cells/mm^3. Baseline 25(OH)D was 17 (14, 22) ng/mL and increased within each dosing group (standard: +11 (9, 19); moderate: +20 (8, 25); high: +25 (19, 38) ng/mL; all P<0.001). Overall, all markers of monocyte activation decreased significantly [sCD14 (-0.8 ng/mL, P<0.0001); CD14+CD16+ (-10.4%, P<0.0001); CD14dimCD16+ (-4.4%, P=0.04)], but CD4+ and CD8+ T-cell activation/exhaustion markers did not. There were no significant differences between marker changes based on randomized arm or correlations between changes in 25(OH)D and changes in markers for all subjects considered together. However, when the analysis included only those with undetectable HIV-1 RNA throughout the study period (N=28), significant correlations were seen between changes in 25(OH)D and changes in proportion of patrolling monocytes (CD14dimCD16+; R=0.44, P=0.03) and activated CD8+ T-cells expressing PD-1 (CD8+CD38+HLA-DR+PD-1+; R=-0.43, P=0.02) with a trend toward significance for activated CD8+ T-cells (CD8+CD38+HLA-DR+; R=-0.33, P=0.09). None of these correlations were seen among the subjects who had detectable HIV-1 RNA at any point during the study (CD14dimCD16+: R=0.03, P=0.86; CD8+CD38+HLA-DR+PD-1+: R=0.04, P=0.82; CD8+CD38+HLA-DR+: R=-0.03, P=0.88) (Figure).

Conclusion: Changes in serum 25(OH)D concentrations were strongly associated with changes in proportions of patrolling monocytes, activated CD8+ T-cells and exhausted CD8+ T-cells, but only in the context of sustained viral suppression. These data suggest an important immunomodulatory role of vitamin D in HIV and should be further investigated as an adjuvant treatment to antiretroviral therapy.



860 SCD163, T CELL ACTIVATION AND HIV PROGRESSION IN PERINATALLY INFECTED HIV+ CHILDREN

Matthew Generoso[1], Patricia Alvarez[1], Adam Kravietz[1], Mussa Mwamzuka[2], Fatma Marshed[2], Aabid Ahmed[2], Alka Khaitan[1]
[1]New York University Langone Medical Center, New York, NY, USA, [2]Bomu Hospital, Mombasa, Kenya

Background: CD163 is a hemoglobin scavenger receptor on monocytes and macrophages, cleaved to soluble CD163 (sCD163) in the plasma following activation. In HIV+ adults, sCD163 is linked to non-AIDS morbidity and predicts

mortality, but there is limited data in children. We investigated sCD163 levels in HIV+ children and their correlations with intestinal damage, immune activation and disease progression.

Methods: In a Kenyan cohort aged 5-20 years of 77 perinatally-infected HIV+ children, with 44 ART-naive (ART-) and 33 virally suppressed on ART (ART+), and 45 HIV unexposed-uninfected (HIV-) controls, we measured sCD163 and intestinal fatty acid binding protein (I-FABP) plasma levels by ELISA (R&D Systems). T cell activation and proliferation cytokine IL-2 were analyzed by flow cytometry on PBMCs with markers CD4, CD8, CD45RO, CD38, HLA-DR, and IL-2. Statistical analysis was performed on GraphPad Prism with Kruskall-Wallis, Spearman's correlation, and Wilcoxon tests.

Results: ART- children have high sCD163 levels compared to HIV- (p=0.004) and ART+ (p=0.01) children, that decrease after 12 months of ART (p=0.02) to levels similar to HIV- controls. ART+ and HIV- children have equivalent sCD163 levels. In HIV+ children, sCD163 levels correlate with HIV disease progression indicated by %CD4 T cells, (p=0.0002, r=-0.41), HIV viral load (p<.0001, r=0.65), and CD4:CD8 T cell ratios (p=0.001, r=-0.36). sCD163 also associates with I-FABP, a marker of gut mucosal disruption (p=0.005, r=0.32). sCD163 correlates with CD4 and CD8 T-cell activation measured by CD38 and HLA-DR coexpression (CD4: p<0.0001, r=0.50; CD8: p=0.001, r=0.36) in HIV+ but not in HIV- children. Finally, there is an indirect correlation between sCD163 and IL-2+ memory CD4 T cells (p=0.0003, r=-0.42).

Conclusion: Untreated HIV+ children have elevated sCD163 levels that normalize with ART. Elevated sCD163 levels correlate with advancing HIV disease, marked by increasing viral load and decreasing %CD4 and CD4:CD8 ratios. Compromised gut barriers and microbial translocation may trigger sCD163 release, as sCD163 directly associates with I-FABP. In HIV+ children, sCD163 strongly correlates with T cell activation, linking inflammation in the innate and adaptive immune systems. Last, the inverse correlation between sCD163 and IL-2 suggests a potential inhibitory role for sCD163 on T cell proliferation. Overall, high sCD163 levels in HIV+ children reflect gut mucosal disruption, global inflammation and disease progression.

861 VIROLOGIC RESPONSE TO ANTIRETROVIRAL THERAPY STARTED AT <12 WEEKS OF AGE

Victoria Iyun[1], Karl Technau[2], Brian Eley[1], Helena Rabie[3], Andrew Boulle[1], Geoffrey Fatti[4], Frank Tanser[5], Robin Wood[6], Lee Fairlie[7], Mary-Ann Davies[1]
[1]University of Cape Town, Cape Town, South Africa, [2]University of the Witwatersrand, Johannesburg, South Africa, [3]Stellenbosch University, Stellenbosch, South Africa, [4]Kheth'Impilo, Cape Town, South Africa, [5]University of KwaZulu-Natal, Durban, South Africa, [6]Desmond Tutu HIV Foundation, Cape Town, South Africa, [7]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa

Background: With recent shifts towards widespread effective prevention of mother-to-child transmission (PMTCT) coverage, and HIV birth testing implementation in South Africa allowing for initiation of antiretroviral therapy (ART) in the first weeks of life, the virologic and immunologic response of infants started on ART at <3 months of age may be different to previous periods. Evidence from large cohorts of infants receiving early ART outside of clinical trial environments is limited. We described the changes in virologic and immunologic outcomes during the first 6 months on ART according to time period of ART initiation.

Methods: We analysed data from a retrospective cohort of HIV-infected infants who started ART aged <12 weeks from 2006-2016 at 8 South African sites within IeDEA-SA, and had ≥1 viral load (VL) measurement between 4-9 months on ART. Descriptive statistical analysis and logistic regression were conducted to describe viral suppression at 6 months on ART and identify determinants. We defined viral suppression as VL <400 copies/ml (cpm) and compared VL outcomes of infants who initiated ART in 2006-2009, 2010-2012 and ≥ 2013.

Results: Of 710 HIV-infected infants included, 56% were female, median age at ART initiation was 9 weeks (Interquartile range (IQR): 5-11), median $\log_{10}$ VL and CD4% were 5.86 (IQR: 4.8-6.4) cpm and 26.4 (IQR 18.6-37) respectively. The proportion of infants that achieved viral suppression by 6 months on ART decreased from 66% in 2006-09 to 50% in 2013-16 (P<0.015) and from 78% in 2006-09 to 58% in 2013-16 among 410 infants with additional VL measured at 12 months on ART. Median CD4 count by 6 months on ART was increased slightly among infants starting ART in 2013-16 vs. in earlier years (2096 vs. 1588 cells/mm^3, p<0.001). VL >1 million cpm and ART initiation ≥2013 were associated with lower odds of viral suppression at 6 months on ART (adjusted Odds Ratio (aOR): 0.43; 95% CI: 0.24-0.75 and aOR: 0.33; 95% CI: 0.18-0.61, respectively).

Conclusion: Poorer virologic suppression in infants who initiated ART ≥ 2013 compared to earlier years is a major concern, especially as infants starting in recent years had higher CD4% and lower VL at ART initiation. Further research is needed to understand reasons for worse VL outcomes in recent years. Ongoing monitoring of these infants is crucial to determine the long-term impact of poorer early viral suppression.

Table 1: Predictors of viral suppression (<400 copies/ml) during the first 6 months of ART (N=542)

Characteristics	Unadjusted Odds Ratio			Adjusted Odds Ratio		
	OR	95% CI	p-value	AOR	95% CI	p-value
Age						
< 1month	Ref.			Ref.		
1-2 months	0.72	0.48-1.06	0.102	0.80	0.46-1.39	0440
2-3 months	0.67	0.47-0.98	0.039	0.82	0.48-1.41	0.494
ART initiation year						
2006 - 2009	Ref.			Ref.		
2010 - 2012	0.65	0.43-0.96	0.034	0.91	0.38-1.04	0.725
>2013	0.53	0.36-0.78	0.001	0.43	0.23-0.61	0.002
Viral load (copies/ml)						
<100,000	Ref.			Ref.		
100,000 - 1million	0.76	0.48-1.20	0.253	0.62	0.38-1.04	0.072
>1million	0.51	0.33-0.77	0.001	0.38	0.23-0.61	0.000

862 MATERNAL ANTIRETROVIRAL THERAPY IN PREGNANCY AND NEONATE PRETREATMENT VIRAL LOAD

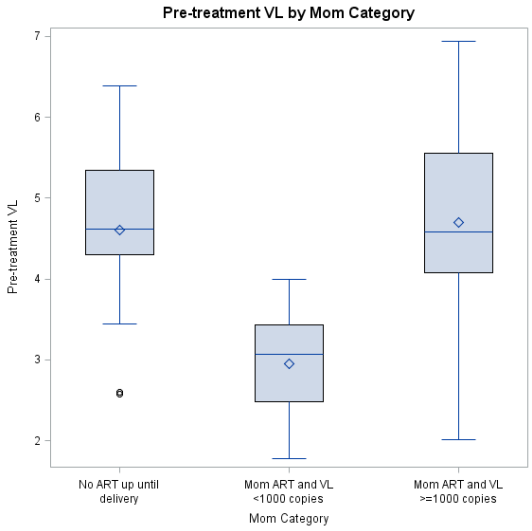
Faeezah Patel[1], **Stephanie Shiau**[2], Renate Strehlau[1], Megan Burke[1], Maria Paximadis[3], Sharon Shalekoff[3], Diana Schramm[3], Caroline Tiemessen[3], Elaine J. Abrams[2], Louise Kuhn[2]
[1]Empilweni Service and Research Unit, Johannesburg, South Africa, [2]Columbia University, New York, NY, USA, [3]National Institute for Communicable Diseases, Johannesburg, South Africa

Background: With expansion of effective maternal antiretroviral therapy (ART), rates of new infant HIV infections are low but a large proportion of infected infants are exposed to antiretrovirals before birth. We investigated relationships between maternal ART in pregnancy and pre-treatment (PT) viral load (VL) profiles in intrauterine-infected neonates.

Methods: Between June 2014-September 2017, 79 neonates with confirmed HIV-infection were identified through a birth testing program at Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa, and had a PT VL available in the neonatal period (28 days of life). VL was measured using the COBAS AmpliPrep/COBAS TaqMan HIV-1 test, v2.0 (Roche). Maternal VLs were measured during late pregnancy, at delivery or soon thereafter using the same assay. Other clinical characteristics were obtained through examination and record review.

Results: Of the 79 intrauterine-infected neonates, 51.9% were female, mean birthweight was 2,843±565 grams and 88.6% were ≥37 weeks of gestation. 13.9% of mothers first learned their HIV status during admission for this delivery, 57% during this pregnancy, and 29.1% prior to this pregnancy. 18% of mothers received no ART before delivery, 37.2% <12 wks and 28.2% >12 wks of ART. All infants were given NVP prophylaxis prior to diagnosis. Neonate PT VL was measured at a median of 1 day (IQR: 1-6) with a median of 28,405 copies/ml (cpm) (IQR: 2,020-224,515) and 20.3% had a VL<1,000 cpm. Neonate PT VL was correlated with maternal VL (r=0.53, p<0.01). Neonate PT VL was significantly (p<0.01) lower (median 1,172 cpm) among those whose mothers received ART and had a maternal VL<1,000 cpm than among those whose mothers reported receipt of ART but with VL>1,000 cpm (median 38,400 cpm) or among those whose mothers had received no ART (median 42,542 cpm). Among neonates with PT VL<1,000 cpm, 47% had mothers on ART with maternal VL<1,000 cpm compared to 15% among neonates with PT VL>1,000 cpm (p=0.04).

Conclusion: PT VL in these intrauterine-infected neonates was lower than expected and correlated with maternal VL. Most (>80%) mothers received ART during pregnancy and for those whose adherence with and duration of ART led to VL<1,000 cpm, the lowest neonate PT VLs were observed. Maternal ART during pregnancy may begin treatment of intrauterine infection.



863 T AND B CELL RESPONSES ASSOCIATE WITH SMALLER HIV RESERVOIR SIZE IN INFANTS AFTER ART

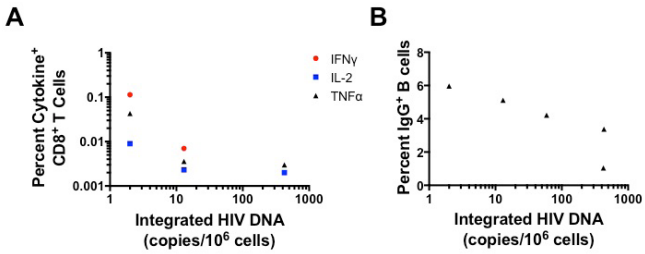
Julie Mitchell[1], Marta Massanella[2], Thanyawee Puthanakit[3], Pope Kosalaraksa[4], Piyarat Suntarattiwong[5], Suparat Kanjanavanit[6], Rawiwan Hansudewechakul[7], Thitiporn Borkird[8], Thidarat Jupimai[3], Panadda Sawangsinth[9], Mark de Souza[9], Nicolas Chomont[2], Jintanat Ananworanich[1], Lydie Trautmann[1]
[1]US Military HIV Research Program, Silver Spring, MD, USA, [2]Centre de Research du Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada, [3]HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [4]Khon Kaen University, Khon Kaen, Thailand, [5]Queen Sirikit National Institute of Child Health, Bangkok, Thailand, [6]Nakornping Hospital, Chiang Mai, Thailand, [7]Chiang Rai Prachanukroh Hospital, Chiang Rai, Thailand, [8]Hat Yai Hospital, Songkhla, Thailand, [9]SEARCH, Bangkok, Thailand

Background: The infant immune system is characterized by reduced HIV-specific immune responses, resulting in an inability to control HIV viremia. We investigated the activation and maturation of T and B cells in HIV+ infants before and after successful antiretroviral therapy (ART).

Methods: Nine HIV-infected Thai infants were included: 4 virally non-suppressed at baseline, either pre-ART (n=2) or on ART 3 weeks (median 4 mo old, range 3-5 mo), and 5 successfully treated for a median of 12 months (range 10-14 mo; median 16 mo old, range 13-19 mo). Comparisons were made with 11 acutely infected Thai adults in RV254 before or after 48 weeks of ART (n=7 and 4, respectively). Integrated HIV DNA levels in CD4 T cells were quantified by ultrasensitive PCR. CD19+CD20+ B cells and CD45RA– CD8 T cells were analyzed by flow cytometry. HIV-specific cytokine production was measured in expanded CD8 T cell lines activated by B-EBV cells pulsed with 74 dominant CRF01_AE HIV peptides.

Results: Despite successful viral suppression, frequencies of activated (CD38+HLA-DR+) and proliferating (Ki-67+bcl-2lo) CD8 T cells remained elevated in infants after one year of ART (median 6.3% and 16.2%, respectively), and were higher than those measured in adults after early ART (2.3%, p=0.05; 2.9%, p=0.02, respectively). HIV DNA levels negatively correlated with HIV specific cytokine production after ART, suggesting that CD8 T cell responses are associated with a smaller HIV reservoir size (Panel A). Infants had immature B cell compartments compared to adults at baseline, with high frequencies of IgD+ (98.6% vs 46.2%) and immature transitional B cells (CD27–CD21–CD10+, 9.9%), together with extremely low frequencies of IgG+ B cells (0.3% vs 22.3%). At baseline, the frequency of immature transitional B cells tended to positively correlate with HIV DNA levels (r=1, p=0.08). Infants had HIV DNA levels that negatively correlated with the frequency of IgG+ B cells after one year of ART (r=-0.9, p=0.08, Panel B), suggesting that B cell maturation is also associated with a smaller HIV reservoir size.

Conclusion: Elevated frequencies of IgG+ B cells and Ki-67+bcl-2lo CD8 T cells in infants after one year of ART reflect maturation and persistent activation of the immune system. After ART, HIV DNA levels correlated with both the HIV-specific cytokine production by CD8 T cells and the percentage of IgG+ B cells. These data suggest that functional cellular immune responses in HIV infected infants aid in controlling the HIV reservoir size.



864 FACTORS ASSOCIATED WITH HIV DNA LEVELS IN CHILDREN STARTING ART EARLY IN INFANCY

Man Chan[1], Alfredo Tagarro[2], Paola Zangari[3], Bridget Ferns[1], Caroline Foster[4], Anita De Rossi[5], Eleni Nastouli[6], M Ángeles Muñoz-Fernández[7], Diana Gibb[1], Paolo Rossi[3], Carlo Giaquinto[5], Abdel Babiker[1], Paolo Palma[3], Pablo Rojo Conejo[2]
[1]University College London, London, UK, [2]Hospital Universitario 12 de Octubre, Madrid, Spain, [3]Bambino Gesu Children's Hospitalital, Rome, Italy, [4]Imperial College Healthcare NHS Trust, London, UK, [5]University of Padova, Padova, Italy, [6]UCL Great Ormond Street Institute of Child Health, London, UK, [7]University Hospital Gregorio Marañon, Madrid, Spain

Background: Future strategies aimed at achieving ART-free HIV remission are likely to target individuals with low levels of HIV-1 DNA who started ART early. We investigated factors associated with HIV-1 DNA levels in children starting ART in early infancy.

Methods: 51 children with perinatal HIV aged<6 months at start of NNRTI or PI-based ART were included from 5 European sites (1 UK, 2 Spain, 2 Italy). Total HIV-1 DNA was measured in isolated PBMCs 6.3 years (median) after initial viral suppression (≥2 consecutive VL<50), whilst suppressed. Factors associated with $\log_{10}$ total HIV-1 DNA were analysed using linear regression. Backward elimination was applied to reach the final multivariable model.

Results: 55% children were female, 29% had previous AIDS diagnosis (73% diagnosed before or at ART start), 16% were from UK, 31% Spain and 53% Italy. At ART initiation, children were aged median [IQR] 2.3 [1.2,4.1] months, CD4% 37 [24,45]%, CD8% 28 [18,36]%, $\log_{10}$VL 5.4 [4.4,5.9] copies/ml. Median age at HIV-1 DNA determination was 7.3 [4.2,10.9] years. Time to viral suppression was 7.98 [4.6,19.3] months and following suppression, 13 (25%) children had suboptimal response [≥2 consecutive VL50-400 followed by VL<50] and/or experienced periods of viral failure [≥2 consecutive VL≥400 followed by VL<50]. Total HIV-1 DNA was 43 [6,195] copies/10^6 PBMC. In multivariable analysis, lower total HIV-1 DNA was associated with younger age at ART start, higher proportion of time spent virally suppressed and absence of viral failure/suboptimal response (Table 1). Although there was suggestive evidence for an association with baseline immunological data (CD4, CD4/CD8 ratio and total lymphocyte; P=0.05-0.10) and AIDS diagnosis (P<0.05), these associations failed to reach significance after adjustment. Effect of site remained significant with highest total HIV-1 DNA values in UK and Rome. Sensitivity analyses (excluding 5 children with viral failure or 6 who took ≥3 years to suppress) produced similar results.

Conclusion: Our study show that even among children initiating ART<6 months of age, starting ART earlier, spending a higher proportion of time suppressed and absence of viral failure/suboptimal response was linked with lower total HIV-1 DNA. Our findings support early ART start and adherence support in children as a strategy to minimise the size of viral reservoir. Future larger independent studies will be required to confirm results.

Table 1. Factors associated with total HIV-1 DNA

Factors	All children (N=51)						
	Univariable Models				Multivariable Model[a]		
	N	% Diff	β (95% CI)	P-value	% Diff	β (95% CI)	P-value
Age at ART start (per month older)	51	27.7	0.24 (0.14 , 0.35)	**2.15E-05**	12.7	0.12 (0.03 , 0.21)	**0.0091**
Age at HIV DNA measure (per year older)	51	5.3	0.05 (0.00 , 0.10)	**0.0395**	---	---	---
Duration of ART (per year longer)	51	5.0	0.05 (-0.00 , 0.10)	0.0528	---	---	---
Proportion of time suppressed (per 10% higher)[#]	50	-3.5	-0.04 (-0.13 , 0.06)	0.4454	-9.9	-0.10 (-0.17 , -0.04)	**0.0022**
Time to VL response (per month longer)[#]	50	0.2	0.00 (-0.01 , 0.01)	0.6976	---	---	---
Previous AIDS Diagnosis	48						
Yes [Ref: No]	15	93.2	0.66 (0.20 , 1.11)	**0.0054**	---	---	---
Composite: Fail/Suboptimal Response	51						
Yes [Ref: No]	13	55.0	0.44 (-0.05 , 0.92)	0.0758	40.1	0.34 (0.00 , 0.67)	**0.0483**
Baseline immunological data							
CD4 count (per 500 cells higher)	27	-8.7	-0.09 (-0.18 , 0.00)	0.0541	---	---	---
CD4% (per 10% higher)	41	-13.2	-0.14 (-0.29 , 0.01)	0.0625	---	---	---
CD4/CD8 ratio (per unit higher)	36	-19.0	-0.21 (-0.42 , -0.00)	**0.0479**	---	---	---
Total lymphocyte (per 500 cells higher)	27	-4.3	-0.04 (-0.09 , 0.00)	0.0678	---	---	---
Site [Ref: Italy: Rome (15)]	51						
UK: CHERUB-YC/CHIPS	8	43.1	0.36 (-0.19 , 0.90)	0.1934	29.5	0.26 (-0.17 , 0.69)	0.2326
Spain: CORISPE-CAT	6	-49.5	-0.68 (-1.29 , -0.08)	**0.0270**	-38.6	-0.49 (-0.97 , -0.01)	**0.0468**
Spain: MADRID	10	-64.1	-1.02 (-1.53 , -0.52)	**0.0002**	-68.3	-1.15 (-1.59 , -0.71)	**4.696E-06**
Italy: PADOVA	12	-46.2	-0.62 (-1.10 , -0.14)	**0.0130**	-59.6	-0.91 (-1.30 , -0.51)	**3.118E-05**

[a]Criteria for inclusion into the multivariable model: univariable model p-value<0.10 or defined a priory[#]
β, regression coefficient estimates; **95% CI**, confidence interval; **% Diff**, % difference in HIV-1 DNA: a unit change in factors investigated is associated with a Y% change in HIV-1 DNA.

865 EARLY CMV AND EBV ACQUISITION PREDICTS HIV DNA LEVELS IN INFANTS ON SUPPRESSIVE ART

Jennifer Slyker[1], Brandon Guthrie[1], Mark D. Pankau[1], Dalton Wamalwa[2], Sarah Benki-Nugent[1], Meei-Li Huang[1], Grace John-Stewart[1], Julie Overbaugh[3], Dara Lehman[1]
[1]University of Washington, Seattle, WA, USA, [2]University of Nairobi, Nairobi, Kenya, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: Defining modifiable factors associated with HIV reservoir size may inform novel interventions to enable post-treatment control of HIV infection. HIV-infected infants in Africa often acquire cytomegalovirus (CMV) and Epstein-Barr virus (EBV) within a few weeks of HIV; primary infection with each of these initiates dramatic changes in immune activation and could impact HIV reservoir formation. We assessed the association between the timing of CMV and EBV infection and levels of plasma viremia with cell-associated HIV DNA (ca-DNA) in children with HIV RNA suppression after 2 years of ART.
Methods: The study was nested into the Optimizing HIV Treatment (OPH) study (NCT00428116). All children started ART at HIV diagnosis, at <6 months of age, and had no prior ART. CMV and EBV DNA were measured in plasma using quantitative real time PCR at enrollment and quarterly thereafter; EBV serology was conducted in EBV-negatives at 24 months. HIV ca-DNA was measured using digital droplet PCR from PBMC at 24 months post-ART in children with at least 6 months of HIV RNA suppression. Linear regression was used to determine the association of the timing of CMV and EBV infection, and cumulative CMV and EBV viremia (area-under-the-curve, AUC over the first 21 months of ART) with the level of HIV ca-DNA at 24 months post ART.
Results: A total of 23 infants were evaluated; 21 (91%) had CMV and 21 (91%) had EBV infection, only 1 child remained both CMV and EBV-uninfected. CMV detection at enrollment (p=0.01), duration of EBV infection (p=0.02) and EBV AUC (p=0.006) were associated with $\log_{10}$ HIV ca-DNA at 24 months. Pre-ART CD4% and HIV RNA level were not associated with HIV ca-DNA level, but there was a trend association between later ART initiation and higher HIV ca-DNA level (p=0.1). Adjusting for age at ART, CMV infection at enrollment (p=0.02), longer duration of EBV infection (p=0.02), and higher EBV AUC (p=0.01) were independently associated with higher HIV ca-DNA level. Baseline HIV RNA level was not associated with CMV or EBV AUCs (p>0.05 for each), but lower baseline CD4% was associated with higher EBV AUC (coeff=-7.6 [-12, -2.7], p=0.004). CMV and EBV AUCs were not significantly correlated (coeff=0.020, p=0.9).
Conclusion: Early acquisition of CMV and EBV, and higher cumulative exposure to systemic EBV DNA replication are associated with higher HIV DNA levels in early-treated infants with HIV RNA suppression. Understanding the basis of this association may reveal novel paths to limit the HIV reservoir.

Table. Predictors of $\log_{10}$ HIV ca-DNA level at 24 months post ART.

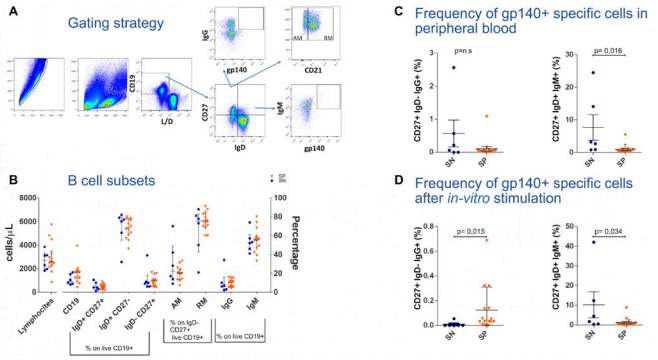
	Univariate		Adjusted for age at ART	
	Coefficient [95%CI]	P value	Coefficient [95%CI]	P value
Age at ART initiation	0.17 [-0.040, 0.38]	0.1		
Baseline $\log_{10}$ HIV RNA	0.037 [-0.23, 0.30]	0.8		
Pre-ART CD4 percent	-0.0075 [-0.032, 0.017]	0.5		
CMV infected at enrollment	0.56 [0.13, 1.0]	0.01	0.52 [0.092, 0.95]	0.02
CMV DNA AUC	0.000034 [-0.00031, 0.00038]	0.8		
Duration of EBV infection*	0.023 [0.0046-0.042]	0.02	0.022 [0.0039, 0.040]	0.02
Log_{10} EBV DNA AUC	5.5 [1.7-9.3]	0.006	5.0 [1.19, 8.8]	0.01

*To include EBV-negatives, duration of EBV infection was calculated as [24 months]-[age EBV first detected]

866 HIV SPECIFIC IGM MEMORY B CELLS DOMINATE IN SERONEGATIVE EARLY-TREATED CHILDREN

Nicola Cotugno[1], **Elena Morrocchi**[2], Ilaria Pepponi[1], Salvatore Rocca[2], Mark Cameron[3], Stefano Rinaldi[4], Silvia Di Cesare[2], Suresh Pallikkuth[4], Stefania Bernardi[1], Nigel Klein[5], Jintanat Ananworanich[6], Paolo Rossi[1], Savita Pahwa[4], Paolo Palma[1]
[1]Bambino Gesu Children's Hospitalital, Rome, Italy, [2]University of Rome Tor Vergata, Rome, Italy, [3]Case Western Reserve University, Cleveland, OH, USA, [4]University of Miami, Miami, FL, USA, [5]London School of Hygiene & Tropical Medicine, London, UK, [6]US Military HIV Research Program, Silver Spring, MD, USA

Background: Previous reports have shown that early initiation of ART (eART) in HIV+ vertically-infected infants results in loss of HIV antibodies (Ab) presumably due to rapid viral control resulting in short antigenic exposure. Whether HIV-specific memory responses are present in eART seronegative patients is still unknown. The present study investigated frequency and immune characteristics of gp140 specific B cells in seronegative (SN) and seropositive (SP) early-treated (ET) HIV+ children.
Methods: 22 ET vertically-infected children, who initiated ART at a mean age of 4.8±3.7 mo. with durable viral control (mean 7.25±5.2 years, plasma HIV-RNA<50cp/mL) were enrolled at Bambino Gesù Children's Hospital. Plasma samples, tested by Abbott Architect HIV Ag/Ab Combo Assay, defined SN or SP status. Cryopreserved PBMC were stimulated O/N with Envelope (Env) peptides and sCD40L or left unstimulated. PBMCs were then stained for analysis by flow cytometry (gating strategy in panel A). B cells were classified as total memory (CD27+IgD-), naïve (CD27-IgD+), unswitched memory (CD27+IgD+), activated memory (CD27+, IgD-, CD21-) and resting memory (CD27+, IgD-, CD21+). B-cell Fluorospot was performed to simultaneously detect IgM and IgG responses to gp160 and gp120.
Results: 6 out of 22 (27.3%) children resulted SN. No differences in B cell subsets were observed between the SN and SP group (panel B). Although frequencies of antigen specific CD19+ gp140+ B cells resulted similar in both groups, SN children presented a higher frequency of HIV-specific IgM memory (CD27+,IgD+) B cells (p=0.016) compared to SP in the peripheral blood (panel C). These data were further confirmed by Fluorospot assay where IgM response to Env-Ags gp160 (p= 0.008) and gp120 (p=0.024) was found higher in SN compared to SP group. Moreover, in vitro stimulation revealed a predominant IgM memory HIV-specific B cell response in SN (p=0.034), while the IgG total memory (gp140+, CD27+, IgD-) response was found higher in SP (p=0.015; panel D).
Conclusion: These data suggest that HIV-specific responses in seronegative patients resides in IgM memory B cells. IgM memory responses were recently reported to be rapid and functional in the context of other infectious diseases (Krishnamurty et al., 2016, Immunity). It is still unknown whether such responses could be targeted by new disease modifying strategies in order to achieve viral remission in HIV+ early treated children.



867 INTESTINAL DAMAGE AND INFLAMMATION IN PERINATALLY HIV-1-INFECTED AFRICAN INFANTS

Wei Li A. Koay[1], Jane Lindsey[2], Priyanka Uprety[3], Mutsa Bwakura-Dangarembizi[4], Adriana Weinberg[5], Myron Levin[5], Deborah Persaud[1]
[1]Johns Hopkins Hospital, Baltimore, MD, USA, [2]Harvard University, Cambridge, MA, USA, [3]University of Pennsylvania, Philadelphia, PA, USA, [4]University of Zimbabwe, Harare, Zimbabwe, [5]University of Colorado Denver, Denver, CO, USA

Background: Heightened inflammation and immune activation are features of HIV-1 infection, for which impaired intestinal integrity with microbial translocation are implicated. We compare markers of gut integrity and inflammation in perinatal HIV-1 infection.

Methods: We compared plasma levels of intestinal barrier markers (iFABP and zonulin) in HIV-1-infected (HIV+) infants and HIV-1-exposed uninfected (HEU) African infants enrolled in a clinical trial (IMPAACT P1072) of rotavirus vaccine (RotaTeq™). In prior analyses, significantly higher levels of sCD14, IFNγ, IL1-β, IL-2, IL-6 and IL-10 were found in the HIV+ vs. HEU infants. iFABP and zonulin were measured pre-vaccine and after the last vaccine (PD3). Categorical variables were compared by Fisher's exact test and continuous variables by Wilcoxon rank sum tests. Spearman correlations and linear regression (log_{10} scale) were used to compare levels by HIV-1, breastfeeding and vaccine received.

Results: This analysis includes 56 HIV+ (ART-treated) and 53 HEU infants of similar age and breastfeeding status (Table 1). At entry, HIV+ had lower WHO weight-for-age Z (WAZ) scores and CD4% than HEU infants. iFABP levels did not differ significantly by HIV-1 status. In HIV+ infants, iFABP levels did not significantly correlate with viral load, CD4%, sCD14 and WAZ scores, but positively correlated with IL-6 (r=0.3, p=0.03) and was lower in breastfed infants. iFABP levels did not change by PD3 and did not correlate with serum anti-rotavirus IgA PD3. Zonulin levels at entry did not differ significantly by HIV-1, breastfeeding, or WAZ scores, and levels in HIV+ did not associate with CD4% or sCD14, but negatively correlated with viral load (r=-0.28, p=0.045) and IL-10 (r=-0.32, p=0.02). In contrast, to iFABP, between entry and PD3, zonulin levels in HIV+ increased compared to a decrease in HEU (p=0.010). In HEU infants, zonulin levels positively correlated serum anti-rotavirus IgA PD3 (r=0.48, p=0.014).

Conclusion: Despite higher levels of inflammation and immune activation in HIV+ compared with HEU at entry, iFABP and zonulin levels did not differ, suggesting alternate mechanisms for HIV-associated inflammation and immune activation in perinatal HIV-1 infection. Across both groups, iFABP was significantly lower in breastfed infants and zonulin differentially increased in HIV+ but decreased in HEU infants by PD3. Changes in zonulin in HIV+ over time may imply the loss of tight junction regulation in perinatal HIV-1 infection despite early ART.

	Pre-vaccine or study entry			Post-dose 3 (PD3)		
	HIV+ (n=56)	HEU (n=53)	p-value[1]	HIV+ (n=55)	HEU (n=53)	p-value[1]
Age (days) Median (Q1, Q3)	93 (89, 96)	92 (79, 96)	0.29			
Ever breast-fed N (%)	37 (66%)	36 (68%)	<0.99			
CD4% Median (Q1, Q3)	30 (23, 37)	36 (32, 41)	<0.001			
WAZ Median (Q1, Q3)	-1.4 (-2.4, -0.2)	-0.6 (-1.2, -0.1)	0.005			
HIV RNA >400 copies/ml N (%)	49 (92%)					
iFABP (pg/ml) Median (Q1, Q3) (Breastfed and not breastfed)	1392 (852, 1939)	1114 (711, 1461)	0.15	981 (632, 1782)	1025 (685, 1464)	0.97
Breastfed	1077 (709, 1659) (n=37)	1015 (532, 1299) (n=36)		838 (593, 1291) (n=36)	881 (554, 1163) (n=36)	
Not breastfed	1875 (1378, 2886) (n=19)	1989 (1114, 2721) (n=17)		1500 (785, 1872) (n=19)	1476 (1020, 2893) (n=17)	
p-value[2]	0.005	<0.001		0.03	0.001	
Zonulin (ng/ml) Median (Q1, Q3) (Breastfed and not breastfed)	24 (13, 33)	25 (17, 30)	0.77	27 (19, 38)	22 (17, 28)	0.018

Table 1. Study population characteristics pre-vaccine and after the last vaccine dose (PD3)
[1] Wilcoxon rank sum test (continuous) and Fisher's exact test (categorical) comparing HIV+ to HEU
[2] Wilcoxon rank sum test comparing iFABP levels between breastfed and non-breastfed infants within HIV-1 status

868 LASTING IMMUNE IMPACTS OF AGE AT START OF ART IN VERTICALLY HIV-INFECTED ADOLESCENTS

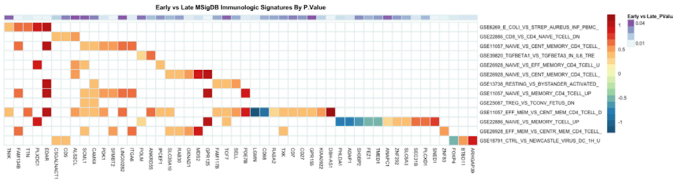
Mark Cameron[1], Stefano Rinaldi[2], Brian Richardson[1], Nicola Cotugno[3], Sion Williams[2], Suresh Pallikkuth[2], Lesley R. de Armas[2], Cheryl Cameron[1], Rajendra Pahwa[2], Paolo Palma[3], Savita Pahwa[2]
[1]Case Western Reserve University, Cleveland, OH, USA, [2]University of Miami, Miami, FL, USA, [3]Bambino Gesu Children's Hospitalital, Rome, Italy

Background: Timely implementation of antiretroviral therapy (ART) in vertically HIV-infected children provides an opportunity to limit the size of reservoir, but whether time of ART treatment initiation can durably impact host immune responses associated with establishment of infection is unknown. We analyzed HIV-specific CD4 T cell functionality along with host transcriptome analysis in young adults who were vertically HIV-infected and initiated ART earlier or later after birth.

Methods: PBMCs were collected from HIV-infected donors between 9-15 Y of age enrolled at Bambino Gesù Children's Hospital. Three groups of donors (n=5-6/group) were profiled via RNA-Seq: (i) Early Treated (ET): Age at ART 0-0.5 Y, (ii) Late Treated (LT): Age at ART 1-12 Y, and (iii) HIV negative controls. All HIV-infected donors had been suppressed for plasma HIV. Low input libraries were generated using Kapa RNA Hyper library kits and sequenced on an Illumina NextSeq500 (75 bp, paired-end, 40 million reads/sample). Differentially expressed genes (DEG) were found by two-group t test (P≤0.05) and organized into top pathways by P value (P≤0.05) via gene set variation analysis (GSVA) in R Bioconductor. Antigen-specific CD40L+ CD4 T cells were evaluated by flow cytometry for intracellular cytokines (IL2, IFNG, TNFA, IL21) following 18hrs stimulation with gp140.

Results: We found that a T cell signaling DEG signature could distinguish ET and LT despite current age. Through GSVA, this signature was ascribed to differences seen in naïve vs central or effector CD4 memory T cell datasets (see figure). Regression analysis revealed that different patterns of T cell signaling pathway DEG correlated with age of ART initiation, % of naïve, central memory, effector memory T cells, and NK cells, e.g. CXCL9/10, GZMA/B, TNFSF8/10/14, and CD160/244. CD4 T cell functional profiles also differed in ET versus LT in that ET showed increased frequencies of gp140-specific polyfunctional CD4 T cells dominated by IL2 production whereas response in LT was paucifunctional. Interestingly, the frequency of gp140sp CD4+ T cells was the same between ET and LT.

Conclusion: Our results suggest that delayed ART initiation in HIV-infected children has a long-term impact on host T cell memory distinguishable by a candidate DEG signature and HIV-specific T cell immune responses. Larger studies are warranted to assess these novel profiles of host immunity in vertically HIV-infected children under ART and whether they can be targeted in functional cure approaches.



Pathway analysis of 1,328 differentially expressed genes by contrast of early vs late start of ART in adolescents who were vertically infected with HIV. Top enriched pathways (source: MSigDB Immunologic Signatures Database) by P value are shown vertically (P≤0.05) along with their populating genes (all P≤0.05, top row) and gene expression on the horizontal (Red = upregulated at earlier start of ART vs late, blue = downregulated). Note that the candidate T cell gene expression signature that distinguishes early vs later start of ART in PBMCs at adolescence can therefore also be found in immunophenotyping studies published at the Gene Expression Omnibus involving naïve vs effector and central memory CD4 T cell signaling.

869 DECREASED DIARRHEAL AND RESPIRATORY DISEASE IN HEUS FOLLOWING RV AND PCV VACCINATION

Gbolahan Ajibola[1], Kara Bennett[2], Kathleen M. Powis[3], Michael D. Hughes[4], Jean Leidner[5], Samuel W. Kgole[1], Kerapetse Botebele[1], Oganne Batlang[1], Chipo Petlo[6], Mompati O. Mmalane[1], Joseph Makhema[1], Shahin Lockman[7], Roger L. Shapiro[4]

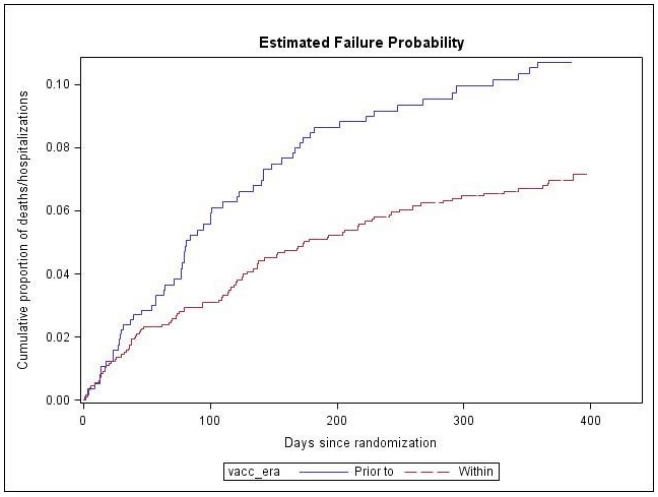
[1]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [2]Bennett Statistical Consulting, Inc, New York, NY, USA, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Harvard University, Cambridge, MA, USA, [5]Goodtables Data Consulting, Norman, OK, USA, [6]Ministry of Health, Gaborone, Botswana, [7]Brigham and Women's Hospital, Boston, MA, USA

Background: Rotavirus vaccine (RV) and pneumococcal vaccine (PCV) decrease diarrheal and respiratory disease incidence and severity, but their impact has not been studied among HIV-exposed uninfected (HEU) children. We assessed the impact of the introduction of RV and PCV vaccination among HEU children in Botswana.

Methods: We recorded RV and PCV vaccination history in HEU infants enrolled 2011-2015 in a double-blind, randomized placebo-controlled trial that studied the effect of cotrimoxazole (CTX) on mortality in HEU children at 3 sites in Botswana. We categorized infants into those enrolled before or after the Botswana government's simultaneous April 2012 introduction of RV and PCV (given at 2, 3 and 4 months of age). We then compared grade 3 or 4 diarrhea and pneumonia diagnoses, hospitalizations, and deaths from the time of randomization to CTX/placebo (14-34 days) through the 12 months study visit (365 + 45days) by vaccine era (before or after April 2012). Kaplan-Meier survival estimates were used to estimate the cumulative incidence of events in the two study eras.

Results: Of 2848 HEU children included in this analysis, 687 (24%) were born in the pre-vaccine era and 2161 (76%) were born in the vaccine era; 49 (7%) children in the pre-vaccine era received either RV or PCV vaccine and 184 (9%) children in the vaccine era did not receive either vaccine. The estimated proportion with a grade 3 or 4 diagnosis of diarrhea by age 12 months was 17.2% in the pre-vaccine era and 7.8% in the vaccine era (difference -9.4%, 95% CI -12·5, -6·3%). The estimated proportion with a grade 3 or 4 diagnosis of pneumonia by age 12 months was 4.7% in the pre-vaccination era and 2.1% in the vaccination era (difference -2.6%, 95% CI -4.3 to -0.9%). A significant difference was also observed for the composite endpoint of hospitalization or death from diarrhea or pneumonia, with estimated proportions of 10.7% in the pre-vaccination era and 7.2% in the vaccination era (difference -3.5%, CI -6.1, -1.0%) (Figure). Differences between eras for all events varied significantly among the three sites (diarrhea p<0.001, pneumonia: p=0.10, hospitalization or death for reason of diarrhea or pneumonia p=0.03).

Conclusion: Although temporal confounding cannot be excluded, significant declines in the burden of diarrheal and respiratory illness were observed among HEU children in a large clinical trial in Botswana following the introduction of RV and PCV vaccines, particularly at the most rural study location.



870 PERSISTENT B CELL DEFICIENCY IN HIV-EXPOSED UNINFECTED INFANTS FOLLOWING IMMUNIZATION

Liane S. Sadder[1], Li Yin[2], Kai-Fen Chang[2], Bernard Fischer[1], Maureen Goodenow[3], John W. Sleasman[1]

[1]Duke University, Durham, NC, USA, [2]NIH, Bethesda, MD, USA, [3]NIH, Rockville, MD, USA

Background: HIV-exposed uninfected (EU) infants are candidates for HIV vaccine trials. However, it is unclear if EU infants have similar immune responses when compared to unexposed healthy infants (HI).

Methods: Longitudinal assessment of vaccine responses and plasma biomarkers associated with B cell responses in a cohort of 48 breastfed (BF) or formula fed (FF) HI were compared to 10 EU infants. Comparisons among groups for vaccination titers to B. pertussis, H. flu, Hep B, and tetanus measured in cord blood samples (CB), 6, and 12 months of age by ELISA. Plasma biomarkers included APRIL, BAFF, sCD163, sCD40L, and IL-10 measured by multiplex ELISA and IgA levels by nephelometry. Statistical comparisons among and within groups used a t test. Regression analysis assessed relationship between vaccine responses and plasma cytokine levels in HI and EU infants.

Results: Post vaccination titers to B. pertussis and tetanus were lower at birth in EU infants as compared to HI (2394 and 6019 U/ml, p= 0.0006, and 99.8 and 383.8 p=0.004, respectively). However, EU infants had higher tetanus titers at 6 and 12 months and higher pertussis titers at 12 months. In contrast, Hep B titers were significantly lower in EU infants compared to HI. Within all groups, CB levels of APRIL, BAFF, sCD40L, and IL-10 were elevated and declined at 6 and 12 months. BAFF levels were lower in EU infants compared to HI in CB, 6 and 12 months (1626, 342, 305 pg/ml vs 7599, 1045, 862 pg/ml, p<0.05). There were no significant differences between EU infants and HI for APRIL, sCD163, sCD40L, IL-10, and IgA. Linear regression analysis showed a negative correlation between CB and 6 month B. pertussis titers in HI (rho= -0.75, p=0.0009) but not in EU infants. There was a strong positive correlation between both APRIL and sCD40L to B. pertussis, tetanus, H flu, and Hep B titers at 12 months in HI (rho > 0.51, p <0.05). However, with the exception of tetanus (rho= 0.73, p= 0.01) this correlation was not evident in EU infants.

Conclusion: Lower CB vaccine titers in EU infants reflects HIV-associated maternal immune suppression. However, while EU infants' vaccine responses are more robust for tetanus and B. pertussis, subtle immune defects were revealed in pro-inflammatory pathways involving BAFF, APRIL and sCD40L. These results indicate persistent B cell developmental defects in EU infants, which may have implications for HIV vaccine trials in this population.

871 INFANT HIV VACCINATION: RELATIONSHIP TO CHILDHOOD VACCINES AND MATERNAL ANTIBODIES

Hannah Itell[1], Erin McGuire[1], Meng Chen[1], Petronella Muresan[2], Sallie Permar[1], Genevieve Fouda[1]

[1]Duke Human Vaccine Institute, Durham, NC, USA, [2]Harvard University, Boston, MA, USA

Background: A pediatric HIV vaccine may be critical to eliminating the 150,000 pediatric HIV infections that occur annually. As previous research has shown

that vaccine co-administration can interfere with elicited immune responses, it is important to evaluate how a potential pediatric HIV vaccine would fit into the current infant immunization schedule. In addition, the impact of maternal antibodies on infant HIV vaccine-elicited response is unknown. The goals of this study were to compare antibody responses to common pediatric vaccines in infant HIV vaccinees and placebo recipients and to evaluate whether maternal antibodies interfere with infant HIV vaccine-elicited antibody responses.
Methods: We developed a pediatric vaccine multiplex assay (PVMA) to measure antibodies against common infant vaccines (HepB, DTaP, rubella, HiB) using minimal sample volume. To verify the PVMA, antibody concentrations in 50 plasma samples determined by PVMA and ELISA were compared. The PVMA was used to measure antibodies in participants from PACTG 230/326 HIV vaccine trials (n=129). To assess the effect of maternal HIV-specific antibodies on HIV vaccine responses, we used a multiplex assay to measure and compare the magnitude of gp120, V1V2, and V3-specific antibodies in vaccine recipients at birth (maternally acquired) and at two post-immunization time points.
Results: Antibody concentrations determined by PVMA and ELISA strongly correlated (r>0.85 for each antigen) and the PVMA demonstrated a high degree of sensitivity and specificity. There was no significant difference in pediatric vaccine antibody concentrations between infant vaccine and placebo recipients (p>0.05). Additionally, there was no correlation between V3 (r=-0.13, p=0.41) or V1V2-specific antibodies (r=0.17, p=0.26) at birth and at peak immunogenicity. Though gp120-specific antibodies at birth and at peak immunogenicity were weakly correlated (r=0.33, p=0.03), likely due to the persistence of maternal antibodies, this correlation was no longer observed 6 months post peak immunogenicity (r=-0.10, p=0.50).
Conclusion: Application of the PVMA to PACTG 230/326 cohorts suggests that there was no interference between the HIV vaccine and other vaccines administered during infancy, supporting the potential to include an HIV vaccine in the infant immunization schedule. We also found no evidence that maternal antibodies interfere with infant HIV vaccine responses. Similar investigations in future trials will inform pediatric HIV vaccine timing and efficacy.

872 GROWTH AND BONE MINERAL ACCRETION IN UGANDAN INFANTS EXPOSED TO MATERNAL HIV AND ART

Florence Nabwire[1], Ann Prentice[1], Matthew M. Hamill[1], Adeodata Kekitiinwa[2], Josaphat Byamugisha[3], Mary G. Fowler[4], Gail R. Goldberg[1]
[1]MRC Elsie Widdowson Laboratory, Cambridge, UK, [2]Baylor College of Medicine Children's Foundation, Kampala, Uganda, [3]Makerere University, Kampala, Uganda, [4]Johns Hopkins Hospital, Baltimore, MD, USA
Background: Initiation of ART in HIV-infected adults is associated with a 2-6% decrease in bone mineral (BM) regardless of ART regimen. Maternal ART may perturb BM mobilisation in the mother during pregnancy and lactation, and/or may directly act on the baby's bone leading to compromised growth/ BM accretion . Lower BM in American and African newborns has been reported following exposure to maternal TDF-based ART. However, there are limited data on infant BM accretion following both in-utero and postpartum exposure to maternal option B+ ART. We compared infant growth and bone mineral accretion between HIV/ART exposed (HEI) and HIV-unexposed infants (HUI).
Methods: HIV-positive (on TDF-3TC-EFV previously ART naïve) and HIV-negative pregnant women were recruited in Kampala, Uganda; and their babies (82 HEI and 72 HUI) were followed at 2 (PP2) and 14 wks of age (PP14). Infant whole body (WB) and lumbar spine (LS) BM content (BMC) was measured by DXA at PP2 and PP14. Body weight (Wt) and length (Lt) were measured and Z-scores generated based on WHO 2006 growth standards. BMC was adjusted for bone area, Wt and Lt. The primary outcome was the difference between the groups in % change (± SE) in infant WB BMC between PP2 and PP14.
Results: Mean gestation was 40.9±1.8 wks and not significantly different between groups. By PP14, the mean duration of exposure to ART was 29.3±5.1 wks. Maternal adherence to ART was >95% and median CD4 count was 403 (IQR 290-528) at PP14. More HEI were exclusively breastfed (EBF) (PP2 82.9% v 58.7%; PP14 86.7% v 66.2%, both p<0.05); showing that the BM accretion was appropriate for achieved infant size. In contrast, HEI had a greater increase in LS BMC (29.5±1.7% v 24.4±1.7%, p<0.05), a difference which remained after size-adjustment (11.4±5.4% v 6.5±5.8%, p<0.05.
Conclusion: These data have shown early slower growth and whole body BM accretion in HEI whose mothers were on option B+ ART compared to HUI in the first 3 mo of life. It is important to determine longer-term infant growth and bone outcomes following exposure to maternal ART in early life.

873 INFLAMMATION, CMV AND THE GROWTH HORMONE AXIS IN HIV-EXPOSED UNINFECTED INFANTS

Ceri Evans[1], Bernard Chasekwa[1], Sandra Rukobo[1], Margaret Ghova[1], Kuda Mutasa[1], Robert Ntozini[1], Jean Humphrey[2], Andrew Prendergast[3]
[1]Zvitambo Institute for Maternal and Child Health Research, Harare, Zimbabwe, [2]The Johns Hopkins University, Baltimore, MD, USA, [3]Queen Mary University of London, London, UK
Background: Stunting (linear growth failure) is of considerable global health importance because it contributes to ±15% of under-5 mortality, impairs neurodevelopment, and reduces economic productivity in adulthood. HIV-exposed uninfected (HEU) infants have more stunting than HIV-unexposed infants, but the causes are uncertain. The growth hormone axis is an important regulator of infant growth through hepatic synthesis of insulin-like growth factor 1 (IGF-1), and may be disrupted by chronic inflammation and acute infections. We hypothesized that inflammation and viral infections disrupt the growth hormone axis in HEU infants, and contribute to linear growth impairment.
Methods: This study used data and stored plasma samples from 243 HEU infants and 100 HIV-unexposed infants recruited to the ZVITAMBO trial in Zimbabwe prior to ART availability. Length was measured at birth, 6 weeks, 3 months and 6 months of age and converted into length-for-age Z-scores (LAZ). Plasma IGF-1, C-reactive protein (CRP) and cytomegalovirus (CMV) viremia were measured at 6 weeks of age by ELISA (IGF-1, CRP) and real-time quantitative DNA PCR (CMV). Unpaired t-tests were used to compare continuous variables and linear regression models were used to determine associations between variables.
Results: Mean IGF-1 concentrations at 6 weeks were significantly lower in HEU compared to HIV-unexposed infants (29.5 vs. 32.6ng/mL; P=0.01). IGF-1 concentrations at 6 weeks were positively correlated with LAZ at 6 weeks, 3 months and 6 months of age, and negatively correlated with CRP (β= -0.84; P=0.03). HEU and HIV-unexposed infants had a similarly high prevalence of CMV viremia at 6 weeks of age (81.4% vs. 74%; P=0.14), but HEU infants had higher mean CMV viral loads (P=0.005). Among infants with CMV viremia, CMV viral loads were inversely associated with IGF-1 concentrations in HEU infants (β= -1.16; P=0.008) but not in HIV-unexposed infants (β = 0.21; P=0.83).
Conclusion: IGF-1 at 6 weeks was associated with subsequent linear growth through 6 months of age. Increased inflammation was associated with lower IGF-1 concentrations, meaning the pro-inflammatory state of HEU infants may be one driver of growth impairment. An inverse relationship between CMV viral load and IGF-1 in HEU infants, but not in HIV-unexposed infants, is consistent with previous findings that suggest poorer handling of viral infections in HEU infants. Targeted interventions for HEU infants may be necessary to reduce stunting and its associated negative effects.

874 METABOLIC OUTCOMES IN OBESE HIV-EXPOSED UNINFECTED CHILDREN: COMPARISON WITH NHANES

Jennifer Jao[1], Denise Jacobson[2], Wendy Yu[2], Matthew McKenna[2], William Borkowsky[3], Mitchell Geffner[4], Rohan Hazra[5], Brad Karalius[2], Elizabeth J. McFarland[6], Kunjal Patel[2], Paige L. Williams[2], Tracie Miller[7]
[1]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [2]Harvard University, Cambridge, MA, USA, [3]New York University, New York City, NY, USA, [4]University of Southern California, Los Angeles, CA, USA, [5]NIH, Rockville, MD, USA, [6]University of Colorado Denver, Denver, CO, USA, [7]University of Miami, Miami, FL, USA
Background: Metabolic perturbations related to obesity in HIV-exposed uninfected (HEU) children may differ from that in the general obese pediatric population due to in utero HIV/antiretroviral (ARV) exposure.
Methods: This study compared metabolic parameters in obese non-pregnant HEU youth enrolled in the Pediatric HIV/AIDS Cohort (PHACS) Surveillance Monitoring of ART Toxicities (SMARTT) study with obese youth from the U.S. general population enrolled in the National Health and Nutrition Examination Survey (NHANES). Obesity was defined as a body mass index (BMI)>95%ile for age and sex. Binary outcomes were systolic and diastolic hypertension (HTN) [blood pressure (BP) z score ≥90%ile for age, sex, and height], total cholesterol (TC) >200 mg/dL, high-density lipoprotein-C (HDL) <35 mg/dL, low-density lipoprotein-C (LDL) >130 mg/dL, triglycerides (TG) >150 mg/dL, and Homeostatic Model Assessment-Insulin Resistance (HOMA) >4. Because NHANES obtains metabolic measures only within certain age groups, 3 analytic samples were created: 1) TC and HDL (≥6 year), 2) systolic and diastolic BP (≥8 year), and 3) LDL, TG, and HOMA (≥12 year). For each group, up to 3 NHANES

youth were matched to each SMARTT participant by age, sex, and race. Modified Poisson regression models were fit for binary outcomes to quantify the prevalence ratio (PR) of each outcome as a function of cohort.
Results: The BP outcome analytic sample included 1096 participants (n=304 from SMARTT), the TC and HDL sample 1301 participants (n=385 from SMARTT), and the LDL, TG, and HOMA sample, 271 (n=83 from SMARTT). Overall characteristics of participants were similar between groups in all analytic samples, but SMARTT participants were more likely to report an annual household income <$20,000 in all samples (p<0.01). Among SMARTT participants, >86% in all samples had in utero exposure to zidovudine, stavudine, didanosine, or zalcitabine. After adjusting for confounders, SMARTT youth had higher rates of systolic and diastolic HTN (PR=3.34, 95% Confidence Interval (CI): 2.48, 4.50; PR=2.04, 95%CI: 1.18, 3.52 respectively) but lower rates of insulin resistance (IR) (PR=0.69, 95%CI: 0.55, 0.88) and hypercholesterolemia which trended towards significance (PR=0.68, 95%CI: 0.44, 1.01) (Table).
Conclusion: Obese HEU youth appear to be at higher risk for HTN, but lower risk for hypercholesterolemia and IR, compared to a matched obese U.S. population. Further studies are warranted to understand the causes and long-term implications of these findings.

Table. Models of Prevalence Ratio Estimates Comparing SMARTT vs. NHANES for Each Metabolic Outcome

Model	Prevalence Ratio (95% CI)	*p*-value
Systolic HTN	3.34 (2.48, 4.50)	<0.01
Diastolic HTN	2.04 (1.18, 3.52)	0.01
Low HDL	1.30 (0.85, 1.88)	0.25
Hypercholesterolemia	0.68 (0.44, 1.01)	0.06
High LDL	0.98 (0.38, 2.54)	0.96
Hypertriglyceridemia	0.99 (0.40, 2.49)	1.00
Insulin Resistance	0.69 (0.55, 0.88)	<0.01

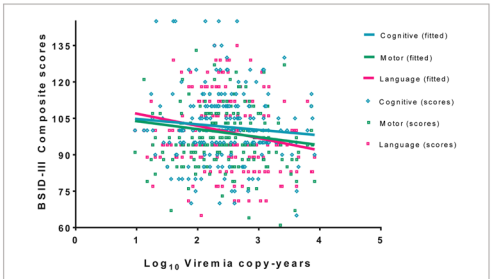
**All models adjusted for age, body mass index z score, sex, and black race. CI=Confidence Interval; HDL=High Density Lipoprotein C; HTN=Hypertension; LDL=Low Density Lipoprotein C*

875 HIV VIRAEMIA IN PREGNANCY AND NEURODEVELOPMENT OF HIV-EXPOSED UNINFECTED CHILDREN

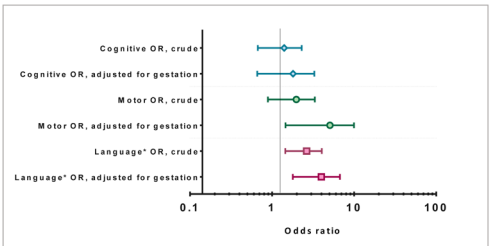
Stanzi M. le Roux[1], Elaine J. Abrams[2], Kirsty Donald[1], Kirsty Brittain[1], Tamsin K. Phillips[1], Allison Zerbe[2], Max Kroon[1], **Landon Myer**[1]
[1]University of Cape Town, Cape Town, South Africa, [2]ICAP at Columbia University, New York, NY, USA

Background: Maternal HIV viraemia in pregnancy is associated with increased mortality,infectious morbidity and immunological abnormalities among HIV-exposed uninfected (HEU) children, but little is known about the effects on early childhood development
Methods: HIV-infected women initiating lifelong ART (TDF+FTC+EFV) were followed through pregnancy and with their breastfed infants to 18 months postpartum for the MCH-ART study. Cognitive, motor and language development (BSID-III) were assessed on a subset of HEU infants at 12 months, [excluding gestational age (GA) at birth<28 weeks, known cerebral palsy, congenital abnormalities or significant prenatal alcohol exposure]. Antenatal intimate partner violence (IPV) and risky drinking were measured with standardized tools. Maternal CD4 cell count (CD4), hemoglobin (Hb) and HIV viral load (VL) were measured at ART initiation; VL was repeated in late pregnancy and close to delivery. Cumulative viraemia in pregnancy was expressed as $\log_{10}$ VL copies x year/mL (viraemia copy-years, VCY). Relationships between VCY and development were tested with linear (difference in mean composite scores) and logistic (odds of delay, BSID-III composite score<85) regression analyses, adjusting for confounders.
Results: Women (median pre-ART $\log_{10}$ VL 4.06, CD4 349 cells/mm^3; 2.4 $\log_{10}$ VCY) commonly reported adverse social circumstances (29% risky drinking, 20% IPV). Infants' (n=214; median age 13 months; 53% male; 13% GA<37 weeks) BSID-III scores were inversely correlated with VCY [per $\log_{10}$ VCY increase: β(95%CI) for cognitive, -1.87(-4.59; 0.84); motor, -2.82(-5.60; -0.03); and language, -3.71(-6.60; -0.83)]. Adjustment for GA strengthened associations across domains [aβ (95%CI) for cognitive, -2.33(-5.05; 0.39); motor, -3.40(-6.16; -0.64); language, -3.74(-6.66; -0.82)]. Further adjustment for IPV, risky drinking, CD4, Hb and breastfeeding attenuated the associations [aβ(95%CI) for cognitive, -1.35(-5.01;2.30); motor, -2.13(-5.85;1.60); and language, -2.54(-6.48;1.39)]. Logistic regression results were largely similar; adjusting for GA, increasing $\log_{10}$ VCY was associated with higher odds of delay in motor (OR 3.82, 95%CI 1.46;3.27) and language (OR 3.46, 95%CI 1.79;6.71), but not cognitive domains (1.47, 95%CI 0.66; 3.27).
Conclusion: HIV viraemia in pregnancy may adversely affect cognitive, motor and language development of HEU infants. Achieving rapid and sustained maternal viral suppression and preventing preterm delivery are critical for promotion of HEU child health.

FIGURE. Effect of $\log_{10}$ maternal viremia copy-years on HIV-exposed uninfected child development: results from linear and logistic regression analysis



(a) Composite cognitive, motor and developmental scores with unadjusted predicted linear regression lines



(b) Relative odds of cognitive, motor and/or language delay (composite BSID-III score <85) per $\log_{10}$ increase in maternal viremia copy-years: logistic regression analysis, unadjusted and adjusted for gestational age at birth

876 DEVELOPMENTAL OUTCOMES AND ARV EXPOSURE IN HIV-EXPOSED UNINFECTED CHILDREN

Micah Piske[1], Matthew A. Budd[1], Annie Q. Qiu[2], Evelyn J. Maan[2], Laura J. Sauve[2], John C. Forbes[2], Ariane Alimenti[2], Patricia Janssen[1], Helene C. Cote[1]
[1]University of British Columbia, Vancouver, BC, Canada, [2]Oak Tree Clinic, Vancouver, BC, Canada

Background: Half of all HIV+ adults worldwide are female, and over 1.4 million children are born annually to mothers living with HIV. Globally, an increasing proportion of HEU children are exposed to ARVs in utero. In Canada, over 200 children are born each year to HIV+ mothers, most of whom are HIV-Exposed Uninfected (HEU). The long-term effects of exposure to maternal HIV "milieu" and ARVs are not well understood. In this study, we aimed to investigate risks of neurodevelopmental disorders (NDs) among HEU children born in British Columbia (BC), Canada, and examine possible associations with ARV exposure, adjusting also for sociodemographic influences.
Methods: Data on 446 HEU children and 1323 HIV-unexposed uninfected (HUU) children (matched ~1:3 for age, sex and geocode) born between 1990-2012 were collected by Population Data BC from provincial data sources: BC Ministry of Health Medical Services Plan (ICD-9 codes), BC Vital Statistics, Perinatal Services BC, and the Oak Tree Clinic, Vancouver, BC. Multivariate logistic regressions were conducted using STATA IC 13.
Results: HEUs had a >2x increased risk for autism, disturbance of emotions, hyperkinetic syndrome, and developmental delay (p<0.0001); but not for intellectual disability or epilepsy compared to controls in unadjusted analyses. They also had a 3-fold increased risk of being born preterm, a known risk factor for NDs. After adjusting for follow-up time, sex, maternal substance use, and/or smoking during pregnancy (in children born after April 2000 when these data were collected; HEU N=309, HUU N=917), HEUs persisted in having an increased risk of ND diagnosis compared to controls (OR=1.7; 1.1-2.5; p=0.01). Regardless of ARV exposure type, (i.e. none, treatment with one or multiple drug classes), HEUs had higher odds of any NDs compared to matched HUUs; however, there

was no evidence suggesting that in utero exposure to ARVs, whether its duration, drug class or combinations, increased the likelihood of NDs.
Conclusion: The results suggest no direct association between ARVs and NDs within HEU children in our cohort. Prevalence of NDs is higher in HEUs; however, sociodemographic factors may play a role, including some we were not able to consider. These findings highlight a need for holistic support for pregnant women as well as careful developmental monitoring of HEU children, and access to early interventions, particularly among those born preterm and those exposed to substances of addiction.

877 MENTAL HEALTH DIAGNOSES, SYMPTOMS, AND SERVICE UPTAKE IN US YOUTH WITH PHIV EXPOSURE

Renee Smith[1], Yanling Huo[2], Katherine Tassiopoulos[2], Richard Rutstein[3], Suad Kapetanovic[4], Claude A. Mellins[5], Deborah Kacanek[2], Kathleen Malee[6]
[1]University of Illinois at Chicago, Chicago, IL, USA, [2]Harvard University, Cambridge, MA, USA, [3]Children's Hospital of Philadelphia, Philadelphia, PA, USA, [4]University of Southern California, Los Angeles, CA, USA, [5]Columbia University, New York, NY, USA, [6]Northwestern University, Chicago, IL, USA

Background: Adolescents and young adults perinatally exposed to HIV in the U.S. are at increased risk for mental health (MH) problems and lower uptake of MH services, raising concerns about increased risk of antiretroviral therapy non-adherence, poor virologic outcome, and secondary transmission for youth with perinatal HIV infection (PHIV). Identifying prevalence and factors associated with these problems in this aging population of youth with a chronic and stigmatizing health condition is critical for their mental and physical wellness, and informing prevention and intervention efforts.
Methods: Data from standardized interviews, behavioral assessments, and chart reviews were used to estimate prevalence of any MH diagnoses, clinically significant (CS) symptoms, and MH treatment uptake among 355 PHIV youth and 196 exposed but uninfected (PHEU) youth, aged 10-22yrs, who were enrolled at 15 U.S. sites of the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS). We used univariable and multivariable logistic regression models to evaluate associations of youth, family, and environmental characteristics with the most prevalent MH diagnoses (mood/anxiety and ADHD) and MH treatment utilization.
Results: Overall, 36% of all youth had a previous or current MH diagnosis, with no significant HIV status group differences. Among youth with a current MH diagnosis, 61% were receiving MH treatment; PHIV youth had greater uptake of services than PHEU youth (67% vs 51%; p=0.04). In each group 15% reported CS symptoms, of whom a third had no diagnosis, and half were not receiving treatment. In multivariable models, viral load and immunologic status were not associated with risk of a MH diagnosis or MH treatment uptake for PHIV youth. Among all youth, caregiver characteristics (previous MH diagnosis, IQ >85, and non-biologic relationship to child) were associated with more treatment uptake. Age and sex of child, stressful life events, HIV status, and caregiver factors (IQ, MH diagnosis, and relationship to child) were associated with anxiety/mood disorders and/or ADHD (see table).
Conclusion: Prevalence of MH diagnoses in this sample was higher than in the general U.S. population, but lower than in similar HIV-affected cohorts. There were unmet service needs, particularly among PHEU youth, yet uptake rates were higher than among those from some national population surveys. Family characteristics are key factors in the early diagnosis and treatment of MH problems of HIV-exposed youth.

Adjusted Associations of Covariates with Mental Health Disorders Reported on Neuropsychological and General Diagnoses Forms Among all AMP Participants (N=551)

		Mood/Anxiety Disorder		ADHD	
Covariate		Adjusted OR[1] (95% CI)	P-value	Adjusted OR[1] (95% CI)	P-value
Age (years) at most recent psychological eval: per one year increase		1.16 (1.02,1.33)	**0.02**	0.90 (0.83,0.99)	**0.02**
Any substance use (cigarette, alcohol or marijuana)		1.27 (0.68,2.36)	0.44		
Caregiver FSIQ < 85		0.48 (0.22,1.02)	0.06	0.50 (0.30,0.83)	**0.01**
Caregiver-ever mental health disorder		3.48 (1.81,6.96)	**< 0.001**	2.07 (1.30,3.33)	**0.002**
Caregiver-ever substance use disorder		1.73 (0.71,4.00)	0.21		
HIV infection status	Infected			0.61 (0.37,1.00)	**0.05**
Number of stressful life events (Ref: 0)	1	1.20 (0.54,2.60)	0.66	2.37 (1.39,4.06)	**0.002**
	2 - 3	1.43 (0.67,3.02)	0.34	1.71 (0.96,3.02)	0.07
	≥ 4	3.37 (1.21,9.20)	**0.02**	1.78 (0.75,4.00)	0.17
Primary caregiver identity: Biological parent		0.58 (0.30,1.10)	0.10	0.32 (0.20,0.52)	**< 0.001**
Male sex				2.91 (1.88,4.59)	**< 0.001**

Adjusted Odds Ratio of MH disorder for participant with a specific characteristic as compared to the reference group. Final multivariable model included covariates with P < 0.1 in the univariable analysis. Missing indicators were created for covariates with >5% missing data (including child any substance use, caregiver FSIQ, caregiver previous or current mental health and substance use disorder).

878 LOPINAVIR/RITONAVIR INDUCES MITOCHONDRIAL TOXICITY IN HIV-EXPOSED UNINFECTED CHILDREN

Audrey Monnin[1], Nicolas Nagot[2], Marianne Periès[3], Roselyne Vallo[3], Nicolas Meda[4], Mandisa Singata[5], James Tumwine[6], Pascal Reynier[7], Thorkild Tylleskär[8], Philippe Van de Perre[2], Jean-Pierre Molès[1]
[1]INSERM, Montpellier, France, [2]CHU de Montpellier, Montpellier, France, [3]L'Université de Montpellier, Montpellier, France, [4]Centre MURAZ, Bobo-Doulasso, Burkina Faso, [5]University of Fort Hare, East London, South Africa, [6]Makerere University, Kampala, Uganda, [7]CHU de Angers, Angers, France, [8]University of Bergen, Bergen, Norway

Background: Long-term ART, such as lopinavir-ritonavir (LPV/r) and lamivudine (3TC) can be given to newborns either for HIV treatment or prophylaxis (PrEP) to prevent maternal transmission through breastfeeding. The potential mitochondrial toxicity of these drugs has never been evaluated without the concurrent confounding effect of HIV. This study aimed to quantify the mitochondrial toxicity of 3TC or LPV/r regimens after 1 year of PrEP among HIV-exposed uninfected infants.
Methods: We have randomly selected 151 participants having completed the ANRS 12174 randomized controlled trial which enrolled HIV-uninfected children from untreated HIV-infected mothers. We showed that infant 3TC and LPV/r PrEP given from day 7 until 1 year could reduce postnatal HIV transmission to 1.3%. The number of mitochondrial DNA copies per cell (MCN) and the percentage of mitochondrial DNA carrying deletions (MDD) were assessed by real time PCR on stored dried blood spots collected at 7 days after birth and at 1 year. PCR protocols were performed according to the criteria for the diagnostic of mitochondriopathies from the French reference center. A clinically-relevant mtDNA depletion was defined as a reduction of 70% of MCN at 1 year.
Results: Before PrEP initiation (D7), the median MCN was within normal range (823, IQR:555-1076), while any MDD was unexpectedly detected in 147/149 children, with a median 11.2% (IQR:8.5-15.1) of mtDNA deleted, without difference between arms. After 1 year of PrEP, overall median MCN dropped by 41.2% (IQR:6.9-64.2) without difference between arms (p=0.59). Twenty-nine (19.2%) children showed a mtDNA depletion, without difference between arms (p=0.19). After adjustment for gender, duration of breastfeeding, duration of pre-partum maternal prophylaxis and gestational age, LPV/r tented to be associated with mtDNA depletion (reference = 3TC; OR=1.98, IC95%:0.81-4.87; p=0.14). Similarly, the rate of MDD remained high in both arms (13.7%, IQR:3.2-16.5 for 3TC and 14.6%, IQR:9.6-19.1 for LPV/r) but without difference between them (p=0,42).
Conclusion: At D7, the mtDNA deletion rate among HIV-exposed infants was close to rates observed in some inherited mitochondrial diseases. After 1 year of PrEP, an unexpected and important mitochondrial toxicity was observed (mtDNA depletion) for LPV/r, which compares to the expected effect of 3TC. The severity of these defects contrasts with the paucity of clinical sign and symptoms related to mitochondriopathies.

879 HEU BLOOD MTDNA CONTENT REMAINS ELEVATED FROM BIRTH INTO EARLY LIFE (0-3 YEARS)

Abhinav Ajaykumar[1], Mayanne Zhu[1], Hugo Soudeyns[2], Fatima Kakkar[2], Jason Brophy[3], Ari Bitnun[4], Ariane Alimenti[1], Deborah M. Money[1], Helene C. Cote[1]
[1]University of British Columbia, Vancouver, BC, Canada, [2]CHU Sainte-Justine, Montreal, QC, Canada, [3]Children's Hospital of Eastern Ontario, Ottawa, ON, Canada, [4]University of Toronto, Toronto, ON, Canada

Background: Maternal combination antiretroviral (ARV) therapy (cART) during pregnancy has been successful in preventing vertical HIV transmission. However, in utero exposure to ARVs, many of which can cross the placenta, could have long term effects on HIV-exposed uninfected (HEU) infants. Some ARVs can cause mitochondrial toxicity and affect mitochondrial DNA (mtDNA) quantity and quality. Previous studies among HEU infants exposed to cART in utero have been inconsistent, with some reporting increased blood mtDNA levels at birth compared to HIV-unexposed uninfected (HUU) infants, while others report a decrease. Our objective was to compare HEU and HUU infant blood mtDNA content at birth and over the first 3 years of life, and investigate any relationship to cART exposure.
Methods: Peripheral blood mtDNA content was measured by monochrome multiplex qPCR in 324 HEU (0-3y, of whom 214 had ≥2 blood samples) and 308 HUU children (0-3y, each with a single blood sample) enrolled in the CARMA cohort study. A subset of these children was randomly age- and sex-matched 1:1 for a cross-sectional comparison of mtDNA content over the first 3y of

life. Factors showing an association univariately ($p<0.1$) were considered in multivariable linear regression models.

Results: mtDNA content at birth (0-3d) was obtained for 114 HEU and 86 HUU children. In a multivariable model of mtDNA content at birth (n=200) that included HEU/HUU status, gestational age (GA) at birth, and maternal smoking during pregnancy, lower GA was the only factor independently associated with higher mtDNA content ($p<0.001$). Among infants born at term (GA>37w, n=168), although HEUs had significantly lower GA at birth (median: 38.9 vs. 39.7, $p<0.01$), the multivariable analysis revealed that only HEU status ($p=0.005$) was independently associated with higher birth mtDNA content. In a separate model that investigated maternal cART parameters among HEUs (n=114), neither duration nor type of in utero cART exposure were associated with mtDNA content at birth. Additionally, infant AZT prophylaxis did not affect mtDNA content at 6w vs. birth. Lastly, among age and sex-matched children (n=214:214), HEU children continued to have higher mtDNA content than HUUs ($p<0.01$) throughout the first three years of life.

Conclusion: HEUs and infants born preterm have higher mtDNA content at birth, an effect that persisted up to age three. This may represent a long-term effect, possibly resulting from adaptive mitochondrial biogenesis in response to in utero stresses.

880 INCREASED INFLAMMATION AND MONOCYTE ACTIVATION IN HIV-EXPOSED UNINFECTED INFANTS

Marisa M. Mussi-Pinhata[1], Adriana Weinberg[2], Qilu Yu[3], Rachel A. Cohen[3], Sahera Dirajlal-Fargo[4], Nicholas Funderburg[5], Emily Bowman[5], Nahida Chakhtoura[6], Grace A. McComsey[4]

[1]University de São Paulo Ribeirão Preto, Ribeirão Preto, Brazil, [2]University of Colorado Denver, Denver, CO, USA, [3]Westat, Inc, Rockville, MD, USA, [4]University Hospitals of Cleveland Medical Center, Cleveland, OH, USA, [5]The Ohio State University, Columbus, Ohio, USA, [6]National Institute of Child Health and Human Development, Bethesda, MD, USA

Background: HIV infection is accompanied by high levels of inflammation that predict increased mortality in adults. HIV-exposed uninfected (HEU) infants also have increased infectious morbidity and mortality, but little is known about their levels of inflammation and immune activation. In this study, we assessed how inflammatory and monocyte activation markers correlated between mothers and HEUs at delivery and compared markers between HEU and HIV-unexposed (HU) infants at birth and at 6 months of life.

Methods: The study enrolled term singletons ≥2500g at birth and their mothers. Samples obtained at birth and 6 months from 86 HEU mother-infant pairs enrolled in the NICHD cohorts in Brazil were analyzed and compared to 88 HU mother-infant pairs. All HIV-infected mothers received ARV during pregnancy. HEUs received neonatal zidovudine prophylaxis and formula. HUs were born to healthy mothers, and most received formula feeding by 4 weeks of age. Infants had clinical and laboratory evaluations at birth and 6 months. IL-6, TNFRI, TNFRII, sCD14, sCD163, IP-10, VCAM, OxLDL, D Dimer, and hsCRP were assayed by ELISA. Data were analyzed using two-sample t-tests, correlation coefficients and linear regression models. $p<0.005$ was used to adjust for multiple comparisons.

Results: Among HIV-infected mothers, 81.4% had HIV-RNA <1,000 copies/mL prior to delivery. In addition, they were older (27 vs. 24 years), and more frequently non-white (64.4% vs. 25.0%) when compared to uninfected mothers. Compared to HU, HEU infants were born more frequently by C-section (59% vs. 32%), with a lower median gestational age (38.6 vs. 39.3wk) and weight (3.2 vs. 3.3kg); and reached lower weight (5.9 vs. 8.5kg) and height (53.5 vs. 68.8 cm) at 6 months of age. Majority of inflammatory markers were significantly higher ($p\leq0.005$) in HEU compared with HU at birth, but at 6 months only TNFRI and IL-6 remained higher (Table). Among HU mother-infant pairs, infant IL-6, TNFRI, TNFRII, sCD14, sCD163 levels at birth were associated with maternal levels at delivery ($r\geq0.31$; $p\leq0.0004$). For HEU pairs, the only association was for IP-10 ($r=0.34$; $p<0.0001$) at birth.

Conclusion: HEU infants had higher inflammation and monocyte activation than HU at birth, which for some markers persisted to 6 months of life, and was related to maternal inflammatory status. Inflammation may contribute to the increased HEU infectious morbidity and poor growth. This hypothesis warrants further investigation.

Visit	Marker	Mean (st.dev) HEU	Mean (st.dev) HU	Difference (95% CI)	p-value
Birth	TNFRI (pg/ml)	3.32 (0.16)	3.15 (0.14)	0.17 (0.12, 0.22)	<0.0001
	IL-6 (pg/ml)	0.78(0.44)	0.42 (0.53)	0.36 (0.21, 0.51)	<0.0001
	IP10	2.06 (0.45)	1.87 (0.22)	0.19 (0.08, 0.30)	0.001
	Ox LDL	4.40 (0.28)	4.14 (0.17)	0.26 (0.19, 0.33)	<0.0001
	VCAM	3.22 (0.11)	3.42 (0.26)	-0.20 (-0.26, -0.14)	<0.0001
	hsCRP	3.27 (0.49)	2.56 (0.45)	0.71 (0.56, 0.85)	<0.0001
	sCD14	3.04 (0.14)	2.80 (0.10)	0.23 (0.20, 0.27)	<0.0001
6 mo	TNFRI (pg/ml)	3.06 (0.11)	2.96 (0.13)	0.10 (0.06, 0.13)	<0.0001
	IL-6 (pg/ml)	0.36 (0.57)	0.13 (0.51)	0.22 (0.06, 0.39)	<0.0001
	D Dimer	2.78 (0.32)	2.95 (0.27)	-0.16 (-0.25, -0.08)	0.0003
	IP10	2.01 (0.40)	2.21 (0.36)	-0.19 (-0.31, 0.08)	0.001
	Ox LDL	4.49 (0.16)	4.57 (0.18)	-0.08 (-0.13, -0.03)	0.003
	VCAM	3.13 (0.13)	3.23 (0.16)	-0.11 (-0.15, -0.06)	<0.0001

881 INNATE IMMUNE ACTIVATION AMONG HIV-1 EXPOSED UNINFECTED INFANTS FROM BOTSWANA

Pilar Garcia Broncano[1], Samuel W. Kgole[2], Gosego Masasa[2], Terence Mohammed[2], Sikhulile Moyo[2], Joseph Makhema[2], Xu G. Yu[1], Jennifer Jao[3], Roger L. Shapiro[4], Mathias Lichterfeld[5], Kathleen M. Powis[6]

[1]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [3]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [4]Harvard University, Boston, MA, USA, [5]Brigham and Women's Hospital, Boston, MA, USA, [6]Massachusetts General Hospital, Boston, MA, USA

Background: HIV-exposed uninfected (HEU) infants continue to experience increased morbidity/mortality from infectious causes compared with infants born to HIV-uninfected women. To explore possible immune etiologies, we conducted an immune profiles analysis, comparing profiles from a Botswana-based cohort of HEU to HIV-unexposed (HU) infants.

Methods: Multiparametric flow cytometry was used to quantify proportions and phenotypic characteristics of innate immune cells (monocytes, dendritic cells and NK cells) and adaptive T and B cell-mediated immune responses using peripheral blood mononuclear cells (PBMCs) collected at 3-months of life from HEU and HU infants enrolled in a longitudinal gut microbiome study in Botswana. All HIV-infected women received ≥6 weeks of ART prior to delivery. All infants were born full-term and all HEU infants tested HIV negative at 3 months of life.

Results: Thirty-three infants (17 HEU and 16 HU) were studied cross-sectionally. HEU infants had lower proportions CD14+ monocytes compared with HU infants ($p=0.013$). The proportion of CD14+ CD16- "classical" monocytes was significantly reduced in HEU infants, while proportions of CD14+ CD16+ non-classical/intermediate monocytes, associated with increased activation and inflammatory responses, were markedly increased (Figure). Proportions of NK cells, the primary innate immune system effector cell, were lower in HEU infants ($p=0.026$). Upregulation of NKp30, a surface marker denoting terminal activation, on CD56hiCD16low NK cell subset was noted among PBMCs of HEU infants. Frequencies of CD4+ and CD8+ T cell subsets, proportions of regulatory T cells and expression of immune activation markers on these T cell populations did not differ between groups. Proportion of late memory B cells (Bm5, IgD- CD38-) was lower in HEU infants ($p=0.026$). While fewer HEU infants exclusively breastfed through 3 months (71% vs 88%), the difference was not significant ($p=0.40$). Despite these findings, there was no significant difference in hospitalizations in the first year of life between the groups.

Conclusion: In this cohort, in utero exposure to HIV-1 and ART was associated with a distinct immunological profile characterized by increased immune activation in the innate immune system. Longitudinal evaluations are needed to determine whether abnormal innate immune activation among HEU has longer-term clinical consequences.

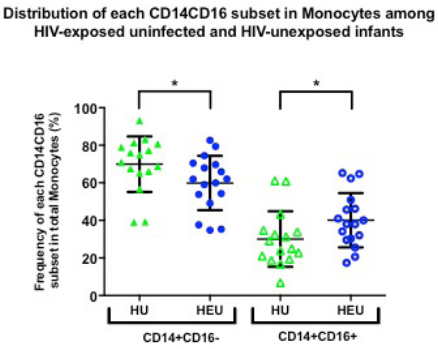


Figure: Distribution of classical (CD14+CD16-) and inflammatory (CD14+CD16+) subsets in monocytes among HIV-exposed uninfected (HEU, n=17) and HIV-unexposed infants (HU, n=16). Values expressed as mean with standard deviation. P-values were calculated by Mann-Whitney U tests, *p<0.05.

882 MICROBIAL TRANSLOCATION, IMMUNE ACTIVATION, AND GUT DYSBIOSIS IN HIV-EXPOSED INFANTS

Charles D. Mitchell[1], Sady Dominguez[1], Varghese George[1], Eddy Perez-Then[2], Carlos V. Castillo[2], Juan L. Santana-Guerrero[2], Jeannette Baez[3], Margaret Roach[1], William Walters[4], Qiaojuan Shi[5], Shao-Pei Chou[4], Ruth Ley[4], Savita Pahwa[1]
[1]University of Miami, Miami, FL, USA, [2]O&M School of Medicine, Santo Domingo, Dominican Republic, [3]Robert Reid Children's Hospital, Santo Domingo, Dominican Republic, [4]Max Planck Institute for Developmental Biology, Tübingen, Germany, [5]Cornell University, Ithaca, NY, USA

Background: The MITABS study (Microbial Translocation[MT], Immune Activation[IA], and Altered Bowel Flora Study[ABS]) is the first prospective, longitudinal study designed to simultaneously assess MT, IA, and alterations in the gut microbiome with clinical events in young (enrolled at < 6 months) HIV perinatally infected (HEI); and perinatally exposed, uninfected(HEU) infants in the Dominican Republic (DR) before and after starting antiretroviral therapy(ART).
Methods: Cellular immune markers of IA (HLADR+CD38+ coexpression) in CD4 and CD8 T cells were determined by flow cytometry using the method of Hanekom et al, J Immune Meth, 2004. Plasma MT and IA (LPS, sCD14 and sCD163) were determined by standard assays. Metagenomic analysis was performed on both stool and plasma. Simultaneous assessments of MT, IA, ABS, and clinical events occurred at Entry, 6 weeks, 3,6, 12, and 18 months post entry. No HEI was on ART at entry. HIV-exposed infants in the DR are formula fed
Results: Between 6/6/13 and 3/1/17, 78 infants (31 HEI; 47 HEU) were enrolled in the DR. Median ages at entry for all 78, the 31 HEI and the 47 HEU were 106, 145, and 89 days respectively. 19/31 HEI started ART. 10/31 developed AIDS (CDC criteria); 4 of whom died. No HEU has died. At entry, compared to HEU of the same age (<6 mo, n= 44), HEI not on ART (n= 15) had higher CD8 T cell Immune activation (HLADR+CD38+, 23.6% vs 4.3%, p=0.0005),CD8 (47% vs 24%, p=0.001), lower CD4 (49% vs 71%, p= 0.002) and lower CD4/CD8 ratio (1.04 vs 2.9). HEI also had higher plasma sCD14 (2523 vs 1473ng/ml, p=0.0001), and a trend for higher sCD163 (1212 vs 932 ng/ml, p=0.06) but surprisingly, the 2 groups had similarly elevated markers of MT (LPS, HEI 250 vs HEU 249pg/ml; iFABP, HIE 3293 vs HEU 2755 pg/ml). On prospective follow-up, MT markers (LPS, sCD163) in HEU normalized by 6-9 months. T cell IA were all within the normal range in HEU over time. In HEI, although IA and MT values decreased following ART, they were higher than in HEU. HEI gut microbiome was associated with lower diversity (richness, n=13) compared to HEU (n=38), and an unknown member of the Megaspheara genus was enriched in HEI on ART compared to HEI not on ART.
Conclusion: HEU infants like HEI have high gut permeability during early infancy which gradually normalizes over time. Increased biomarkers of MT and IA in HEI are prevalent from early infancy and persist after starting ART. HEI have a less diverse microbiome than HEU, with enrichment of the genus Megaspheara in HEI on ART

883 WILL TARGETED COMMUNITY OUTREACH IMPROVE HIV TESTING UPTAKE AMONG CHILDREN IN KENYA?

Samuel Ndolo[1], Nicollate A. Okoko[1], Mary A. Guzé[2], George Nyanaro[1], Lenah Nyabiage[3], Elizabeth A. Bukusi[1], Craig R. Cohen[2], Jeremy Penner[1], Jayne L. Kulzer[2]
[1]Kenya Medical Research Institute, Kisumu, Kenya, [2]University of California San Francisco, San Francisco, CA, USA, [3]US CDC Nairobi, Nairobi, Kenya

Background: Less than one third of children have ever been tested for HIV in the Nyanza region of western Kenya. Delayed HIV identification is associated with poor health outcomes and risk of virus transmission when older children begin sexual activity. This study examined whether targeted community outreach events (TCOE) increased HIV testing and identification of HIV-infected children in western Kenya.
Methods: In Jul–Dec 2015, 493 TCOEs were implemented for children, ages 18 months – 14 years, and their caregivers within 148 health facility catchment areas supported by Family AIDS Care & Education Services (FACES). TCOEs were conducted in community venues and included HIV education, HIV testing, and linkage to care. This pre- and post-study compared HIV testing uptake (number tested) and yield (number HIV positive) in the 5 months before (Jan– Jun 2015) and during (Jul – Dec 2015) TCOE implementation among children (<15 years) eligible for testing at facilities or TCOE's. Aggregated testing and yield data for both facility-based and TCOE testing, were captured in routine facility level tools. Negative binomial models clustered by facility were used to assess changes in uptake and yield after TCOE implementation overall and by sex, and to estimate monthly means.
Results: Overall, TCOE implementation did not increase uptake (p=0.43) and average yield decreased (p<0.01). Pre-TCOE, the estimated mean number of children tested per facility was 34.4 (95% CI 29.1, 40.7) compared to post-TCOE, 36.4 (95% CI 30.8, 42.9). The estimated mean yield per facility pre- and post-TCOE was 0.48 (95% CI 0.40, 0.57) versus 0.26 (95% CI 0.21, 0.34), respectively. Findings by sex indicated that pre-TCOE more females than males per facility were tested, with estimated means of 37.4 (95% CI 31.8, 44.0) and 31.4 (95% CI 26.3, 37.5), respectively, (p<0.01). Adjusting for pre-TCOE levels, the change in number of males tested per facility from pre- to post-TCOE increased compared to females, 37.6 (95% CI 30.5, 46.3) and 35.0 (95% CI 30.1, 40.6) respectively, (p<0.01). There was no significant difference in yield by sex pre-TCOE (p=0.35) or when comparing yield overtime (p=0.68).
Conclusion: TCOE's did not increase HIV testing overall, and yield decreased when testing extended outside of facilities. TCOEs increased testing in males more so than females demonstrating the value of targeted testing for males. Additional approaches or redesign is required to improve strategies to reach children.

884 ENGAGEMENT IN CARE AND INFANT HIV TESTING AMONG LOST TO FOLLOW-UP OPTION B+ PATIENTS

William J. Reidy[1], Harriet Nuwagaba-Biribonwoha[2], Siphesihle Shongwe[2], Ruben Sahabo[2], Kieran Hartsough[1], Simangele Mthetwa[3], Elaine J. Abrams[1]
[1]ICAP at Columbia University, New York, NY, USA, [2]ICAP at Columbia University–Swaziland, Mbabane, Swaziland, [3]Ministry of Health, Mbabane, Swaziland

Background: Option B+ has been adopted across sub-Saharan Africa, resulting in increased ART uptake among HIV+ pregnant women. However, concerns of sub-optimal maternal and infant retention have emerged. High loss to follow-up (LTF) among mothers and HIV-exposed infants (HEI) has been reported, but limitations in accurately assessing retention in HIV care using health facility (HF) data have been documented. We collected additional information on engagement in care for women and HEI classified as LTF from Option B+ in Swaziland to provide updated outcomes.
Methods: Women and HEI were classified as LTF (no visit within 3 months of expected visit) by 6 months postpartum using routine HF data. Additional information on engagement in HIV services was gathered by: 1) review of national ART patient database and paper records; 2) patient tracing via phone and community; and 3) patient interviews and abstraction from patient-held records. Data from these sources were combined with routine HF data to classify outcomes for LTF women and babies for whom sufficient information on clinic visits, vital status, and infant HIV testing, as applicable, was obtained. Self-reported information on care received as well as information documented by HF, as well as any reported evidence of maternal or infant death or pregnancy loss were included in the classification of outcomes. We conducted descriptive analyses to summarize frequencies of outcomes among LTF women and HEI.
Results: Of 1,221 pregnant women initiating Option B+ at 10 HF from October 2014-September 2015, 434 (36%) women and 510 (42%) HEI were classified as LTF. Of 193 (44%) LTF mothers with outcome data, 119 (62%) were engaged in care, 60 (31%) disengaged from care, 11 (6%) had moved out of the country, and 3 (2%) had died. Among the 510 HEI classified as LTF, 48 (9%) were pregnancy

losses, 15 (3%) mothers were documented as transferring facilities, and 11 (2%) mothers moved out of the country. Among the remaining 436 HEI, 192 (44%) had outcome data, including 143 (74%) who were engaged in care, 31 (16%) disengaged, and 18 (9%) who had died after delivery. Of 113 HEI with data on HIV testing, 75 (66%) completed HIV testing at 6 weeks and 53 (47%) at 6 months.

Conclusion: Majorities of pregnant women and HEI classified as LTF under Option B+ were engaged in care. These findings highlight a need to obtain more accurate outcome measures via strengthened systems for capturing and utilizing HF data for pregnant women and HEI.

885LB OPTIMIZING EID: A CLUSTER-RANDOMIZED TRIAL OF THE HIV INFANT TRACKING SYSTEM IN KENYA

Sarah Finocchario Kessler[1], Catherine Wexler[1], An-Lin Cheng[2], Niaman Nazir[1], Brad Gautney[3], May Maloba[3], Kathy Goggin[4], Melinda Brown[1], Elizabeth Muchoki[5], Shadrack Babu[5], Eric Muriithi[5], Martin Ochieng[5], Samoel Khamadi[5], Matthew Sandbulte[1], Raphael Lwembe[5]

[1]University of Kansas Medical Center, Kansas City, KS, USA, [2]University of Missouri–Kansas City, Kansas City, MO, USA, [3]Global Health Innovations, Dallas, TX, USA, [4]Children's Mercy Hospital, Kansas City, MO, USA, [5]Kenya Medical Research Institute, Nairobi, Kenya

Background: Outcomes for HIV-exposed infants (HEI) depend on the quality and efficiency of early infant diagnosis (EID) services. In Kenya, we evaluated the impact of the HITSystem (system-level intervention linking EID stakeholders via e-alerts for providers and text messages for mothers of HEI) on key EID outcomes.

Methods: In this non-blinded, phased, cluster randomized controlled trial (NCT02072603), 6 hospitals matched on geographic region, resource level, and volume were randomized to receive the HITSystem (n=3) or standard of care (SOC; n=3). Eligible participants (HIV+ women >18 yrs with HEI <24 weeks) enrolled between February 2014 and December 2016 were followed to evaluate the primary outcome of complete EID care; defined as receipt of all key EID services through 18-months (HIV-uninfected infants) or through ART initiation (HIV+ infants) per Kenyan guidelines. The HITSystem was hypothesized to improve retention, ART initiation, and results turnaround times (TAT) compared to SOC. Using a stepwise approach, we conducted separate multivariate logistic and Poisson regression analyses with intervention group, site volume, and significant covariates included as fixed effects in the models. Bonferroni corrections for multiple comparisons were applied.

Results: Among 809 eligible HEI, data from 690 were analyzed (n=392 intervention, n=298 SOC); excluding 28 deaths and 91 documented transfers/moved. Median age at enrollment was 6.0 weeks; 50% were male. Infants enrolled in HITSystem were significantly more likely to receive complete EID services compared to controls (85.2% [.82-.89] vs. 61.02% [.55-.66], p<0.001), including the following: receipt of OI prophylaxis (99.7% vs 89.6%), PCR results returned to the hospital (100% vs 96.98%), mothers notified of test result (98.9% vs 89.3%), re-testing among HIV-uninfected infants at 9 months (96.8% vs 91.1%) and 18 months (84.7% vs 69.3%), and ART initiation for HIV+ infants (100% vs. 72.7%). Mean results TAT (24.6 vs 49.2 days, p=0.003) and mother notification (19.0 vs 29.8 days, p=0.003) were faster at intervention sites. Receipt of initial HIV test was similar and time to ART was faster at SOC sites (median 68 vs. 51 days, p=0.045).

Conclusion: HITSystem significantly increased completion of EID services and reduced TAT for results and notification. Hindered by intervention settings that required multiple adherence counseling sessions prior to initiation, time to ART was faster in SOC sites.

Table 1. Impact of the HITSystem on Complete EID Services (Quality) and TAT (Efficiency)

EID Variables	Intervention N=392 N (%), 95% CI or Mean(sd) Median; n, CI	Control N=298 N (%), 95% CI or Mean(sd) Median; n, CI	P value
OI prophylaxis	391 (99.74%), .98-1.0	267 (89.60%),.86-.93	0.003
Initial DBS collected	392 (100%), 1.0-1.0	296 (99.33%), .98-1.0	0.80
PCR result returned to hospital	392 (100%), 1.0-1.0	289 (96.98%), .95-.98	.004
Mother notified of result	388 (98.98%), .98-1.0	266 (89.26%), .86-.93	<.001
HIV+ infants started on ART	21 (100%), 1.0-1.0	8 (72.73%), .46-.99	.08
Retested at 9M	360 (96.77%), .95-.98	265 (91.07%), .88-.94	0.013
Retested at 18M	315 (84.68%), .81-.88	201 (69.31%), .64-.75	<.001
Complete EID[1]	**334(85.2%), .82-.89**	**180(61.02%), .55-.66**	**<.001**
TAT: DBS collection to PCR results	Mean 24.59 (14.0) Med 20; 392, CI 19.40-31.44	Mean 49.23 (37.0) Med 38; 297, CI 43.36-55.51	.003
TAT: PCR results to mother notification	Mean 19.03(22.2) Med 14; 388, CI 14.26-25.55	Mean 29.75(39.5) Med 23; 267, CI 23.82-35.58	.003
TAT: Mother notification to ART initiation	51.05 (84.2) 21; 21, 0-150.62	68.00(173.77) 1; 7, 0-189.37	.045

[1] Complete EID is an aggregate measure including receipt of all key EID services through retesting at 18M (HIV-uninfected infants) or through ART initiation (HIV+ infants).
Bonferroni calculations were applied to p values to adjust for multiple tests.

886 TRENDS IN CAUSE-SPECIFIC MORTALITY ON THE HIV CARE CASCADE, SOUTHERN & EASTERN AFRICA

Kathryn A. Risher[1], Clara Calvert[1], Basia Zaba[1], Emma Slaymaker[1], Kobus Herbst[2], Jessica Nakiyingi-Miiro[3], Amelia C. Crampin[1], Mark Urassa[4], Baltazar Mtenga[4], Georges Reniers[1]

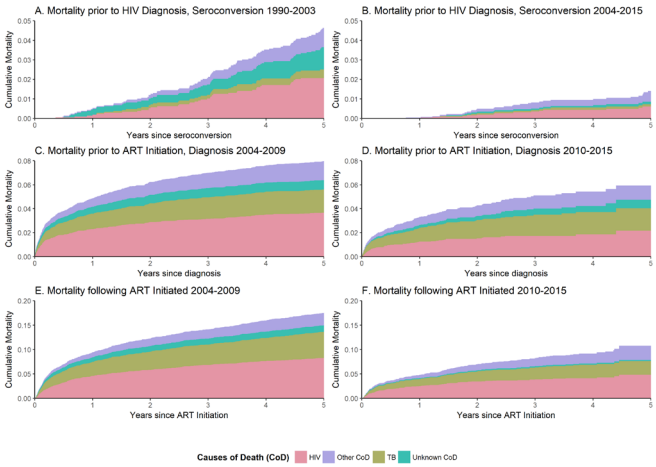
[1]London School of Hygiene & Tropical Medicine, London, UK, [2]Africa Health Research Institute, Mtubatuba, South Africa, [3]MRC/UVRI Research Unit on AIDS, Entebbe, Uganda, [4]National Institute for Medical Research, Kisesa HDSS, Mwanza, Tanzania, United Republic of

Background: Population-based studies have found decreasing mortality among those living with HIV, but it is unclear at what level of care engagement these deaths take place, to what causes the deaths are attributable, or how these patterns change as antiretroviral therapy (ART) programs mature.

Methods: We assess trends in cause-specific mortality along the cascade of HIV care in data from four population-based HIV surveillance sites in eastern and southern Africa. Deaths are assigned to a most likely cause using InSilicoVA following verbal autopsy. We conduct a competing risks analysis of four cause-of-death groups at three key transitions on the HIV care cascade (i) among seroconverters prior to HIV diagnosis, (ii) among those diagnosed prior to ART initiation and (iii) among those on ART. Cox proportional hazards models are used to estimate cause-specific hazard ratios (HR) for period of HIV seroconversion, diagnosis or ART initiation, controlling for age and sex, meta-analysed by site.

Results: Following seroconversion, HIV diagnosis, and ART initiation (respectively), 5,435, 13,186 and 7,778 adults contribute 19,213, 29,051, and 34,799 person-years of follow-up, and 226, 908 and 1,197 deaths. Overall five-year mortality on each step of the cascade decreased over time (Figure). However, these decreases were not evenly distributed across causes of death. The cause-specific hazard of mortality due to HIV decreased in the later cohort among seroconverters not yet diagnosed with HIV (HR=0.36, 95%CI=0.18-0.75), those diagnosed but not yet initiated on ART (HR=0.51, 95%CI=0.39-0.66), and among those initiated on ART (HR=0.60, 95%CI=0.40-0.89). Mortality due to TB decreased over time among those who had initiated ART (HR=0.57, 95%CI=0.44-0.75) but not among seroconverters not yet diagnosed or those diagnosed but not yet on ART. There was no change in non-HIV/TB mortality with changing year of seroconversion, diagnosis or ART initiation. Men had increased cause-specific mortality for all causes of death both following diagnosis prior to ART initiation and following ART initiation (HR range=1.34-4.48), but only for TB among seroconverters who had not yet been diagnosed (HR=3.43).

Conclusion: In these population-based studies, the cause-specific mortality among those living with HIV is changing over time as ART becomes more widely available. The mortality gains at three stages of the HIV care cascade appear to be attributable largely to HIV (seroconversion and diagnosis) or HIV and TB (ART) improvements.



887 ADVANCED HIV AND THE CARE CASCADE IN THE BOTSWANA COMBINATION PREVENTION PROJECT

Refeletswe Lebelonyane[1], Lisa A. Mills[2], Chipo Mogorosi[2], Shenaaz El-Halabi[1], Janet Moore[3], Lisa Block[4], Huisheng Wang[5], Joe Theu[1], Joseph Makhema[6], Stembile Matambo[2], Tafireyi Marukutira[2], Etienne Kadima[6], Max Kapanda[1], Pamela J. Bachanas[3], Joseph N. Jarvis[2]

[1]Botswana Ministry of Health, Gaborone, Botswana, [2]CDC Botswana, Gaborone, Botswana, [3]CDC, Atlanta, GA, USA, [4]Intellectual Concepts, Atlanta, GA, USA, [5]Northrop Grumman Corp, Atlanta, GA, USA, [6]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana

Background: Individuals starting antiretroviral treatment (ART) with advanced HIV-disease (CD4 count ≤200 cells/μL) may have higher rates of early attrition from care due to HIV-related morbidity and mortality. We evaluated the impact of advanced HIV disease on treatment linkage and retention in a routine clinical setting in Botswana.

Methods: The Botswana Combination Prevention Project (BCPP) is a cluster-randomized trial evaluating the impact of a combination prevention package on HIV incidence in 30 rural and semi-urban communities. This sub-analysis of the 15 intervention communities compares rates of linkage to care, ART initiation, retention in care, and virological suppression in patients identified through community testing between November 2013 and May 2016 with CD4 counts ≤200 cells/μL versus those with CD4 counts >200 cells/μL. Patients were eligible for ART if CD4 counts were ≤500 cells/μL or viral load ≥10,000 copies/ml. Data were censored at the end of July 2017.

Results: BCPP assessed HIV status in 44,223 individuals; 10,359 (23%) were HIV-infected, 2,706 (26%) of whom were not on ART and were referred for HIV care. Of the 2,560 who had a point-of-care CD4 test, 519 (20%) had CD4 ≤200 cells/μL. 2041 (80%) had CD4 >200 cells/μL of whom 1578 were elgible for ART. Rates of linkage to care were lower in individuals with CD4 ≤200 cells/μL compared to ART eligible individuals with CD4 >200 cells/μL (78% vs 88% at 6 months, p<0.001 and 93% vs 96% overall, p=0.005), as were rates of ART initiation (84% vs 89%, p=0.003). Mortality was 2.3% (12/519) in those with CD4 ≤200 cells/μL compared 1.1% (18/1578) with CD4 >200 cells/μL, p=0.05. By July 2017, 392 (76%) individuals in the CD4 ≤200 cells/μL were in care and on ART compared to 1301 (82%) with CD4 >200 cells/μL, p=0.001 (Table 1). Among those who initiated ART at least 6 months prior to data censoring, retention in care was 89% (365/408) in the low CD4 group and 93% (1,231/1,331) in the CD4>200 cells/μL group, p=0.05. Rates of viral suppression among those in care were similar in the two groups.

Conclusion: Twenty percent of HIV-infected individuals not on ART had advanced HIV-disease. Those with advanced disease had lower rates of linkage to care, ART initiation, and retention in care, and higher mortality compared to healthier HIV-infected individuals. Once retained in ART care, rates of viral suppression were high. These data highlight the need to focus efforts on earlier identification of HIV-infected persons.

	Baseline CD4 ≤200 cells/μL	CD4>200 cells/μL and ART eligible	*p-value*
	N = 519	N = 1578	
Linked within 6 months	404 (78%)	1391 (88%)	*<0.001*
Linked ever (to July 2017)	482 (93%)	1514 (96%)	*0.005*
Initiated within 6 months	310 (60%)	993 (63%)	*0.19*
Initiated ever (to July 2017)	435 (84%)	1400 (89%)	*0.003*
Dead*	12 (2.3%)	18 (1.1%)	*0.05*
In care and on ART at end of follow-up*	392 (76%)	1301 (82%)	*0.001*
*The following cells are limited to those who **initated** **ART ≥ 6** months prior to data censoring*			
	N = 408	N = 1331	
Retained at 6 months	376 (92%)	1280 (96%)	*0.001*
Retained at end of follow-up*	365 (89%)	1231 (93%)	*0.05*
Viral Load Testing performed	339 (83%)	1122 (84%)	*0.56*
Viral Suppression Rates (VL<400)	331/339 (98%)	1101/1122 (98%)	0.57

**End of follow-up is defined as end July 2017 when data for these analyses were censored.*

888 IMPROVED VIRAL SUPPRESSION BUT STABLE MORTALITY IN PEOPLE WHO INJECT DRUGS, 1997-2015

Becky L. Genberg[1], Gregory D. Kirk[1], Jacquie Astemborski[1], Hana Lee[2], Shruti H. Mehta[1]

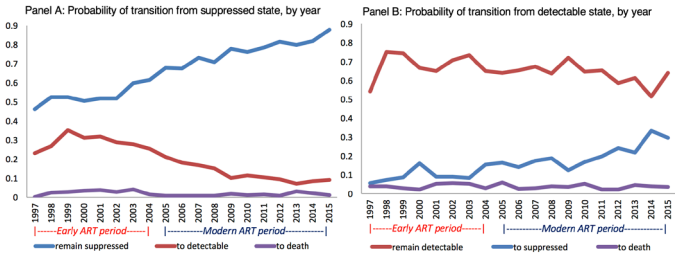
[1]Johns Hopkins University, Baltimore, MD, USA, [2]FDA, Silver Spring, MD, USA

Background: People who inject drugs (PWID) face disparities in HIV treatment outcomes compared to other groups. While it is recognized that PWID may cycle in and out of care (and consequently viral suppression), less is known about whether the modern ART era has led to reduced transitions in and out of suppression for PWID. We used multi-state models to characterize mortality and transitions in and out of viral suppression from 1997-2015 among a community-based observational cohort of PWID.

Methods: We included data from all HIV+ PWID in ALIVE (AIDS Linked to the IntraVenous Experience) in follow-up on or after 1997. We operationalized a multi-state model with the following states: detectable, suppressed, lost-to-follow-up (no visit > 9 months), and death. We examined changes in state transition probabilities over time, comparing early (1997-2004) and modern (2005-2015) ART periods.

Results: Among 990 HIV+ PWID, median age was 43, 32% female, 93% African-American, 59% recently injected, and 54% died over a mean 10 years of follow-up. Probabilities of continued suppression, becoming detectable, or death when suppressed were: 0.54, 0.30, and 0.03 in the early period, and 0.78, 0.11, and 0.01 in the modern period, respectively (Figure). Probabilities of staying detectable, becoming suppressed, or death were: 0.70, 0.10, and 0.04 in the early period, and 0.64, 0.19, and 0.04 in the modern period, respectively. Adjusting for sex and race, transitions from detectable to suppressed increased over time in the early (relative risk ratio [RRR]=1.06, 95% CI:1.00-1.11) and modern (RRR=1.08, 95% CI:1.03-1.12) periods, and transitions from suppressed to detectable decreased in the modern era (RRR=0.89, 95% CI:0.85-0.93). The probability of death from both suppressed and detectable states in both periods remained stable over time. Recent injection was positively associated with suppression when detectable (RRR=1.88, 95% CI:1.44-2.45) and negatively associated with transitions from detectable to suppressed (RRR=0.49, 95% CI:0.41-0.59), but was not associated with death from either state.

Conclusion: In the modern ART era, PWID experienced improved HIV treatment outcomes, with a higher probability of sustained suppression and transitions from being detectable to suppressed; however, these have not yet translated to reduced mortality even among suppressed PWID. Additional research is needed to understand stable mortality among HIV+ PWID despite drastic improvements in the modern ART era.



889 FACTORS ASSOCIATED WITH DELAYED HIV DIAGNOSES IN WASHINGTON, DC, 2006-2015

Rupali K. Doshi[1], Jessica Li[1], Kerri Dorsey[1], Auntre D. Hamp[2]
[1]The George Washington University, Washington, DC, USA, [2]District of Columbia Department of Health, Washington, DC, USA

Background: Delayed diagnosis of HIV, defined by a short interval between HIV diagnosis and meeting criteria for stage 3 HIV (AIDS), is a critical indicator on the HIV care continuum. Washington, DC, has a high burden of HIV disease and the DC Department of Health (DOH) has implemented various public health strategies to increase routine opt-out HIV testing since the number of new infections peaked in 2007. We examined delayed diagnosis of HIV in DC over 10 years and the association with demographic and transmission risk factors.

Methods: Reports of HIV cases diagnosed in DC residents over age 12 between January 1, 2006, and December 31, 2015, were extracted from the DC DOH Enhanced HIV/AIDS Reporting System. Cases were matched to CD4 counts reported to the DC DOH. Cases were excluded if AIDS diagnosis or CD4 count were missing or unreported. Delayed diagnosis was defined as stage 3 diagnosis within 90 days of the HIV diagnosis. Covariates assessed were year of HIV diagnosis, gender, race/ethnicity, mode of transmission and age at diagnosis. Cochran-Armitage test of trend and Chi-square were used for univariate analyses. The multivariable analysis was modeled using a log-binomial analysis, and we report adjusted prevalence ratios (aPR).

Results: 8172 DC residents were diagnosed with HIV in Washington, DC, between January 1, 2006, and December 31, 2015; 473 were excluded due to missing data, resulting in 7699 eligible for the analysis. 2162 (28.1%) had a delayed HIV diagnosis. Delayed HIV diagnoses declined from 2006 (36.4%) to 2015 (21.8%). In the multivariate analysis, Black or Hispanic/Latino race/ethnicity (vs. White, aPR 1.45 and 1.51, respectively) and persons with other or unknown mode of transmission (vs. sexual contact, aPR 1.28) were independently associated with the outcome. Female gender (vs. male, aPR 0.91), ages 13-49 at diagnosis (vs. ages 60 and older, aPR range 0.42 to 0.83), and later year of HIV diagnosis (aPR for each 1 year increase beyond 2006 was 0.97) were less likely to have delayed HIV diagnosis.

Conclusion: Delayed HIV diagnoses decreased from 2006 to 2015, even while controlling for demographic factors, indicating that over the analysis time period, people were diagnosed with HIV earlier in the disease course. The results suggest a need for better risk assessment and more targeted HIV testing among the populations identified (Black or Hispanic/Latino race/ethnicity, people over 50, men) to optimize health outcomes.

Delayed Diagnosis of HIV in Washington, DC, 2006-2015

Variables	Adjusted prevalence ratio	95% Confidence Interval	p-value
YEAR OF HIV DIAGNOSIS (2006 to 2015) [a]	0.97[e]	(0.95, 0.98)	<0.0001
AGE AT DIAGNOSIS (years) [b]			
13-19	0.42	(0.32, 0.57)	<0.0001
20-24	0.41	(0.34, 0.50)	<0.0001
25-29	0.65	(0.55, 0.76)	<0.0001
30-39	0.77	(0.67, 0.88)	0.0002
40-49	0.83	(0.73, 0.95)	0.0070
50-59	0.90	(0.78, 1.03)	0.1251
>=60	1.00	Reference	
GENDER			
Male	1.00	Reference	
Female	0.91	(0.83, 0.98)	0.0187
Transgender	1.05	(0.81, 1.36)	0.7083
RACE / ETHNICITY [b]			
White	1.00	Reference	
Black	1.45	(1.28,1.64)	<0.0001
Hispanic/Latino	1.51	(1.27, 1.80)	<0.0001
Other[c]	1.25	(0.99,1.59)	0.0641
MODE OF TRANSMISSION [b]			
Sexual contact	1.00	Reference	
IDU	1.06	(0.93, 1.20)	0.4183
Sexual contact/ IDU	0.91	(0.71,1.17)	0.4591
Other[d]/ Risk not identified	1.28	(1.18,1.39)	<0.0001

[a] Univariate analysis Cochran-Armitage test for trend p-value <.0001
[b] Univariate analysis Chi-square p-value <.0001
[c] Other race/ethnicity includes: mixed race individuals, Asians, Alaska Natives, American Indians, Native Hawaiian, Pacific Islanders, and unknown
[d] Other mode of transmission includes: perinatal transmission, hemophilia, blood transfusion, and occupational exposure (healthcare worker)
[e] 1 year difference

890 LOWER MITOCHONDRIAL DNA COPY NUMBER IS ASSOCIATED WITH HIV & PREDICTIVE OF MORTALITY

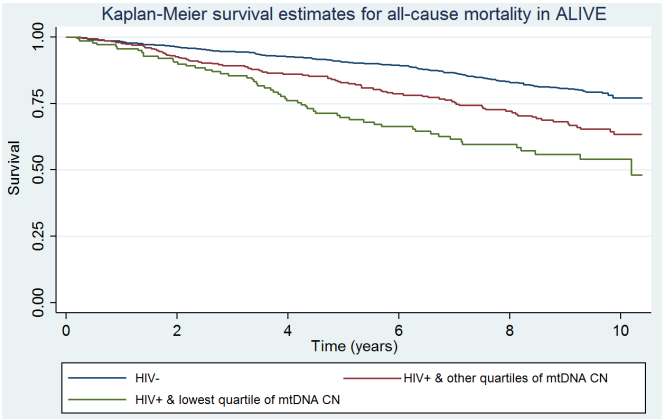
Jing Sun, Ryan Longchamps, Damani A. Piggott, Jason A. Sumpter, Shruti H. Mehta, Dan Arking, Gregory D. Kirk
Johns Hopkins University, Baltimore, MD, USA

Background: Lower mitochondrial DNA copy number (mtDNA CN), a marker of mitochondrial depletion, reduced energy reserves, and oxidative stress, was recently found to be predictive of adverse aging outcomes and mortality in the general population. HIV infection and its treatment may impact mitochondrial function, yet little data exist on the relationship of mtDNA CN to health outcomes in HIV infected population. We examine the relationship of mtDNA CN to HIV disease markers and mortality among persons who inject drugs (PWID) with and without HIV.

Methods: mtDNA CN was measured using the qPCR of DNA isolated from buffy coats of participants of the AIDS Linked to the IntraVenous Experience (ALIVE) cohort of current and former PWID. We used the difference of cycle threshold value between the nuclear genome (RPPH1), found in 2 copies in all humans, and mt gene (ND1) as a measure of mtDNA CN, and standardized for platelet and white blood cell counts. We further categorized the mtDNA CN into quartiles, and compared the lowest quartile vs. the other 3 quartiles (high mtDNA CN). All-cause mortality was ascertained through linkage to the National Death Index from 1988 to 2015. The relationship of mtDNA CN to HIV clinical parameters was assessed using chi2 and T tests. Cox proportional hazards regression models (controlled for age, race, gender, education, HCV infection, smoking, alcohol consumption, and current IDU) were used to assess the relationship of mtDNA CN to mortality.

Results: Of 825 participants, 41% were ≥50 years, 62% male, 86% black, 43% had less than high school education, and 59% were HIV-infected. mtDNA CN was lower among HIV+ vs. HIV- ($p<0.01$), had a dose-response effect by CD4+ count (HIV+ & CD4+>500: 0.034, HIV+ & CD4+ in 200-500: -0.234, HIV+ & CD4+≤200: -0.317, $P=0.03$), and was lower among those who were not on ART ($p<0.01$). Over a median of 7.3 yrs, there were 219 deaths (26.6%). Compared to HIV- individuals with high mtDNA CN, being HIV+ with high mtDNA CN was associated with a 1.69 fold increased risk of death (95% CI: 1.16-2.47), and being HIV+ and in the lowest quartile of mtDNA CN was associated with a 2.6 fold increased risk of death (95% CI: 1.72-3.94). mtDNA CN and HIV infection had a synergistic impact on mortality ($p=0.03$).

Conclusion: mtDNA CN is a novel biomarker strongly associated with HIV infection, particularly with advanced HIV disease, and is predictive of all-cause mortality among people living with HIV.



891 SHIFTING MORTALITY TRENDS AMONG PERSONS WITH HIV AND INJECTION DRUG USE OVER 30 YEARS

Jing Sun, Damani A. Piggott, Abimereki D. Muzaale, Jacquie Astemborski, Shruti H. Mehta, Gregory D. Kirk
Johns Hopkins University, Baltimore, MD, USA

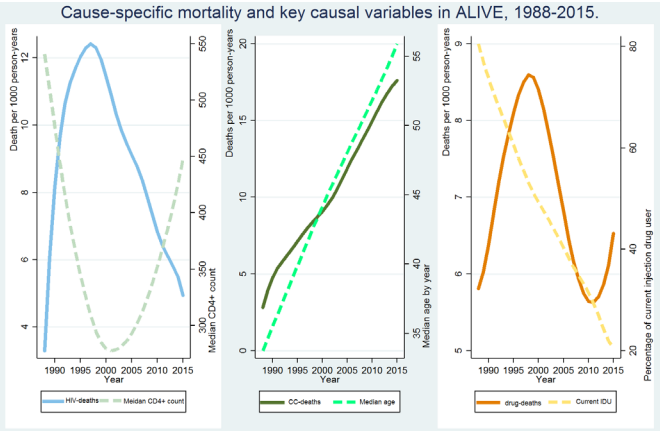
Background: With antiretroviral therapy (ART), HIV-infected persons are living longer. Yet severe disparities in morbidity and mortality remain for HIV-infected persons who inject drugs (PWID). Understanding trends in cause-specific mortality are critical to effectively directing interventions to improve health outcomes in this highly vulnerable group. We sought to characterize

temporal trends in cause-specific mortality over ~30 years among HIV-infected and uninfected PWID.

Methods: Mortality was ascertained in the AIDS Linked to the IntraVenous Experience (ALIVE) cohort of PWID from 1988 to 2015 through linkage to the National Death Index. Deaths were classified into HIV and infectious related (HIV-deaths), chronic conditions (CC-deaths), and overdose and drug-related (drug-deaths). All-cause and cause-specific mortality rates were assessed for each calendar year. Figure displays HIV-deaths against the median CD4+, CC-deaths against the median age, and drug-deaths against the % of current IDUs within the cohort. Drug abuse information was further assessed through the Drug Abuse Screening Test (DAST-20).

Results: Of 4,794 participants (25.8% HIV-infected) contributing 75,327 person-years (pys), there were 2,070 deaths. The median age increased from 34.6 in 1988 to 44.2 in 2015. A higher proportion of those who died were male, black, less educated, and HIV or hepatitis C infected. All-cause mortality increased from 15.4 per 1000-pys in 1988 to 31.4 per 1000-pys in 2001, with a subsequent plateau through 2015 (32 per 1000-pys). HIV-deaths peaked at 19.6 per 1000-pys in 1994 then continuously declined to 5.7 per 1000-pys in 2015. CC-deaths increased from 2.7 per 1000-pys in 1988 to 17.7 per 1000-pys in 2015. drug-deaths peaked at 11.1 per 1000-pys in 1998, had a nadir of 3.8 per 1000-pys in 2012, then most recently doubled to 7.9 per 1000-pys in 2015. Though active injection drug use declined overall in this period, moderate/severe drug abuse based on the DAST increased after 2013, coincident with increased drug-related deaths.

Conclusion: Besides the expected decline in HIV-deaths due to ART, the rising rates of chronic disease mortality demonstrate the critical importance of chronic disease management in this aging population. Though drug-related deaths initially declined with decreasing active injection, a recent resurgence in drug-related deaths is likely related to non-injection drug use and prescription opioids and critically requires prompt intervention for this vulnerable population.



892 INDIVIDUAL AND SITE-LEVEL FACTORS ASSOCIATED WITH RISK OF DEATH AMONG PEOPLE WITH HIV

Amanda D. Castel, Lindsey Powers Happ, Anne K. Monroe, Maria Jaurretche, Arpi Terzian, Alan Greenberg
The George Washington University, Washington, DC, USA

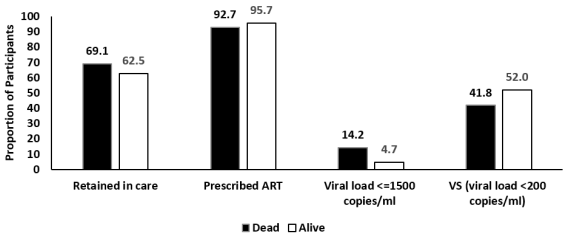
Background: Although antiretroviral therapy allows persons with HIV (PWH) to live longer, healthier lives, many PWH may not be receiving comprehensive HIV care, resulting in shortened survival. To identify factors potentially associated with improved survival, we sought to compare individual, clinic-level, and care continuum patterns among those who died and those who survived in a cohort of PWH receiving care in Washington, DC.

Methods: Participants of the DC Cohort, a longitudinal observational cohort of PWH in care, at 14 sites as of 12/31/2016 were examined. Clinic-level variables were assessed with a site survey which queried available services (e.g., hours, referrals, visit intervals, re-engagement services, subspecialty care). An overall clinic assessment score (range 0-9) was assigned to each site. Other clinic-level variables examined were systematic retention in care monitoring and routine review of medication pick up (ART monitoring). Care continuum outcomes were assessed for the 6-months prior to death. Univariate analyses were used to compare participants who died vs. survived. Cox proportional hazards models were used to identify associations between clinic-level variables and time to death.

Results: Among 6,608 participants, 292 (4.4%) died from 2011-2016; 1.06 deaths per 100 person-years. Deaths were among males (71.6%), blacks (81.8%), and mean age at death was 56.5 yrs. From death certificates, 25% of deaths were HIV-related, 13% cardiovascular disease related and 11% due to non-AIDS related cancers. Median time from HIV diagnosis to death was 14.3 years (IQR:9.1, 21.1). The mean number of days from last care encounter to death was 78 (IQR:30.5-188) with a median CD4 closest to death of 346 cells/μl (IQR:159, 562). In separate multivariate analyses, an increased risk of death was observed among those in care at clinics with no ART monitoring (aHR 1.82; 95%CI:1.36, 2.45), no retention monitoring (aHR1.54; 95%CI: 1.15, 2.06), and those with lower clinic assessment scores (≤6) (aHR1.43; 95%CI: 1.08, 1.90). HIV care continuum outcomes among PWH who died vs. survived found that higher proportions of those who died were retained in care in the 6-months prior to death (p=0.0359), yet lower proportions were prescribed ART (p=0.0223) and virally suppressed (VL<200 copies/ml)(p<0.0001)(Figure).

Conclusion: Our findings suggest that despite PWH being relatively well-engaged, comprehensive site-level services may improve quality of care, thereby mitigating poor outcomes and improving survival.

Figure. Comparison of HIV care continuum outcomes among those who died (n= 246) vs. those who survived (n=6,063), DC Cohort, 2011-2016*



*Care continuum outcomes were assessed among participants who had data in the 6 months prior to death, or had at least 6 months of follow-up for those who survived. Retention in care was defined as a visit, CD4, or viral load indicative of HIV care receipt. P<0.05 for all care continuum outcomes comparing those who died with those who survived.

893 MORTALITY IS HIGHER AMONG SUCCESSFULLY TREATED PWH COMPARED TO MATCHED CONTROLS

Veronica Svedhem-Johansson[1], Zaake de Coninck[1], Laith Hussain-Alkhateeb[2], Anna Mia Ekström[1], Göran Bratt[3], Magnus Gisslén[4], Max Petzold[4]
[1]Karolinska Institute, Stockholm, Sweden, [2]Sahlgrenska University Hospital, Gothenburg, Sweden, [3]Södersjukhuset, Stockholm, Sweden, [4]Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Background: There is an ongoing debate among researchers about whether the lifespan of successfully treated people living with HIV (PLHIV) is comparable to that of the general population. In this 15 years follow up cohort study we present a survival analysis of People With HIV (PWH) and HIV-negative persons in relation to socio-demographic, virus load, CD-4 count, ART and mortality data from the national Swedish HIV cohort, InfCareHIV.

Methods: A total of 4,066 people living with HIV were matched against 8,072 HIV-negative controls according to age, gender, and region of birth. Furthermore the association between viral load and CD-4 level at diagnosis, treatment outcome and mortality was assessed over a 15-year period by Cox regression estimates to compare the overall crude and adjusted Hazard Ratios for mortality.

Results: Mortality rates/100 PY, HIV-Positive n=275/4,066 1.13 (1.00-1.27) as compaired to HIV-Negative n=110/8,072, 0.22 (0.18-0.26)p <0.001. After a 15 year follow up period, successfully treated PLHIV were found to be 3 times more likely to die when compared to HIV-negative controls (HR 3.01, 95%, CI 2.05-4.44, p<0.001). The risk of mortality decreased from HR 6.02 after the first year of successful treatment. Only 11 of 58 patients in our cohort died from an AIDS-related condition. When AIDS-attributed mortality is excluded, successfully treated PWH are still 2.4 times more likely to die compared to HIV negative persons (HR 2.43, 95%, CI 1.61-3.65, p<0.001). Among the 275 that died, the initial VL was ≥30,000 c/ml among 171 of the patients (62.2%) and <30,000 c/ml among 83 of the patients (30.2%). Patients with VL≥30,000c/mL at HIV diagnosis were associated with a 1.74 (95% CI 1.34-2.26) greater hazard of death comparedto patients with VL< 30,000 at diagnosis (p<0.001).

Conclusion: Although effective viral suppression has led to significant increases in longevity and quality of life, ART is not yet able to fully restore life expectancy to a level comparable to that found in HIV-negative persons even when PWH are successfully treated in our Swedish context. If we were used the cut off at ≤ 50/mL the result might have been different. The risk of mortality decreases the longer an HIV patient is able to suppress their VL. Even when PLHIV are successfully treated there are several other important areas related to death, such as smoking and social factors, where data are still missing.

894 RATES OF MORTALITY AMONG SCHIZOPHRENIC PEOPLE LIVING WITH AND WITHOUT HIV

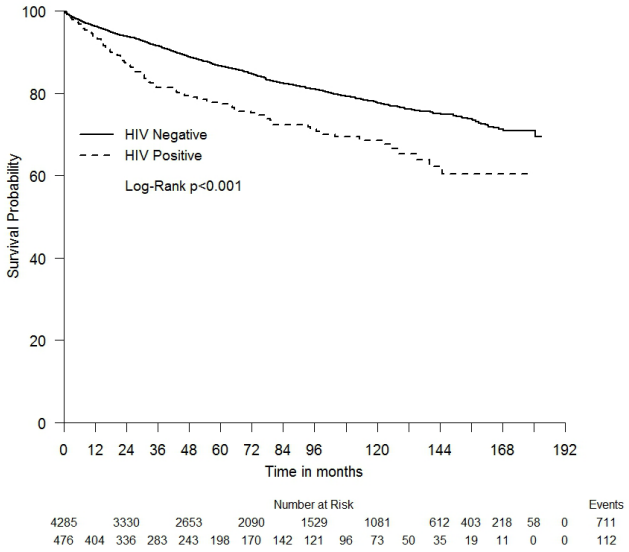
Kalysha Closson[1], Kate Salters[1], Thomas L. Patterson[2], Oghenowede Eyawo[1], William Chau[1], Monica Ye[1], Mark Hull[1], Viviane D. Lima[1], Julio S. Montaner[1], Robert S. Hogg[1]
[1]*British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada,* [2]*University of California San Diego, San Diego, CA, USA*

Background: Schizophrenia (SZO) is a mental health condition that has important implications for morbidity and mortality outcomes, particularly for people living with HIV (PLHIV). As of yet, few studies have explored the impact of HIV and SZO on mortality.

Methods: Using the Comparative Outcomes and Service Utilization Trends cohort study, a population-based retrospective cohort study examining health outcomes and service use of PLHIV and a 10% random sample of individuals in British Columbia (BC), SZO prevalence and mortality outcomes were estimated from 1998-2013. Prevalence of SZO was assessed using physician and hospital-based administrative data and International Classification of Disease 9/10 codes. Survival time by HIV-status was accessed by a Kaplan-Meier (KM) plot, with log-rank test for comparison. Age and sex–adjusted mortality rates were calculated by using 2016 Canada population as reference. The association between HIV and all-cause mortality among SZO+ individuals were examined using logistic regression.

Results: Of 515,913 BC residents accessing medical services from 1998-2013 in our study sample, 2.6% (n=13,412) were PLHIV and were significantly more likely to be SZO+ compared to HIV- individuals (6.3% vs. 1.1%, p<0.001). Compared to SZO+/HIV-, SZO+/PLHIV were significantly (all p<0.001) more likely to be male (75% vs. 56%), live in an urban setting (91% vs. 88%), have a history of injection drug use (IDU) (75% vs. 20%), and ever be on anti-psychotic medication (49% vs. 39%). Age and sex standardized all-cause mortality rates (ASMR) were highest among PLHIV/SZO+ (66.9/1,000 person years [PY], 95%CI=50.6-83.1), compared to PLHIV/SZO- (SMR=39.5/1,000PY, 95%CI=36.6-42.3) and SZO+/HIV- (ASMR=28.2/1,000PY, 95%CI=26.5-30.0). The KM plot (Figure 1) indicate that time from SZO diagnosis to death was significantly shorter among PLHIV compared to HIV- individuals (p<0.001). In a confounding logistic regression model of all SZO+ individuals, HIV-status remained significantly associated with mortality (aOR=2.31, 95%CI=1.84-2.89), controlling for sex, baseline age, and IDU.

Conclusion: PLHIV experience a six-times higher SZO prevalence compared to HIV- individuals, and among SZO+ individuals HIV is a risk factor for mortality. Moreover, PLHIV/SZO+ have higher mortality rates than PLHIV/SZO-. Physicians working with PLHIV/SZO+ that have high levels of IDU, should closely monitor treatment for SZO and HIV, so as to reduce mortality for this under-served, high-risk population.



895 CAUSES OF DEATH AND EARLY MORTALITY IN PEOPLE WITH HIV IN MEXICO (2004-2015)

Yanink Caro-Vega[1], Pablo F. Belaunzaran-Zamudio[1], Jesús Alegre-Díaz[2], Brenda Crabtree-Ramírez[1], Raul Ramirez-Reyes[2], Pablo Kuri-Morales[2], Malaquias Lopez-Cervantes[2], Juan Sierra-Madero[1]
[1]*Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico,* [2]*Secretaría de Salud, Mexico City, Mexico*

Background: Antiretroviral therapy (ART) use was followed by mortality reductions and a shift in the causes of death from AIDS to non-AIDS deaths in most settings. In Mexico, mortality due to HIV/AIDS has remained constant even after the expansion of ART use in 2004. Information regarding time from HIV diagnosis to death and causes of death may provide important information on the contribution of late diagnosis on mortality and therefore help to identify gaps in the early phases of the continuum of care. We aimed to estimate the proportion of people dying in the first year after HIV diagnosis, and to describe their causes of death in recent years.

Methods: Using national death registry data, we identified all registered deaths among HIV-infected people between 2004-2015. We define early mortality (EM) as deaths occurring within the first year after HIV-diagnosis and very early mortality (VEM) as deaths in the first month after HIV–diagnosis. We describe changes in the proportion of EM by calendar year and stratified by gender using logistic models. We classified the main cause of death according to ICD-10, and described the most frequent causes of death by gender, calendar year and EM condition.

Results: Between 2004 and 2015 there were 10,872 deaths in HIV-infected women and 48,824 in men. AIDS-related deaths occurred in 74% of all subjects. The most frequent AIDS-related causes of death were: pneumonia (n=14070, 23%), tuberculosis (n=4646, 8%), pneumocystis (n=2197, 4%), and AIDS malignancy (n=1281, 2%); non-AIDS-related causes were: sepsis (n=7352, n=12%) and non-AIDS malignancy (n=1281, 2%) (Fig 1A). When stratified by sex there were non-significant differences in causes of death over time. Fifty three percent (n=3,677) and 57% (n=17,824) were classified as EM in women and men, respectively and did not change along time in both groups. VEM increased from 15% to 22% p<0.001, with no differences by sex (Fig 1B). AIDS explained 75% of EM. Overall, men had a higher risk of EM (OR: 1.14 [95%CI: 1.09-1.18], p<0.01).

Conclusion: The stable EM, increasing VEM and the high percentage of deaths related to AIDS are markers of late HIV diagnosis, which persists along time in Mexico. Non-AIDS causes of death are a small proportion, with modest increase in later years in acute myocardial infarction and non-AIDS malignancies. These results support that policy efforts should be directed to expand HIV diagnosis and early linkage to care.

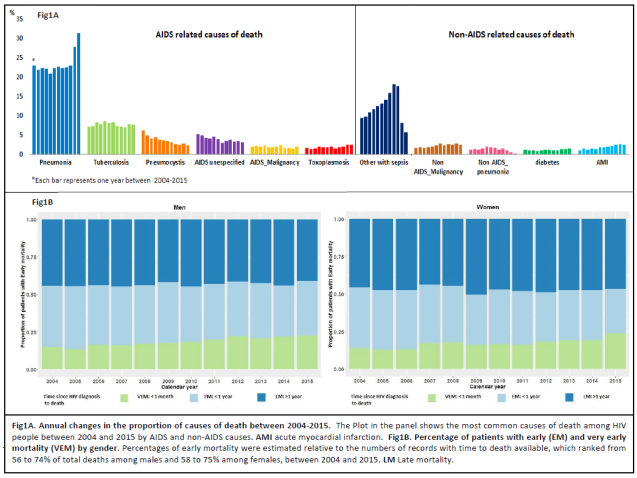


Fig1A. Annual changes in the proportion of causes of death between 2004-2015. The Plot in the panel shows the most common causes of death among HIV people between 2004 and 2015 by AIDS and non-AIDS causes. **AMI** acute myocardial infarction. **Fig1B. Percentage of patients with early (EM) and very early mortality (VEM) by gender.** Percentages of early mortality were estimated relative to the numbers of records with time to death available, which ranked from 56 to 74% of total deaths among males and 58 to 75% among females, between 2004 and 2015. **LM** Late mortality.

896 LATE PRESENTATION WITH HIV IN AFRICA: PHENOTYPES, RISK AND RISK STRATIFICATION

Abraham Siika[1], Leanne McCabe[2], Mutsa Bwakura-Dangarembizi[3], Cissy Kityo[4], Jane E. Mallewa[5], Kath Maitland[6], Anna Griffiths[2], Keith Baleeta[4], Shepherd Mudzingwa[3], James Abach[4], Kusum Nathoo[3], Andrew Prendergast[7], Sarah Walker[2], Diana Gibb[2]

[1]Moi University, Eldoret, Kenya, [2]MRC Clinical Trials Unit at UCL, London, UK, [3]University of Zimbabwe, Harare, Zimbabwe, [4]Joint Clinical Research Centre, Lubowa, Uganda, [5]Malawi–Liverpool–Wellcome Trust Clinical Rsr Prog, Blantyre, Malawi, [6]KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya, [7]Queen Mary University of London, London, UK

Background: In sub-Saharan Africa, severely immunocompromized individuals are at high risk of mortality during the first few months after starting ART. We aimed to determine predictors of this early mortality and whether such "late presenters" could be grouped into phenotypes with different mortality risks.

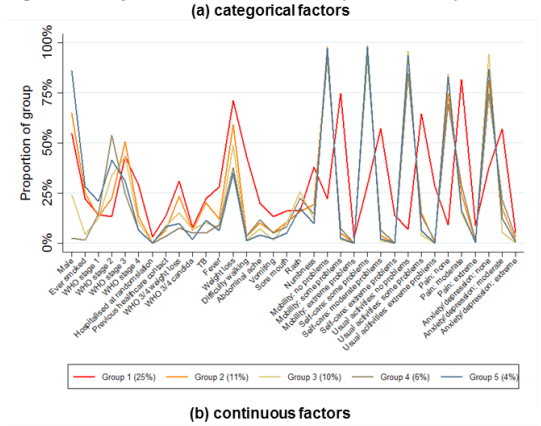
Methods: ART-naïve adults/children ≥5y with CD4<100 cells/ul initiating ART in Uganda, Zimbabwe, Malawi and Kenya were included in the REALITY trial (ISRCTN43622374). Baseline predictors of mortality through 48 weeks on ART were identified using Cox regression with backwards elimination (exit p>0.1). Late presenter phenotypes were identified using hierarchical clustering.

Results: Final multivariable models included 1711 participants (26<13y) of whom 203(12%) died. Mortality was independently higher in those who were older (p=0.002), with lower CD4s (p<0.001), lower albumin (p=0.001), lower haemoglobin (p=0.01) and weaker grip strength (p=0.01); those in whom physicians reported WHO stage 3/4 weight loss (p=0.04); and in those patients reporting fever (p=0.001), vomiting (p=0.02), some problems with mobility (p=0.005) and inability to wash or dress themselves (p=0.003) at baseline. Five "late presenter" groups were identified (figure), with mortality ranging from 4-25%. Group-1 had the highest mortality (25%) and median CD4 28 cells/ul; they had a high burden of symptoms/signs other than rash, weight loss, and problems with mobility and self-care; they also had lower albumin and haemoglobin. Group-2 (11% mortality; median CD4 43 cells/ul) had higher white blood cells, platelets and neutrophils, despite only 31% reporting infections at baseline. Group-3 (10% mortality) were mainly younger women; they had similarly low CD4s (median 27 cells/ul), haemoglobin and BMI to Group-1, but low symptom burden and maintained fat mass. The remaining two groups had lower (4-6%) mortality, higher CD4 (median 42 and 48 cells/ul) and had predominantly maintained their weight within normal ranges. Of note, the effect of the randomized enhanced prophylaxis bundle on mortality was similar across all groups (interaction p=0.32).

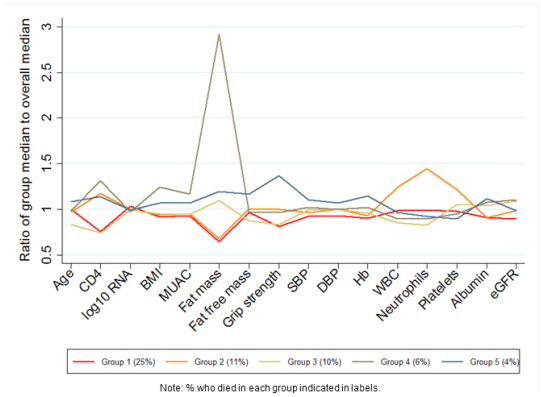
Conclusion: Clinical and laboratory characteristics identified groups at highest risk of mortality following ART initiation. A screening tool appropriate to the level of facility could therefore help identify which patients with low CD4 counts should be prioritized, e.g. for same-day ART initiation, more intensive follow-up, and enhanced prophylaxis.

Figure Summary of characteristics of different patterns of late presenters

(a) categorical factors



(b) continuous factors



Note: % who died in each group indicated in labels.

897 SMOKING, CHRONIC DISEASES, AND MORTALITY OF PEOPLE RECEIVING ART IN BRITISH COLUMBIA

Erin Ready[1], Monica Ye[2], William Chau[2], Viviane D. Lima[2], Paul Sereda[2], Katherine Lepik[2], Robert S. Hogg[2], Rolando Barrios[2], Julio S. Montaner[2], David Moore[2]

[1]University of British Columbia, Vancouver, BC, Canada, [2]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

Background: Chronic diseases, especially those associated with cigarette smoking, are increasingly recognized as leading causes of premature morbidity and mortality for people living with HIV (PLWH). We conducted a cross-sectional analysis to understand the burden of chronic diseases and their associations with mortality among PLWH receiving antiretroviral therapy (ART) in British Columbia (BC).

Methods: In BC, all medically eligible PLWH who are receiving publicly funded ART are enrolled in the HIV Drug Treatment Program (DTP). Beginning in 2014, physicians of DTP patients were mailed Clinical Status Report Forms (CSRF) designed to measure the prevalence of chronic diseases, blood pressure, body mass index (BMI), and cigarette smoking on an annual basis. We analyzed data obtained from CSRFs sent to physicians between June 17, 2014 and September 30, 2016. Follow-up for mortality was conducted through data linkages with the provincial vital statistics agency until August 2017. Multivariate logistic regression models were developed to determine factors associated with mortality.

Results: We analyzed data from 3307 DTP patients whose physicians returned at least one CSRF, representing 41.5% of DTP participants. Among these patients, the median age was 50.5 years, 79.4% were male and 86.7% had viral load measurements <200 copies/mL. Among individuals with reported smoking status, 40.8% were current smokers, 20.6% were former smokers, and 38.6% had never smoked. At least one chronic condition was reported for 55.0% of DTP patients whose physicians returned at least one CSRF, with hepatitis C infection (reported for 24.4%), dependence on drugs other than alcohol (20.3%) and depression or bipolar disease (12.6%) being the most common. In multivariate modeling, current smoking (adjusted odds ratio [aOR] 2.73; 95% confidence interval [CI] 1.40-5.33), diabetes mellitus (aOR 1.99; 95% CI 1.05-3.77), alcohol

dependence (aOR 1.65; 95% CI 1.05-2.60), and non-AIDS defining cancers (aOR 3.17; 95% CI 1.52-6.59) were all associated with mortality.

Conclusion: Current cigarette smoking, alcohol dependence and other chronic diseases are strongly associated with mortality among PLWH in BC. Focused attention to smoking cessation, treatment for alcoholism and better diabetes management may further reduce mortality among PLWH.

Variable	Univariate Analysis	Multivariate Analysis
	Adjusted Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)
HIV Risk Exposure		
MSM	1.00	1.00
Blood	1.67 (0.57, 4.89)	1.47 (0.48, 4.46)
Heterosexual	1.27 (0.63, 2.56)	0.80 (0.38, 1.68)
IDU	3.94 (2.51, 6.18)	2.55 (1.49, 4.35)
MSM/IDU	2.39 (1.20, 4.75)	1.82 (0.87, 3.80)
Other/Unknown	1.37 (0.78, 2.42)	1.55 (0.85, 2.83)
Smoking Status		
Never	1.00	1.00
Current	4.63 (2.52, 8.51)	2.73 (1.40, 5.33)
Former	2.05 (0.96, 4.41)	1.20 (0.54, 2.69)
Unknown	4.41 (2.44, 7.96)	2.69 (1.41, 5.15)
Body Mass Index		
Normal (≥18.5, <25)	1.00	1.00
Underweight (<18.5)	3.61 (1.65, 7.91)	3.33 (1.45, 7.62)
Overweight (≥25, <30)	0.78 (0.37, 1.62)	0.89 (0.41, 1.92)
Obese (≥30)	0.90 (0.38, 2.13)	0.83 (0.33, 2.08)
Unknown	1.89 (1.19, 3.00)	1.79 (1.06, 3.03)
CD4 (Closest Value within 3 Months Before or After Time CSRF was Received)		
≥500 cells/mm^3	1.00	1.00
<200 cells/mm^3	5.21 (3.26, 8.33)	3.32 (2.00, 5.50)
200-349 cells/mm^3	3.38 (2.15, 5.34)	2.25 (1.39, 3.64)
350-499 cells/mm^3	2.06 (1.29, 3.27)	1.91 (1.18, 3.08)
Unknown	3.54 (2.16, 5.79)	2.62 (1.56, 4.40)
Adherence to ART in Year Prior to Time CSRF was Received		
≥95%	1.00	1.00
<95%	1.92 (1.38, 2.68)	1.34 (0.93, 1.92)
Unknown	1.72 (1.07, 2.75)	2.66 (1.47, 4.81)
Diabetes Mellitus		
No or Unknown	1.00	1.00
Yes	1.85 (1.06, 3.22)	1.99 (1.05, 3.77)
Chronic Renal Disease		
No or Unknown	1.00	1.00
Yes	2.38 (1.31, 4.33)	1.80 (0.93, 3.52)
Alcohol Dependence		
No or Unknown	1.00	1.00
Yes	2.79 (1.85, 4.21)	1.65 (1.05, 2.60)
Dependence on Other Drugs		
No or Unknown	1.00	1.00
Yes	2.40 (1.74, 3.31)	1.45 (0.96, 2.17)
Non-AIDS-Defining Cancer		
No or Unknown	1.00	1.00
Yes	4.05 (2.07, 7.91)	3.17 (1.52, 6.59)
Age (10 years)	1.45 (1.27, 1.65)	1.70 (1.43, 2.01)
Class of 3rd Drug in ART Regimen at Time CSRF was Received		
Protease inhibitor	1.00	1.00
NNRTI	0.62 (0.41, 0.94)	0.76 (0.49, 1.18)
Integrase inhibitor	0.56 (0.35, 0.91)	0.64 (0.39, 1.06)
Other	0.93 (0.55, 1.57)	0.77 (0.43, 1.35)
Not on therapy	2.39 (1.35, 4.23)	1.66 (0.84, 3.26)

898 PERSONS LIVING WITH HIV (PLHIV) WITH ADVANCED HIV DISEASE: NEED FOR NOVEL CARE MODELS

Wafaa M. El-Sadr, **Chloe A. Teasdale**, Katharine Yuengling, Peter Preko, Maureen Syowai, Felix Ndagije, Miriam Rabkin, Elaine J. Abrams
ICAP at Columbia University, New York, NY, USA

Background: Differentiated service delivery (DSD) has highlighted the importance of developing diverse, patient-centered models of care for stable patients on antiretroviral therapy (ART). However, similar innovations are not yet available for PLHIV with advanced disease who are at high risk for poor outcomes and have received little attention beyond recognition of their need for prompt ART initiation.

Methods: We analyzed data on PLHIV ≥15 years starting ART with CD4 cell count ≤200 cell/mm^3 at PEPFAR-funded ICAP-supported clinics in Ethiopia, Kenya, Mozambique and Tanzania 2004-2015. PLHIV with low CD4 at start of ART were divided into 3 groups: CD4 101-200, CD4 50-100 and CD4<50 cell/mm^3 to examine a combined endpoint of attrition (loss to follow up (LTF) and death) following ART start using Kaplan-Meier estimators and log-rank tests. LTF after ART initiation was defined as no visit >6 months; deaths were ascertained from medical records. The combined endpoint was used as deaths are under-recorded. Cox proportional hazards models examined the effect of CD4 at ART start on attrition adjusted for sex, age, country and intrasite clustering.

Results: 477,086 PLHIV started ART at 350 clinics, of whom 203,622 (42.7%) had CD4 ≤200 cell/mm^3 at ART start. Among these, 60.2% were female, median age was 35.0 years [IQR: 28.9-42.1], and 60.7% were WHO stage III/IV. Among those with CD4 <50 cell/mm^3, 70.6% were stage III/IV compared to 52.9% of those with CD4 101-200(p<0.0001). Overall, for patients with CD4 ≤200, attrition at 3, 6 and 12 months was 14.8% (95%CI 14.6-14.9), 19.7% (95%CI 19.6-19.9) and 25.1% (95%CI 24.9-25.3), respectively. Attrition was significantly higher with lower CD4 counts; at 12 months 32.2% (95%CI 31.8-32.6) of those with CD4<50 cell/mm^3 at ART start were lost or had died compared to 20.8% (95%CI 20.6-21.1) with CD4 101-200 cell/mm^3 (p<0.0001)(Table 1). In multivariable models, PLHIV with CD4<50 cells/mm^3 had 40% increased risk of attrition compared to those with CD4 101-200 cell/mm^3 (adjusted hazard ratio 1.4, 95%CI 1.3-1.4).

Conclusion: Even after ART initiation, PLHIV with advanced disease had notably inferior outcomes within lower CD4 strata. With the transition of stable patients to less intensive DSD models requiring less provider time, the opportunity exists to focus on optimizing outcomes for PLHIV with advanced HIV disease. Novel DSD models that include biomedical, psychosocial and structural interventions are urgently needed.

Table 1. LTF, death and combined attrition outcomes for patients starting ART with CD4 cell count ≤200 cells/mm3 in Ethiopia, Kenya, Mozambique and Tanzania

	All CD4 ≤200 cells/mm^3	CD4 101-200 cells/mm^3	CD4 50-100 cells/mm^3	CD4 <50 cells/mm^3
	Cum. Inc. (95%CI)	Cum. Inc. (95%CI)	Cum. Inc. (95%CI)	Cum. Inc. (95%CI)
LTF at 3 months	10.8 (6.9-7.1)	8.9 (8.8-9.1)	11.1 (10.8-11.4)	14.0 (13.7-14.3)
LFT at 6 months	15.1 (14.9-15.3)	12.7 (12.5-12.9)	15.7 (15.4-16.1)	19.0 (18.6-19.3)
LTF at 12 months	20.0 (19.8-20.1)	16.8 (16.5-17.0)	20.6 (20.2-21.0)	24.2 (23.8-24.6)
Death at 3 months	4.4 (4.3-4.5)	2.6 (2.5-2.7)	4.6 (4.4-4.8)	7.5 (7.3-7.7)
Death at 6 months	5.4 (5.3-5.5)	3.4 (3.3-3.5)	5.7 (5.5-5.9)	9.0 (8.7-9.2)
Death at 12 months	6.4 (6.3-6.5)	4.1 (4.0-4.3)	6.8 (6.6-7.1)	10.4 (10.1-10.7)
Attrition at 3 months	14.8 (14.6-14.9)	11.4 (11.2-11.6)	15.1 (14.8-15.4)	20.5 (20.2-20.8)
Attrition at 6 months	19.7 (19.6-19.9)	15.7 (15.5-15.9)	20.6 (20.2-20.9)	26.3 (26.0-26.7)
Attrition at 12 months	25.1 (24.9-25.3)	20.8 (20.6-21.1)	26.1 (25.7-26.5)	32.2 (31.8-32.6)

899 HIGH MORTALITY AMONG PLHIV WITH TB IN LESOTHO DESPITE HIGH ART UPTAKE

Andrea Howard[1], Kieran Hartsough[1], Kathryn Curran[2], Koen Frederix[3], Fred Asiimwe[4], Llang Maama-Maime[5], Simon G. Marealle[5], Eric Pevzner[2]
[1]ICAP at Columbia University, New York, NY, USA, [2]CDC, Atlanta, GA, USA, [3]ICAP at Columbia University–Lesotho, Maseru, Lesotho, [4]CDC, Maseru, Lesotho, [5]Ministry of Health, Maseru, Lesotho

Background: World Health Organization guidelines include the recommendation that people living with HIV (PLHIV) with tuberculosis (TB) should receive antiretroviral therapy (ART) as soon as possible within eight weeks of initiating TB treatment, and within two weeks if their CD4 count is <50 cells/µl. We evaluated the extent to which these guidelines were implemented and whether there was an impact on survival during TB treatment for PLHIV in Lesotho.

Methods: We conducted a retrospective review of routinely collected clinical data from 25 purposively selected health facilities in five districts of Lesotho to evaluate ART uptake and TB treatment outcomes for PLHIV diagnosed with TB between January and June 2016. Descriptive and bivariate analyses were conducted. All statistical analyses accounted for clustering by health facility, using generalized linear mixed models.

Results: Among 912 patients with TB/HIV we identified through record review, median age was 37 years (interquartile range [IQR] 31-45); 57% were male, 87% were new TB cases and 89% had pulmonary TB. Among 508 (56%) patients with available data, median CD4 count at TB diagnosis was 196 (IQR 93-344). Overall 783 (86%) were on ART during TB treatment. Of 751 patients with initiation dates, 315 (42%) were on ART prior to, and 436 (58%) started ART during TB treatment. Median time to ART initiation after TB treatment initiation was 17 days (IQR 14-29); 410 (94%) started ART within eight weeks, and 174 (40%) within two weeks of TB treatment initiation. Of 46 patients with CD4 count <50 who started ART during TB treatment, 22 (48%) started within two weeks of TB treatment initiation. Among all 912 patients, 27% achieved cure, 43% completed treatment, <1% failed treatment, 8% were lost to follow-up, 17% died and 5% had no TB treatment outcome recorded (Table). Mortality was higher among those with CD4 count <50 as compared to CD4 count ≥50 (25% vs. 11%, p=0.004) and among those who never started ART (54% vs. 14%, p <0.0001). There was no difference in mortality between those who started ART before vs. during TB treatment (15% vs. 13%, p=0.37).

Conclusion: Over half of patients with TB/HIV were not on ART when diagnosed with TB. Despite high ART uptake during TB treatment, mortality was unacceptably high. Scale up of 'Test and Treat' holds promise as a TB prevention strategy for PLHIV. However, these findings support the critical need for an enhanced package of care for PLHIV with advanced disease to mitigate mortality among PLHIV with TB.

TB Treatment Outcomes among Patients with TB/HIV by CD4 Count and ART Status

	Total n=912 (%)	Cured n=243 (27)	Treatment Completed n=393 (43)	Treatment Failure n=2 (<1)	Lost to Follow-Up n=74 (8)	Died n=153 (17)	Missing n=47 (5)
CD4 count, cells/μl							
<50	71	27 (38)	22 (31)	0 (0)	2 (3)	18 (25)	2 (3)
≥50	437	126 (29)	218 (50)	1 (<1)	27 (6)	50 (11)	15 (3)
Missing	404	90 (22)	153 (38)	1 (<1)	45 (11)	85 (21)	30 (7)
ART Initiation							
Before TB treatment	315	89 (28)	145 (46)	2 (1)	21 (7)	46 (15)	12 (4)
During TB treatment	436	136 (31)	211 (48)	0 (0)	24 (6)	55 (13)	10 (2)
On ART, time of start unknown	32	7 (22)	5 (16)	0 (0)	7 (22)	6 (19)	7 (22)
No ART	57	2 (4)	4 (7)	0 (0)	14 (25)	31 (54)	6 (11)
Missing	72	9 (13)	28 (39)	0 (0)	8 (11)	15 (21)	12 (17)

900 SUBSTANTIAL MORTALITY AND LOSS PRIOR TO TREATMENT IN ART-ELIGIBLE PATIENTS IN ZAMBIA

Aaloke Mody[1], Izukanji Sikazwe[2], Theodora Savory[2], Kombatende Sikombe[2], Paul Somwe[2], Mwanza wa Mwanza[2], Carolyn Bolton Moore[2], Nancy Padian[3], Charles B. Holmes[4], Elvin Geng[1]

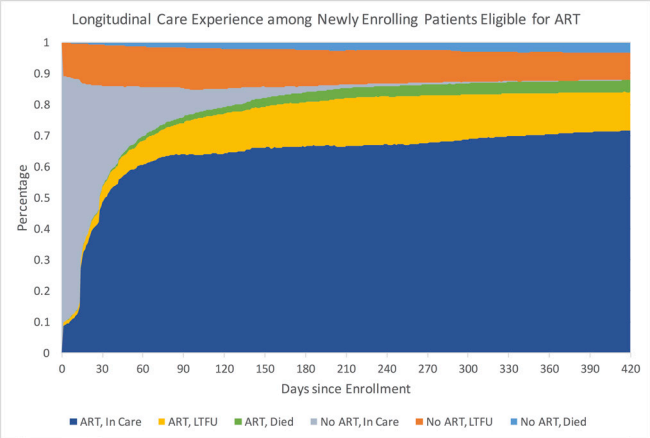
[1]University of California San Francisco, San Francisco, CA, USA, [2]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, [3]University of California Berkeley, Berkeley, CA, USA, [4]Johns Hopkins University, Baltimore, MD, USA

Background: An effective cascade in the treat-all era must include timely and complete ART initiation. Most epidemiologic studies begin with ART initiation, and thus neglect failures to initiate, loss to follow-up (LTFU), and deaths prior to treatment, thereby failing to identify important opportunities for improvement.

Methods: We analyzed a population-representative sample of newly-enrolling, ART-eligible adults (CD4≤500 cells/μl or pregnant/breastfeeding women) at 64 clinics in Zambia between April 1, 2014 and July 31, 2015. We used data from electronic medical records supplemented by active tracing of a random sample of lost (>90 days late for last visit) patients to ascertain outcomes (e.g., mortality, care status, reasons for LTFU, virologic suppression [DBS HIV RNA≤1000 copies/ml]). We used a weighted multistate analysis to estimate the prevalence and incidence of six retention states over time: 1) In Care prior to ART 2) In Care on ART 3) LTFU prior to ART 4) LTFU on ART 5) Died prior to ART 6) Died on ART. We estimated overall virologic suppression and identified predictors of mortality prior to initiation using a modified Poisson regression with robust variances.

Results: 23,229 patients (58% female; median age 34y [IQR 29-41], median CD4 234 cells/μl [IQR 120-365]) were eligible for ART at enrollment. At one year, 87.4% of patients had been initiated on ART (95% CI 86.0-88.8%), 70.5% were still in care and on ART (CI 69.8-71.1%), 22.3% (CI 21.5-23.2%) were LTFU (9.2% prior to vs. 13.1% after ART), and 7.0% (CI 6.5-7.5%) had died (3.2% prior to vs. 3.8% after ART). 11.8% of patients were LTFU after only one visit (CI 11.3-12.4%). Among those who died, younger age (aRR 1.23 per 10y decrease, p<0.01), lower CD4 (aRR 1.19 per 50 cell/μl decrease, p<0.01), and attending a clinic with higher proportions of follow-up scheduled at 1m (aRR 1.16 per 10% increase, p=0.025) were associated with dying prior to, as opposed to after, ART initiation. Among those LTFU, patients lost prior to ART were more likely to be out of care rather than silent transfers (77.8% prior to vs. 38.2% after ART, p<0.01). In Lusaka province, virologic suppression amongst alive patients was 80.0% in those started on ART (CI 64.1-93.6%) and 56.9% overall (CI 45.7-68.3%).

Conclusion: There is substantial loss and mortality even prior to treatment initiation among ART-eligible patients. Efforts to ensure engagement prior to treatment and rapid ART initiation are needed to optimize the population-level effects of treat-all.



901 LONG-TERM MEASURES OF HIV EXPOSURE AND MORTALITY IN THE HIV OUTPATIENT STUDY

Frank J. Palella[1], Carl Armon[2], Stephen R. Cole[3], Rachel Hart[2], Nabil Rayeed[2], Ellen Tedaldi[4], Bienvenido Yangco[5], Richard Novak[6], Linda Battalora[7], Stacey Purinton[2], Kate Buchacz[8]

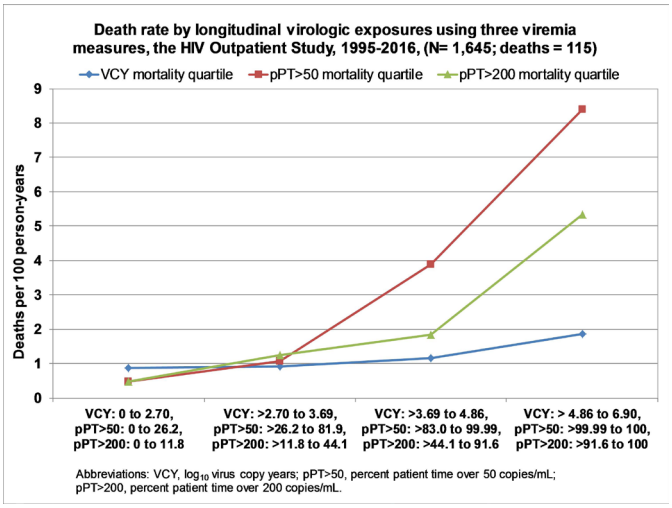
[1]Northwestern University, Chicago, IL, USA, [2]Cerner Corp, Kansas City, MO, USA, [3]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [4]Temple University, Philadelphia, PA, USA, [5]Infectious Disease Research Institute, Tampa, FL, USA, [6]University of Illinois at Chicago, Chicago, IL, USA, [7]Colorado School of Mines, Golden, CO, USA, [8]CDC, Atlanta, GA, USA

Background: Elucidating associations between long-term HIV viral exposure (VE) measures and mortality can inform the management and monitoring of ART-treated patients.

Methods: We analyzed medical records of HIV Outpatient Study (HOPS) participants seen at 12 US HIV clinics who initiated ART between March 1995 and June 2015, were followed for ≥ 6 months, had ART prescribed ≥ 75% of time, and had ≥ 2 plasma viral load (VL) and ≥ 1 CD4+ cell count (CD4) during observation. We evaluated all-cause mortality from 6 months after ART start until 30 June 2016. VE was quantified using two time-updated variables: viremia copy-years (VCY) and percent of person-time (pPT) spent above 200 or 50 copies/mL. We fit Cox models to estimate associations between VE and mortality.

Results: The 1,645 patients had median age at ART start (baseline, BL) of 38 years (interquartile range [IQR]: 31-45), 78% were male, 37% non-Hispanic black, 14% Hispanic/Latino, 57% were men who have sex with men (MSM), 6% had injection drug use (IDU) risk, and 31% had public health insurance. Median BL CD4 was 293 (IQR 140-460). Patients contributed 10,453 person years [py], with median 14 VLs (IQR: 7-24) per patient. Median pPT > 200 or > 50 were 10% (IQR: 1%-47%) and 26% (IQR: 6%-72%), respectively, and median VCY was 3.0 $\log_{10}$ (IQR: 2.3-4.2). There were 115 deaths; among decedents median pPT > 200 or > 50 were 44% (IQR: 12%-92%) and 82% (IQR: 26%-100%) respectively, and median VCY was 3.7 $\log_{10}$ (IQR: 2.7-4.9). In Cox models, mortality was associated with BL age (Hazard Ratio [HR] 1.7, 95% confidence interval [CI]: 1.4-2.0, per 10 years), IDU risk (HR 3.8, CI: 2.2-6.5), heterosexual HIV risk (HR 1.7, CI: 1.1-2.7), and BL CD4 (HR 0.8, CI: 0.8-0.9 per 100 cells/mm^3). When pPT > 200 or > 50 was added to the model, HR for death was 1.22 (CI: 1.15-1.28) and 1.19 (CI: 1.12-1.25) for each 10% increase in pPT above VE threshold value, respectively. Each $\log_{10}$ increase in VCY was associated with 70% greater mortality risk (HR=1.70, CI: 1.45-1.99). When VCY and pPT > 50 were both added to the model, each remained significant, but when VCY and pPT > 200 were both added, only pPT > 200 remained independently predictive of death.

Conclusion: Each measure of long-term VE was independently associated with mortality. Combined VCY and pPT > 50 captured more independent information about mortality than combined VCY and pPT > 200, suggesting pPT > 50 is a better indicator of viral danger in ART-treated patients.



902 POST-HOSPITAL MORTALITY AND READMISSION AMONG HIV-INFECTED ADULTS IN SOUTH AFRICA

Chris Hoffmann[1], Minja Milovanovic[2], Deanne Kerrigan[1], Neil A. Martinson[2], Ebrahim Variava[2]

[1]Johns Hopkins University, Baltimore, MD, USA, [2]University of the Witwatersrand, Johannesburg, South Africa

Background: Despite the scale-up of the antiretroviral (ART) program in South Africa, HIV continues to cause substantial mortality. Hospitalization presents an opportunity to stabilize and engage individuals in ongoing care. Among a cohort of HIV-infected adults we describe health care use and survival following an index hospital admission.

Methods: From April to June 2016, 121 hospitalized HIV-infected adults were enrolled, by convenience sampling, in a prospective cohort and followed to six months post-discharge. We sought to describe characteristics associated admission and mortality using multivariate logistic regression.

Results: The median age of cohort members was 40 years (interquartile range (IQR) 31, 50), 56% were women, the median CD4 count was 260 (IQR: 113, 464), 11 had a discharge diagnosis of TB. The median duration of hospitalization among survivors was 5.5 days (IQR: 3, 9). 96 had a prior HIV diagnosis of which 73 (74%) reported being on ART, and 70% reported having at least one HIV clinic visit in the prior 6 months. A routine follow-up was scheduled for 98z%, this was within 2 weeks of discharge for 51%; 92% of visits were scheduled at the hospital specialty clinics. Among a sample of 15 participants who did attend clinic, the median time of a clinic visit was 4.3 hours and the median cost was 2% of the monthly household income. After discharge, 83 (68%) participants reported a clinic visit, 45% to a local primary care clinic, the median time after discharge to follow-up clinic was 5 weeks (IQR 3, 8). By 6 months following the index discharge, 43 (36%) participants had been readmitted and 31 (26%) died. Older age (OR 3.1, p=0.05, >51 versus 17-35 years), failure to attend clinic (OR 4.7, p=0.003), reporting "skipping going to clinic because it is hard to get to" (OR 2.9, p=0.03), and longer length of stay were all associated with death or readmission.

Conclusion: HIV-infected adults admitted to hospital remain at high risk of death and readmission after discharge despite access to ART. While most participants had a post-discharge clinic visit, this occurred later and at a different location than scheduled. Notably, self-reports of difficulty getting to the clinic and not attending a clinic visit were both associated with hospital re-admission and mortality. Our results suggest that improving post-discharge outcomes may require strategies that improve access, acceptability, and use of timely follow-up care after discharge.

903 LIFE EXPECTANCY IN KEY POPULATIONS OF ADULTS WITH HIV IN THE US AND CANADA

Keri N. Althoff[1], Richard D. Moore[1], Michael John Gill[2], Michael A. Horberg[3], Amy C. Justice[4], Mari Kitahata[5], Marina Klein[6], Fidel A. Desir[1], W. C. Mathews[7], Angel Mayor[8], Peter F. Rebeiro[9], Michael J. Silverberg[10], Stephen J. Gange[1], Robert S. Hogg[11]

[1]Johns Hopkins University, Baltimore, MD, USA, [2]University of Calgary, Calgary, AB, Canada, [3]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [4]VA Connecticut Healthcare System, West Haven, CT, USA, [5]University of Washington, Seattle, WA, USA, [6]McGill University, Montreal, QC, Canada, [7]University of California San Diego, San Diego, CA, USA, [8]Universidad Central del Caribe, Bayamon, Puerto Rico, [9]Vanderbilt University, Nashville, TN, USA, [10]Kaiser Permanente Northern California, Oakland, CA, USA, [11]Simon Fraser University, Vancouver, BC, Canada

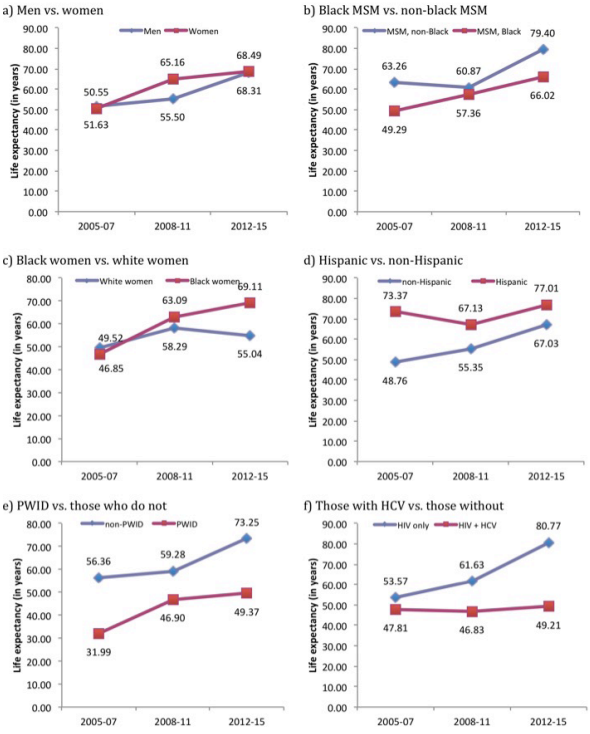
Background: ART has improved the life expectancy (LE) of those with HIV. However, there is less information on LE changes in certain key populations living with HIV in the US, including Black men who have sex with men (MSM), Black women, Hispanics, people with a history of injecting drugs (PWID), and individuals co-infected with hepatitis C (HCV) in the more recent treatment era.

Methods: Using data from NA-ACCORD, we estimated LE after ART initiation in three time-periods (2005-07, 2008-11, 2012-15). Cohorts in the NA-ACCORD have previously demonstrated good ascertainment of deaths using active and passive methods. Standard abridged life table methodology was used to estimate LE for Black MSM (vs. white MSM), Black women (vs. white women), Hispanic (vs. non-Hispanic) adults, PWID (vs. those who do not) and HCV+ (vs. HCV-) adults with HIV.

Results: Among 55,858 ART initiators who contributed 248,931 person-years and 3,123 deaths between 2005 to 2015, the LE increased in both men and women (Figure). LE increased in Black MSM over time, but was consistently lower than non-Black MSM in all time periods. Black women had a similar LE compared to white women in 2005-07, but had a greater LE in 2012-15. Hispanic adults had a greater LE compared to non-Hispanic adults in all time periods. Although PWID had little increase in LE, non-PWID saw an increase in LE from 2008-11 to 2012-15. Similarly, adults with HCV saw little increase in LE and did not exceed 50 years in any time period; however those without HCV had consistent increases in LE across time.

Conclusion: Although LE has improved since 2005 for most of these underserved populations, disparities persist. Factors that may be influencing the higher LE in Black compared to white women may be related to forces that are decreasing survival in whites in the US. The increased LE in Hispanics vs. non-Hispanics is reflective of what has been shown in the general US population. Adults with HIV and HCV saw very little (<2 years) increase in LE; further analysis reducing the influence of PWID are underway. Our LE results may be overestimated if NA-ACCORD cohorts under-represent those who are less likely to remain in care after ART initiation; estimates from 2012-15 are projections that are influenced by data truncated prior to 31 Dec 2015. The impact of the "treat all" era and HCV direct acting agents may further increase LE, but may not narrow disparities in key populations if maintaining HIV RNA suppression is playing a significant role in these disparities.

Figure: Life expectancy estimates from age 18 years (and 95% confidence intervals) among ART initiators in key populations (red) and the comparison group (blue) in the NA-ACCORD, 2005 to 2015



904 RATE AND RISK OF TRANSMISSIBLE HIV RNA (>1500 COPIES/ML) AMONG ADULTS ON ART

Keri N. Althoff[1], Kate Buchacz[2], Richard D. Moore[1], Stephen J. Gange[1], Mari Kitahata[3], Michael A. Horberg[4], Ronald Bosch[5], Jennifer S. Lee[1], Jeffrey N. Martin[6], Kenneth H. Mayer[7], Pragna Patel[2], Charles Rabkin[8], Jennifer E. Thorne[1], John T. Brooks[2]

[1]Johns Hopkins University, Baltimore, MD, USA, [2]CDC, Atlanta, GA, USA, [3]University of Washington, Seattle, WA, USA, [4]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [5]Harvard University, Cambridge, MA, USA, [6]University of California San Francisco, San Francisco, CA, USA, [7]Fenway Health, Boston, MA, USA, [8]National Cancer Institute, Bethesda, MD, USA

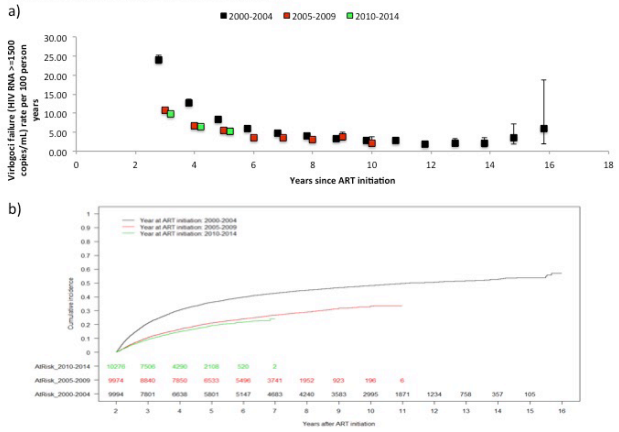
Background: U.S. guidelines recommend that clinicians consider decreasing the frequency of viral load monitoring after two years of persistent suppression. We estimated the incidence of transmissible HIV RNA among U.S. patients under these circumstances.

Methods: We defined transmissible HIV RNA as a single plasma HIV RNA 1500 copies/ml (≥1500) after suppression with ART to <1,500 copies/mL; this viral load value represented a lower threshold at which sexual transmission of HIV could occur excluding "blips." We included NA-ACCORD participants who initiated ART between 1 Jan 2000 and 31 Dec 2015 then achieved and maintained HIV RNA <1500 for two years. Observation continued until HIV RNA ≥1500, death, last CD4 cell count or plasma HIV RNA measurement + 1.5 years (as a surrogate for loss to follow-up), or 31 Dec 2015, whichever came first. Incidence rates (95% confidence intervals) per 100 person years (100py) and Kaplan Meier cumulative incidence rates of HIV RNA ≥1500 were estimated, stratified by age, sex, race, HIV transmission risk group, and calendar year of ART initiation.

Results: Among 30,103 eligible adults with median follow-up of 2.8 years (interquartile range [IQR] 1.3, 5.4) and a median of 8 (IQR 7, 10) HIV RNA tests per participant, annual incidence of viral rebound decreased from 14.9 (14.5, 15.4) per 100py at 3 years after ART initiation to 2.9 (2.4, 3.5) per 100py at 10 years after ART initiation. Adults who rebounded (8,730 or 29%) were more likely to be younger, male, black, had injection drug use (IDU) HIV transmission risk factor, initiated ART in the earlier years, and had CD4 counts <200 cells/mm^3 at ART initiation compared to those who did not; they did not differ by HIV RNA at ART initiation. Persons who were younger, women, black, and with IDU risk consistently had higher incidence rate than older, men, non-black, those without IDU risk (respectively) until 7 years after ART initiation when differences decreased (Figure 1a). Cumulative transmissible HIV RNA incidences at 5 years after ART initiation were 36%, 21%, and 19% for participants who initiated ART during 2000-04, 2005-09 and 2010-14, respectively (Figure 1b).

Conclusion: After achieving and maintaining suppression within 2 years of ART initiation, annual rate and risk of plasma HIV RNA rebound to levels associated with sexual transmission of virus declined with continued suppression. The annual rate and risk of transmissible HIV RNA were lowest in 2010-2014, but had not improved significantly compared with 2005-2009.

Figure 1: Incidence rates and 95% confidence intervals (a) and cumulative incidence estimates (b) of HIV RNA ≥1500 copies/mL



905 INFECTION PRESSURE IN MEN WHO HAVE SEX WITH MEN AND THEIR SUITABILITY TO DONATE BLOOD

Ward P. van Bilsen[1], Hans L. Zaaijer[2], Amy Matser[1], Katja van den Hurk[2], Maarten F. Schim van der Loeff[1], Ed Slot[2], Maria Prins[1], Thijs J. Van de Laar[2]

[1]Public Health Service Amsterdam, Amsterdam, Netherlands, [2]Sanquin Research, Amsterdam, Netherlands

Background: Since the HIV outbreak, most Western countries (temporarily) have excluded men who have sex with men (MSM) from blood donation. The rationale for MSM deferral has weakened over time with the implementation of sensitive tests for HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV). We compared the infection pressure between MSM and donors to provide scientific evidence to reevaluate current MSM donor deferral policies.

Methods: In 2016, we studied 520 MSM from the Amsterdam Cohort Studies and 594 age-matched repeat male donors from Amsterdam. MSM were classified as eligible/non-eligible using the Dutch donor criteria for permanent exclusion and as low/high sexual risk based on self-reported behavior. Low-risk was defined as no anal sex, a monogamous relationship or consistent condom use in the past year. MSM and donors were tested for 10 blood-borne and sexually transmitted infections (see table). Infection pressure was calculated by summing antibody-reactive infections with major infections (i.e. HIV, HBV, HCV, HTLV and syphilis) weighted double. Stored samples of MSM were tested to distinguish recent (within last year) from past major infection. Willingness to donate was measured on a seven-point Likert scale.

Results: We identified 197 eligible low-risk MSM (lrMSM), 48 non-eligible lrMSM, 183 eligible high-risk MSM (hrMSM) and 92 non-eligible hrMSM. Median infection pressure was 3 (IQR 2-4) among both eligible lrMSM and eligible hrMSM, and was higher than in donors (infection pressure 2; IQR 1-2; P-value<0.001). Neither eligible lrMSM nor donors had antibodies to HIV, HCV, HTLV or syphilis; 15 eligible lr-MSM and 6 donors had antibodies to HBV. None of the lrMSM had recent infections. Eligible hrMSM had antibodies to syphilis (n=5) and HBV (n=17); 4 eligible and 7 non-eligible hrMSM had recent infections. Antibody prevalence to herpes viruses was higher in MSM than in donors (P-value <0.001). 73% of MSM had a moderate to high intention to donate. Intention did not differ between MSM groups (P-value 0.223).

Conclusion: Infection pressure in MSM is higher than in male donors; in hrMSM partly due to recent infections and antibodies to major infections, but in lrMSM solely due to a higher prevalence of herpes viruses. The absence of recent infections in lrMSM and similar antibody-reactivity to major infections in male donors and 'eligible' lrMSM suggest that self-declared lrMSM form a low threat for blood safety and should be considered for blood donation.

Table. Characteristics of 594 repeat male blood donors and 520 MSM according to sexual risk behaviour and donor eligibility

Characteristics	Repeat male blood donors (n = 594)		MSM eligible for donation						MSM non-eligible for donation			
			Low sexual risk (n = 197)			High sexual risk (n = 183)			Low sexual risk (n = 48)		High sexual risk (n = 92)	
	n	%	n	%	P-value*	n	%	P-value*	n	%	n	%
Demographic												
Age (median, [IQR])	42	[34 - 48]	42	[36 - 47]	0.826	40	[34 - 49]	0.918	45	[40 - 49]	44	[37 - 52]
Serology												
major infections												
HIV	0	0%	0	0%	-	0	0%	-	0	0%	0	0%
HBV [a]	6	1%	15	8%	<0.001	17	9%	<0.001	6	13%	26	28%
HCV	0	0%	0	0%	-	0	0%	-	1	2%	2	2%
HTLV	0	0%	0	0%	-	0	0%	-	0	0%	1	1%
Syphilis	0	0%	0	0%	-	5	3%	<0.001	23	48%	51	55%
minor infections												
HEV	117	20%	29	15%	0.119	23	13%	0.028	11	23%	18	20%
CMV	224	38%	134	68%	<0.001	140	77%	<0.001	39	81%	85	92%
HSV	274	46%	160	81%	<0.001	154	84%	<0.001	40	83%	83	90%
Parvo B19	441	74%	145	74%	0.859	142	78%	0.359	43	90%	71	77%
HHV8	30	5%	77	39%	<0.001	86	47%	<0.001	31	65%	57	62%
Recent infection												
HIV			0	0%		0	0%		0	0%	0	0%
HBV			0	0%		2	1%		0	0%	1	1%
HCV			0	0%		0	0%		0	0%	0	0%
HTLV			0	0%		0	0%		0	0%	0	0%
Syphilis			0	0%		2	1%		0	0%	6	7%
Outcome												
Infection pressure (median, [IQR])	2	[1 - 2]	3	[2 - 4]	<0.001	3	[2 - 4]	<0.001	4	[3 - 5]	4	[4 - 6]

[a] antibodies to hepatitis B core antigen; * P-value when compared to repeat male donors; using Chi-square for categorical data and the Mann-Whitney U test or unpaired T-test for numerical data.

MSM, men who have sex with men; HIV, human immunodeficiency virus; HBV, hepatitis B virus; anti-HBc, antibodies to hepatitis B core; anti-HBs, antibodies to hepatitis B surface antigen; HCV, hepatitis C virus; HTLV, human T-cell lymphotropic virus; HEV, hepatitis E virus; CMV, cytomegalovirus; HSV, herpes simplex virus; Parvo B19, parvo B19 virus; HHV8, human herpes virus 8; IQR, interquartile range.

906 INDIVIDUAL AND NETWORK DRIVERS OF RACIAL DISPARITIES AMONG YMSM

Brian Mustanski, Ethan Morgan, Richard D'Aquila, Michelle Birkett, Patrick Janulis, Gregory Phillips, Michael E. Newcomb
Northwestern University, Chicago, IL, USA

Background: Individual sexual risk behaviors have failed to explain the observed racial disparity in HIV acquisition. To increase understanding of potential drivers in these disparities, we assessed differences across individual and network domains.
Methods: Data come from the first wave of RADAR (N=1015), an ongoing longitudinal cohort study of multilevel HIV risk factors among young men who have sex with men (YMSM) aged 16-29 in Chicago. Data collection includes biological specimens; network data, including detailed information about social, sexual, and drug-use networks of cohort members; and psychosocial characteristics of YMSM.
Results: Compared to White YMSM (24.8%) and Hispanic YMSM (30.0%), Black YMSM (33.9%) had a higher prevalence of both HIV (32%;p<0.001) and rectal STIs (26.5%;p=0.011) with no observed differences in PrEP use. Black YMSM reported lower rates of sexual risk behaviors compared to all other YMSM as well as a greater number of lifetime HIV tests (p<0.001), however, HIV-positive Black YMSM were significantly less likely to achieve viral suppression than all other YMSM (p=0.01). Black YMSM, compared to all other YMSM, had the highest rate of cannabis use (p=0.03) and reported greater levels of stigma (p<0.001), victimization (p=0.04), trauma (p<0.001), and childhood sexual abuse (p<0.001). White YMSM reported higher rates of depression (p<0.001) and also had the highest rates of alcohol (p<0.001) and prescription drug use (p<0.001). In network analyses, Black YMSM reported a greater number of sexual partners identifying as non-male and non-gay, and reported more HIV-positive sexual partners (p<0.001). Black YMSM were also more likely to report having stronger ties (p<0.001) and greater racial homophily with sexual partners (p<0.001). Significant differences existed across network characteristics with Black YMSM having the lowest transitivity (p=0.002), the highest density (p<0.001), and the highest concurrency of YMSM alters (p<0.001).
Conclusion: Black YMSM do not report higher rates of HIV risk behaviors, however, they do report more HIV-positive sexual partners and more concurrent sexual partners, have more homogeneous sexual networks, higher rates of rectal STIs, and are less likely to have viral suppression when HIV-infected. These results support the role of network factors in racial disparities in HIV acquisition and the types of interventions that may be useful to reduce disparities.

907 HIV DIAGNOSES AND TRENDS IN THE SOUTHERN UNITED STATES, 2010-2015

Meg Watson, Andre Dailey, Alexandra M. Oster
CDC, Atlanta, GA, USA

Background: Previous studies have documented disproportionate rates of HIV diagnosis in the southern United States compared to other regions, with half of all HIV diagnoses occurring in the South. U.S. national HIV prevention goals will be difficult to achieve without success in the region. To monitor prevention efforts, we provide updated information about current rates and trends in HIV diagnoses in the South.
Methods: Using National HIV Surveillance System data for persons aged ≥13 years, we analyzed HIV diagnosis rates, counts, and trends for 2010–2015 by U.S. Census region, and in the South by race/ethnicity, age at diagnosis, transmission category, and population size of area of residence at diagnosis. We calculated estimated annual percent change (EAPC) in diagnoses; significance is assessed at p<0.05. Rates use U.S. census data for denominators and are per 100,000 population.
Results: HIV diagnoses among persons aged ≥13 years declined significantly in all regions during 2010–2015, most steeply in the Northeast (EAPCs: Northeast=-4.5; Midwest=-1.6, South=-1.5, West=-1.1). In 2015, rates were highest in the South (Northeast=13.6; Midwest=9.0, South=20.2, West=11.7), and 52% (20,348) of the 39,393 diagnoses were in the South. Diagnoses in the South declined among blacks and persons of multiple races, and increased among Hispanics/Latinos, American Indian/Alaska Natives and Asian/Pacific Islanders (Table). In the South, diagnoses attributable to male-to-male sexual contact increased. Declines by mode of transmission were steepest for diagnoses attributable to injection drug use (EAPC for males=-9.08, females=-9.18). Metropolitan statistical areas (MSAs) had the highest rates, as well as the steepest declines in diagnoses (Table). In 2015, more than half of HIV diagnoses in the South were among blacks, with about one-fifth among whites and one-fifth among Hispanics/Latinos. Half of all new diagnoses were attributable to male-to-male sexual contact, and three-fourths of new diagnoses were among residents of MSAs.
Conclusion: The South continues to be disproportionately affected by HIV. Although decreasing diagnoses are encouraging, especially among blacks and in MSAs, continued disparities are cause for concern. Increased, ongoing efforts to reach at-risk populations and addressing contextual factors unique to the region will be critical to reducing ongoing disparities and ultimately, to achieving national prevention goals.

Table. HIV DIAGNOSES AND TRENDS IN THE SOUTH AMONG ADOLESCENTS AND ADULTS, 2010–2015.

	2010		2015		
	No.	Rate	No.	Rate	EAPC
Race/ethnicity					
American Indian/Alaska Native	36	6.0	70	10.8	8.79
Asian/Pacific Islander	166	6.1	279	8.2	8.64
Black/African American	12,711	72.7	11,103	59.0	-3.85
Hispanic/Latino	3,500	25.4	4,004	25.1	1.45
White	4,750	8.0	4,569	7.5	-2.38
Multiple Races	748	67.5	323	23.7	-10.34
Population size of area of residence at diagnosis					
Metropolitan statistical areas (population ≥500,000)	16,963	28.9	15,386	24.2	-3.07
Metropolitan areas (population 50,000-499,999)	3,658	14.7	3,545	13.7	-1.92
Nonmetropolitan areas	1,155	10.2	1,132	10.0	-1.57
Unknown	135		285		

EAPC= Estimated Annual Percent Change.
Rates are per 100,000 population.

908 DEGREE OF HOUSING INSTABILITY SHOWS INDEPENDENT "DOSE-RESPONSE" WITH HIV SUPPRESSION

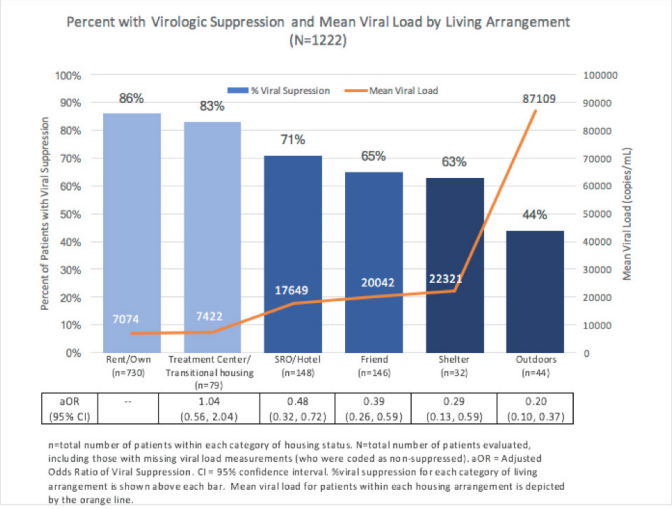
Angelo A. Clemenzi-Allen[1], Elvin Geng[1], Katerina A. Christopoulos[1], Hali Hammer[2], Susan P. Buchbinder[2], Diane V. Havlir[1], Monica Gandhi[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]San Francisco Department of Public Health, San Francisco, CA, USA

Background: Housing instability is associated with worse clinical outcomes among people living with HIV (PLHIV), but housing status is often dichotomized to homeless vs not without a nuanced evaluation of the continuum of unstable housing. We evaluated the association of multiple levels of housing status and virologic suppression (VS) among PLHIV in a large clinic-based cohort.
Methods: We collected self-reported housing status data in a safety-net HIV clinic in San Francisco ("Ward 86") from 2/1/17-7/21/17. Patients circled current housing status at check-in on a pictorial survey depicting 6 different living arrangements: 1) Rent/Own; 2) Treatment/Transitional Program; 3) Hotel/Single Room Occupancy (SRO); 4) Staying with Friend; 5) Homeless Shelter; 6) Outdoors/In Vehicle. Viral loads (VL) performed ±90 days of survey completion

were abstracted from the medical record. We defined viral suppression (VS) as HIV-RNA level <200 copies/mL. Patients without VL measures in this window were categorized as non-suppressed. We calculated the odds of VS in each strata of housing status via logistic regression adjusting for age, gender, and race/ethnicity. Sensitivity analyses excluding participants with missing VL and also counting them as suppressed were performed.

Results: 1,222 patients completed the survey, of whom 39 had no VLs within the pre-specified window. Median age was 50 years (IQR 41 to 57); 13% were female; 40% white, 25% black, 26% Latino, 9% other. Across a continuum of housing types, VS rates ranged from 86% (rent/own) to 44% (outdoors) (Figure). Greater housing instability was associated with lower rates of VS in a "dose-response" fashion. The adjusted odds of VS among participants with unstable living arrangements (SRO/hotel, living with friend, shelter, outdoors) were each statistically significantly lower compared to those who rented/owned (all p-values<0.005), except when comparing those in treatment/transitional housing to those who rent/own (p-value 0.84). Results were unchanged in both sensitivity analyses.

Conclusion: We demonstrate strong associations between dwelling type and VS among PLHIV across a continuum of unstable housing arrangements. Although living outdoors is associated with the lowest proportion of VS, other forms of instability (including living in a shelter, "couch-surfing", and being in an SRO) are also associated with lower levels of VS compared to being housed. Interventions are needed to increase VS among PLHIV across a spectrum of unstable housing arrangements.



909 ONGOING NEED FOR BEHAVIORAL HIV PREVENTION INTERVENTIONS FOR HIV-POSITIVE MSM OVER 50

Mary Ann Chiasson, Martin J. Downing, Irene Yoon, Steven Houang, Sabina Hirshfield
Public Health Solutions, New York, NY, USA

Background: Most newly diagnosed HIV infections in the U.S. occur among MSM. Moreover, only 50% of MSM living with HIV are virally suppressed, raising concerns about continued HIV transmission. In 2014, 58% of MSM living with HIV were aged 45 years or older. Currently, most HIV prevention activities are targeted to young MSM, but, as the population of MSM living with HIV continues to age because of improved diagnosis and treatment, a better understanding of sexual risk and HIV prevention gaps in older MSM is needed. This analysis compares demographic and sexual risk behaviors between HIV-positive MSM <50 and ≥50.

Methods: HIV-positive MSM were recruited from social and sexual networking websites and apps. Of 16,299 men completing the study screening survey, 13,036 U.S. MSM who reported being HIV-positive were eligible for this analysis. Self-reported condomless anal sex (CAS), sex partners' HIV status, participant viral load (all past 6 months), and STD diagnoses (past 3 months) were compared for MSM <50 and ≥50 in bivariate and multivariable logistic regression analyses (p = <0.001 in all analyses presented).

Results: Among 13,036 HIV-positive MSM participants, 73% were <50 and 27% ≥50. Race/ethnicity varied by age group. Compared to MSM ≥50, MSM <50 were significantly more likely to be Black (34% vs 16%) or Hispanic (17% vs 8%) and less likely to be White (44% vs 74%). Overall, 27% reported a detectable viral load, a substantial proportion of both MSM <50 and ≥50 (30% vs. 18%, OR=2.0); CAS (90% vs. 78%, OR=2.4); and CAS with an HIV-negative man (48% vs. 38%, OR=1.5). In addition, MSM <50 and MSM ≥50 were equally likely (29% vs 30%, OR=.95) to report CAS with 5 or more men in the past 6 months. In separate multivariable analyses, MSM <50 and ≥50 reporting CAS with 5 or more men were significantly more likely to report an STD diagnosis (AOR=2.2 and 2.9) and having any HIV-negative partners (AOR=3.0 and 2.4).

Conclusion: The vast majority of HIV-positive MSM in this large online survey reported CAS regardless of age group and more than a quarter reported a detectable viral load. These findings, taken together with the finding that nearly one third of MSM >50 and <50 reported CAS with 5 or more partners in the last 6 months, reinforces the need for ongoing behavioral risk reduction and antiretroviral adherence education for older HIV-positive MSM, a group that has received considerably less risk reduction attention.

910 UNDISCLOSED HIV INFECTION AMONG MSM IN NATIONAL HIV BEHAVIORAL SURVEILLANCE

Brooke Hoots, Cyprian Wejnert, Amy Martin, Richard Haaland, Silvina Masciotra, Catlainn Sionean, Amanda Smith, William M. Switzer, Gabriela Paz-Bailey
CDC, Atlanta, GA, USA

Background: Many men who have sex with men (MSM) are unwilling to disclose their HIV status, and surveys that rely on self-reported HIV status may be limited by participant misreport. As a proxy for undiagnosed HIV, National HIV Behavioral Surveillance (NHBS) monitors participants who report being unaware of their HIV infection, defining unaware as self-reporting an HIV-negative or unknown status but testing HIV-positive in NHBS. However, participants considered unaware may include some who choose not to disclose their status. To evaluate the validity of the NHBS measure of awareness among MSM, we tested HIV-positive participants for the presence of antiretrovirals (ARVs), which may indicate active treatment.

Methods: MSM with HIV-positive test results in 19 U.S. cities in 2014 were included. MSM reporting pre exposure prophylaxis (PrEP) use in the past 12 months (n=3) were excluded. Dried blood spots were tested for 7 ARVs by liquid chromatography-tandem mass spectrometry and viral load (VL) using a validated Abbott RealTime HIV-1 VL assay. Persons unaware with ≥1 ARV detected were defined as misreporters. Prevalence ratios (PRs) and 95% confidence intervals (CIs) were calculated from Poisson regression models to compare unaware misreporters, unaware non-misreporters (defined as unaware and no ARVs detected), and those who correctly self-reported as HIV-positive.

Results: Of 1,818 HIV-positive MSM, 299 (16%) self-reported as HIV-negative or unknown infection status. Of the 299 unaware, 145 (49%) were considered misreporters based on ARV detection. Among the unaware, misreporters were more likely than non-misreporters to be older (aged >35 vs 18-34 years) (PR 1.66, CI 1.36-2.04, and have health insurance (PR 1.33, CI 1.16-1.54). Compared to self-reported HIV-positive MSM, misreporters were more likely to be black (PR 1.60, CI 1.40-1.84), and bisexual (PR 2.62, CI 2.01-3.42), and have perceived discrimination (PR 1.18, CI 1.00-1.38). Of 138 misreporters with viral load data, 116 (84%) had a viral load below the limit of detection.

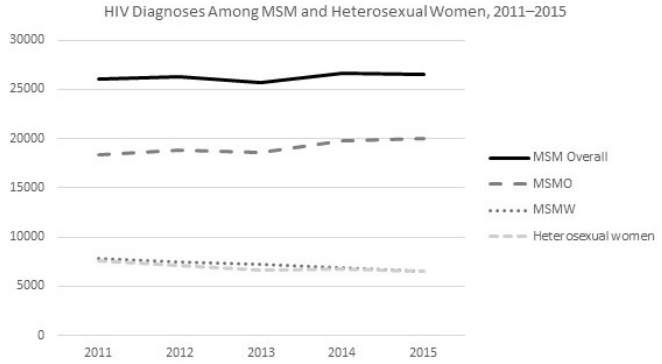
Conclusion: ARV testing revealed that half of MSM who reported being unaware of their HIV infection misreported their status. While off-label PrEP use might explain the presence of ARVs, it is an unlikely explanation because many misreporters were virally suppressed and likely would not have become infected had they been taking ARVs as PrEP. Biomarker validation of behavioral data can improve data quality and usefulness in NHBS and other studies.

911 HIV TRANSMISSION BETWEEN MEN WHO HAVE SEX WITH MEN AND HETEROSEXUAL WOMEN

Alexandra M. Oster, Nivedha Panneer, Sonia Singh
CDC, Atlanta, GA, USA

Background: Previous analyses of U.S. molecular HIV surveillance data have suggested that a substantial percentage of HIV diagnoses among heterosexual women originate from men who have sex with men (MSM). HIV diagnoses among heterosexual women have decreased substantially in recent years, while diagnoses among MSM have not. One possible explanation for these disparate

trends is that transmission of HIV between MSM and women has decreased. We explored temporal changes in HIV transmission between MSM and women.
Methods: Using National HIV Surveillance System data reported through December 2016, we calculated the annual number of HIV diagnoses during 2011–2015 for 1) heterosexual women and 2) MSM, overall and in two subgroups: men who have sex with men and women (MSMW) and men who have sex with men only (MSMO), using standard CDC methodology to adjust for missing risk information. Estimated annual percentage changes (EAPCs) and 95% confidence intervals (CIs) were calculated. Using HIV-TRACE, we also analyzed partial HIV-1 polymerase sequences to identify potential transmission partners (persons whose HIV strains are extremely similar) between MSM and heterosexual women at a genetic threshold of ≤ 1.5%.
Results: From 2011 to 2015, HIV diagnoses among heterosexual women decreased from 7563 to 6483 (EAPC: -3.6; CI: -4.6, -2.7) (Figure). During the same time period, diagnoses among MSM overall were stable at 26,107 in 2011 and 26,539 in 2015 (EAPC: 0.5; CI: 0.0, 0.9). However, diagnoses among MSMW decreased from 7781 to 6545 (EAPC: -4.3; CI: -5.3, -3.3). Among 38,364 MSM with a potential transmission partner identified, the percentage linked to a heterosexual woman decreased from 4.4% during 2008–2011 to 3.5% during 2012–2015.
Conclusion: These data indicate that the number of HIV diagnoses among MSM who also report sex with women has declined in recent years and that the already small percentage of MSM with possible transmission linkages to heterosexual women has decreased further in recent years. These findings suggest that reduced HIV diagnoses among heterosexual women may be attributable, at least in part, to reduced transmission from MSM to women.



912 RELIABILITY OF SELF-REPORTED HIV STATUS AMONG AFRICAN MSM SCREENED FOR HPTN 075

Jessica M. Fogel[1], Yinfeng Zhang[1], Xu Guo[2], William Clarke[1], Autumn Breaud[1], Vanessa Cummings[1], Erica Hamilton[3], Arthur Ogendo[4], Noel Kayange[5], Ravindre Panchia[6], Karen Dominguez[7], Ying Q. Chen[2], Theodorus Sandfort[8], Susan H. Eshleman[1]
[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]FHI 360, Durham, NC, USA, [4]Kenya Medical Research Institute, Kisumu, Kenya, [5]Malawi Coll of Med–Johns Hopkins Univ Rsr Proj, Blantyre, Malawi, [6]University of the Witwatersrand, Soweto, South Africa, [7]University of Cape Town, Cape Town, South Africa, [8]Columbia University, New York, NY, USA

Background: In many research studies, individuals who test positive for HIV infection are asked if they had a prior HIV diagnosis. We evaluated the reliability of self-report of HIV status among men who have sex with men (MSM) who were screened for participation in the HIV Prevention Trials Network (HPTN) 075 study. This study evaluated the feasibility of recruiting and retaining MSM in sub-Saharan Africa for HIV prevention trials.
Methods: The HPTN 075 study population included HIV-infected and HIV-uninfected MSM ages 18-44 years at four study sites (Kisumu, Kenya; Blantyre, Malawi; Soweto and Cape Town, South Africa). Men who were on antiretroviral therapy (ART) or in HIV care were not eligible for the study. Knowledge of HIV status at screening was assessed with self-report and retrospective antiretroviral (ARV) drug testing using an assay that detects 20 ARV drugs. Men were classified as previously diagnosed if they reported being HIV-infected or had ARV drugs detected that indicated that they were on ART. Logistic regression was used to compare characteristics of previously diagnosed men who did or did not report a prior HIV diagnosis.
Results: We analyzed samples and data from 183 men who were HIV-infected at screening; 67 (36.6%) of the 183 men reported that they were HIV infected. Among the 116 men who did not report a prior HIV diagnosis, 36 (31.0%) had ARV drugs detected (30 reported a negative HIV status, one reported not knowing his status, and five reported no prior HIV test). After accounting for ARV drug use, 103 (56.3%) of the men were classified as previously diagnosed and 80 (43.7%) were classified as newly diagnosed. Among previously diagnosed men, the following groups were more likely to report a positive HIV status: men from Soweto, South Africa (compared to men from Kenya, p=0.006) and men who reported having sex with men only (compared to men who reported having sex with men and women, p=0.002).
Conclusion: In this cohort, ~30% of the HIV-infected men screened for the study who did not report that they were HIV-positive were on ART. HIV-infected men who reported having sex with men only were more likely to report knowledge of their HIV status. The accuracy of self-report for identifying individuals who are aware of their HIV-positive status has serious limitations. Understanding factors associated with disclosure of HIV status in different populations and settings may help inform HIV treatment and prevention studies.

913 FACTORS ASSOCIATED WITH VIRAL SUPPRESSION AMONG MSM IN WASHINGTON, DC

Auntre D. Hamp, **Jenevieve Opoku**, Adam Allston
District of Columbia Department of Health, Washington, DC, USA

Background: Between 2012 and 2016, new diagnoses amongst MSM decreased by 54% in the District of Columbia (DC). Despite the decrease in new infections, Black MSM represented 57.8% of all diagnosed and living cases in DC in 2016. In order to sustain decreases in new infections in MSM of color, the examination of HIV care patterns and viral suppression among this group is critical. The aim of this study is to examine factors associated with viral suppression amongst MSM in DC.
Methods: Data were extracted from the DC HIV surveillance system. All newly diagnosed HIV cases, who were diagnosed between 2011 and 2015 and living DC at the end of 2015 were included in this analysis. Continuous retention in care was defined as having at least two CD4 counts or viral load (vl) laboratory tests, at least 90 days apart in 2015. Sporadic retention in care was defined as having at least one CD4 count or vl laboratory test in 2015. Viral suppression was defined as having a last known lab in 2015, of less than or equal to 200 copies/mL. Logistic regression was used to identify factors associated with viral suppression in 2015. Race/ethnicity, age, retention in care in 2015 and year of diagnosis were evaluated in this model.
Results: Between 2011 and 2015, there were 1,350 MSM and MSM/IDU newly diagnosed and living in DC at the end of 2015. Logistic regression analysis revealed that those aged 25 to 29 (OR 1.96; CI 1.21, 3.20), aged 30 to 39 (OR 3.00; CI 1.77, 5.10), aged 40 to 49 (OR 3.11; CI 1.68, 5.76) and aged 50 to 59 (OR 6.27; CI 2.59, 15.17) were more likely than those aged 20 to 24 to be virally suppressed. Persons who were Black (OR .35; CI .20, .59) or Hispanics (OR .47; CI .24, .91) were less likely than white, non-Hispanics to be virally suppressed. Persons who were sporadically retained in care (OR .31; CI .22, .43) were less likely than those who were continuously retained in care to be virally suppressed. Additionally chi-squared tests showed that while there was no difference in retention in care by race (p=.49), Black MSM were more likely to not be virally suppression than other racial groups (<.01).
Conclusion: Results of this analysis identify factors related to viral suppression amongst MSM in DC. These findings provide increased insight that being continuously retained in care may be a critical factor in treatment and ultimately viral suppression, but the current measurement of retention in care may not take into account various other factors that impact viral suppression for certain populations.

Table 1. Logistic Regression Predicting Viral Suppression in 2015 From Age, Race/Ethnicity, Retention In Care and Year of Diagnosis

Predictor	B	Wald x	p	Odds Ratio	CI 95%	
					Lower	Upper
Age Group						
13-19	0.67	0.69	.33	1.96	0.51	7.56
20-24 (Reference)	-	-	-	-	-	-
25-29	0.67	7.34	<.01	1.96	1.21	3.20
30-39	1.10	16.64	<.01	3.00	1.77	5.10
40-49	1.14	13.04	<.01	3.11	1.68	5.76
50-59	1.84	16.59	<.01	6.27	2.59	15.17
60 and older	0.53	1.03	.31	1.71	0.61	4.78
Race/Ethnicity						
White, non-Hispanic (Reference)	-	-	-	-	-	-
Black, non-Hispanic	-1.07	15.54	<.01	0.35	0.20	0.59
Hispanic	-0.76	5.07	.02	0.47	0.24	0.91
Other*	-0.42	0.48	.48	0.66	0.20	2.17
Retention in Care						
Continuously Retained (Reference)	-	-	-	-	-	-
Sporadically Retained	-1.19	43.99	<.01	0.31	0.22	0.43
Year of Diagnosis						
2011	-	-	-	-	-	-
2012	0.26	0.98	0.32	1.29	0.78	2.15
2013	0.12	0.20	0.65	1.12	0.68	1.87
2014	0.56	3.47	0.06	1.74	0.97	3.12
2015	0.32	1.21	0.27	1.38	0.78	2.64

914 RACIAL DIFFERENCES IN EGOCENTRIC NETWORK PROPERTIES AMONG GAY, BISEXUAL AND OTHER MSM

Meagan Zarwell[1], William T. Robinson[2]
[1]Medical College of Wisconsin, Wauwatosa, WI, USA, [2]Louisiana State University, New Orleans, LA, USA

Background: The alarming HIV burden among gay, bisexual, and other men who have sex with men (MSM) of color may be related to variations in network characteristics of the individual's social and sexual network. This study investigates variations in egocentric network properties among Black, Latino, and other race (Non-White) and White MSM.

Methods: During the New Orleans arm of the National HIV Behavioral Surveillance in 2014, 258 Non-White (47%) and 295 White (53%) were recruited via venue-based sampling to complete a structured survey. Participants provided information on up to 10 people in their egocentric networks with whom they interacted in the past three months: five people who provided social support and five sex partners. Indicators for diversity were operationalized as the proportion of network members who were different than ego by age, race, gender or HIV status. Egocentric network properties and network diversity indicators were aggregated to the participant level as means or proportions. Associations between network measures and race were examined using PROC GLM.

Results: Non-White participants were younger (p<.0001), reported lower education (p<.0001) and income levels (p<.0001), were more likely to identify as bisexual (p =0.001), and less likely to report condomless sex at last sexual intercourse (p=0.017). Significant variations in network properties were also found. White participants reported larger networks (p=0.008), had known network members longer (p=0.002), and were more likely to list last male partners as a social support connection (p=0.037). In addition, White participants reported more drug (p=0.005) and alcohol use (p<.0001) within networks. Non-White participants reported networks with fewer men (p=0.008) and younger members (p =0.010) than those of White MSM. Social group memberships also varied by race: White MSM reported larger proportions of network members who belonged to the leather (p=0.002), bear (p=0.0004), and radical faerie (p=0.003) communities. Significant network diversity indicators included age (p=0.002) and race (p<.0001), such that White MSM reported a greater proportion of network members of a different age but a lower proportion of network members of a different race.

Conclusion: Results of this study indicate that network properties of MSM differ by race in New Orleans. This may be important to note when designing prevention interventions that prioritize MSM of color, especially those that capitalize on network strategies or peer–driven approaches.

915 ECONOMIC DEPENDENCE AND HIV RISK AMONG YOUNG, BLACK MEN WHO HAVE SEX WITH MEN

Kalysha Closson[1], Gbolahan Olarewaju[1], Richard Crosby[2]
[1]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, [2]Other Institution, Email institution information to CROIabstracts@iasusa.org

Background: In the United States, young Black gay, bisexual or other men who have sex with men (YBMSM) bear the largest burden of HIV incidence. Within gay men's sexual health literature, little is known about how economic dependence on a sexual partner influences sexual negotiation including positioning and sexual health outcomes. We aim to examine prevalence and correlates of economic dependence on a sexual partner stratified by HIV-status among YBMSM living in Jackson, Mississippi.

Methods: Baseline data from 589 YBMSM (Mean age= 22) participating in a brief sex-positive HIV/STI prevention randomized control trial, was used to measure the association between six sexual behaviours including sexual positioning (e.g. bottom and/or top) and condomless anal (insertive, receptive, any) intercourse, three sexual health outcomes including STI acquisition (oral and genital), and economic dependence, stratified by HIV-status. Bivariate chi-square associations were tested and regression models adjusted for education level (≤highschool), and income ≤1,000USD/month (vs. >1,000USD/month).

Results: Of YBMSM living with HIV 18.2% reported being economically dependent on their sexual partners compared to only 11.4% of YBMSM not living with HIV. In regressions, of the six behavioural sexual behaviours assessed economically dependent YBMSM living with HIV were more likely to have >3 sex partners as a bottom in the last 90 days (L90D) (aOR=2.56, 95%CI=1.14-5.72), and YBMSM not living with HIV reporting economic dependence were more likely to report having anal sex >3 times as a bottom in L90D (aOR= 2.62, 95%CI=1.13-6.12). Economically dependent YBGBM living with HIV were 3.85 times more likely to be diagnosed with oral gonorrhoea, compared to non-dependent YBMSM living with HIV (95%CI=1.29-11.48).

Conclusion: Economic dependence was found to be more common among YBMSM living with HIV compared to those not living with HIV. Thus, our findings highlight the need for interventions to consider how poverty, unemployment and economic dependence interact to influence relationship power imbalances, sexual positioning, and in turn sexual health outcomes for YBMSM living with and without HIV in contexts with high HIV incidence, such as Mississippi.

Table 1. Adjusted Odds Ratios and 95% Confidence Intervals for Six Outcomes, Stratified by HIV Status

	YBMSM living without HIV			YBMSM living with HIV		
	AOR	95% CI	P-value	AOR	95% CI	P-value
Any condomless anal receptive sex						
Not employed	1.15	.71/1.86	.56	1.51	.65/3.49	.34
High school education or less	.72	.44/1.15	.17	1.37	.60/3.10	.45
Dependence on partner	1.80	.93/3.50	.08	2.28	.91/5.71	.08
Three or more sex partners as a top						
Not employed	1.36	.83/2,24	.22	not applicable		
High school education or less	.80	.49/1.32	.41	not applicable		
Dependence on partner	**1.98**	**1.01/1.87**	**.046**	not applicable		
Three or more sex partners as a bottom						
Not employed	.90	.55/1.49	.69	.85	.44/1.66	.64
High school education or less	1.13	.69/1.85	.62	1.32	.68/2.56	.42
Dependence on partner	1.79	.91/3.51	.09	**2.56**	**1.14/5.72**	**.02**
Three or more times anal sex as a bottom						
Not employed	1.26	.74/2.13	.40	not applicable		
High school education or less	1.24	.75/2.06	.41	not applicable		
Dependence on partner	2.62	1.13/6.12	.02	not applicable		
Tested positive for oral gonorrhea						
Not employed	.93	.27/3.15	.90	.53	.19/1.45	.22
High school education or less	1.77	.54/5.77	.34	.73	.26/2.05	.55
Dependence on partner	2.95	.79/11.06	.11	**3.85**	**1.29/11.48**	**.02**

*Results **Bold** are significant at the <0.05 level

916 WITHDRAWN

917 HIV DIAGNOSES AMONG WOMEN IN RURAL VS NON-RURAL AREAS, UNITED STATES, 2010-2016

Ndidi Nwangwu-Ike[1], Neeraja Saduvala[2], Meg Watson[1], Alexandra M. Oster[1]
[1]CDC, Atlanta, GA, USA, [2]ICF International, Atlanta, GA, USA

Background: Although most people who receive HIV diagnoses are MSM, women are also at risk of acquiring HIV. Women in rural areas face unique challenges to HIV diagnosis and care, including limited access and transportation to testing and treatment facilities. Although recent U.S. HIV surveillance reports point to substantial declines in HIV diagnosis rates among women (from 7.3/100,000 in 2010 to 5.4/100,000 in 2015), little is known about how demographic and clinical characteristics differ for women with diagnosed HIV by population size of area of residence.

Methods: We examined demographic and clinical characteristics from National HIV Surveillance System data for women aged ≥13 years with HIV diagnosed during 2010–2016. Assessment of trends included 2010–2015. We also used data from 38 jurisdictions with complete laboratory reporting to determine viral suppression during 2014 among women with HIV infection diagnosed by year-end 2013 and alive at year-end 2014. Analyses were stratified by three categories of population size of area of residence: rural (nonmetropolitan area. population <50,000), metropolitan (population 50,000–499,000) and metropolitan statistical areas (MSAs; population ≥500,000), based on residence at diagnosis (for analyses of diagnoses) and current residence (for analyses of viral suppression).

Results: Of 56,941 women with HIV diagnosed during 2010–2016, 2,387 (4.2%) resided in a rural area, this percentage remained stable (4.0% -4.3%) during 2010–2015. The majority of diagnoses were among black/African American women (rural: 57%, metropolitan: 56%, MSAs: 63%). However, rural women were more likely to be white than women in other areas (rural: 30%, metropolitan: 27%, MSAs: 15%). A high percentage of rural women with HIV diagnoses were located in the South (rural: 79%, metropolitan: 70%, MSA: 52%). A slightly higher percentage of rural women had Stage 3 infection (AIDS) at diagnosis (rural: 30%, metropolitan: 28%, MSAs: 25%), and a slightly smaller percentage were virally suppressed (rural: 50%, metropolitan: 54%, MSAs: 56%).

Conclusion: During our study period, most women with an HIV diagnosis resided in urban areas. Women in rural areas had slightly higher levels of late diagnosis and lower levels of viral suppression, which may result from differences in access to testing and treatment services. Efforts to improve access to testing and care, particularly in the South, may benefit from considering access issues for persons in both urban and rural settings.

918 FACTORS ASSOCIATED WITH HIV INFECTION AMONG FEMALES AGED 15-24 IN ZAMBIA

Haotian Cai[1], Danielle T. Barradas[2], Sundeep Gupta[2], Kathy Hageman[2], Andrea Low[3], Nzali Kancheya[2], Katrina Sleeman[4], Dan B. Williams[4], Karampreet Sachathep[3], Hetal Patel[4], Omega Chituwo[2], Lloyd Mulenga[5]
[1]Association of Schools and Programs of Public Health, Washington, DC, USA, [2]CDC Zambia, Lusaka, Zambia, [3]ICAP at Columbia University, New York, NY, USA, [4]CDC, Atlanta, GA, USA, [5]Government of Zambia Ministry of Health, Lusaka, Zambia

Background: The Zambia Population-based HIV Impact Assessment (ZAMPHIA), a nationally-representative cross-sectional household survey conducted in 2016, found that adolescent girls and young women (AGYW) aged 15-24 are disproportionately infected with HIV compared to male peers. HIV prevalence was found to be 5.7% (95% CI: 4.9-6.5%) among AGYW, more than three times the prevalence found among males of the same age (1.8%, 95% CI: 1.3-2.3%). Only 40.1% of AGYW who tested positive reported awareness of their status. This analysis explores the demographic, behavioral, and biological factors associated with HIV infection among AGYW using preliminary ZAMPHIA data.

Methods: Among 5,205 eligible AGYW household members, 4,587 AGYW provided questionnaire responses (88.1% unweighted), of which 4,165 AGYW provided blood samples (90.8% unweighted), representative of more than 1.66 million AGYW in Zambia. Multivariate logistic regression models were used to assess the association between HIV infections and demographic, behavioral, and biological variables among AGYW who reported having at least one sexual partner in the past 12 months (n=2,188, unweighted). Figures presented are weighted unless otherwise specified and account for the complex survey design.

Results: Two-thirds of AGYW reported having ever had sexual intercourse. Of these, 81.0% reported having had one or more sexual partner in the past 12 months. Variables significantly associated with higher odds of HIV infection included urban residence (referent: rural; AOR[95% CI]=2.3[1.6, 3.4], p=<.0001), having a reactive syphilis test showing past or active infection (referent: nonreactive syphilis test; past syphilis AOR[95% CI]=2.4[1.1, 5.2], p=.022; active syphilis AOR[95% CI]=3.4[1.8, 6.3], p<.0001), and being in the 20-24 year old age group (referent: 15-19 years old; AOR[95% CI]=2.2[1.4, 3.5], p<.001).

Conclusion: These findings provide additional evidence for the factors that may require special consideration in Zambia regarding the provision of HIV services for AGYW, like syphilis infection and urban residence. HIV testing in this age group is of particular concern since ZAMPHIA 2016 found that awareness of HIV status among those who tested positive for HIV was less than half of the UNAIDS target for achieving epidemic control. Additional analyses are needed to clarify these associations, explore interaction terms, and examine other factors, like past pregnancy, upon availability of the final ZAMPHIA 2016 dataset.

Multivariate logistic regression model of factors associated with HIV infection among females aged 15-24 who reported one or more sexual partners in the past 12 months (ZAMPHIA 2016, N = 2188 unweighted)				
	Adjusted Odds Ratio	95% CI		*P*-value
Age group				
15-19	Referent			
20-24	2.2	1.4	3.5	<.001
Residence				
Rural	Referent			
Urban	2.3	1.6	3.4	<.0001
Marital status				
Never married	Referent			
Married or living together	1.0	0.9	2.3	0.964
Divorced or separated	1.6	0.8	3.2	0.138
Widowed	1.9	0.3	11.7	0.474
Education				
No education	Referent			
Primary	1.0	0.3	2.8	0.973
Secondary	1.0	0.3	2.8	0.928
More than secondary	0.9	0.3	3.4	0.931
Age at first sexual intercourse				
≥ 20	Referent			
< 16	1.4	0.7	2.8	0.294
16–17	1.1	0.6	2.2	0.785
18–19	0.9	0.4	1.9	0.785
Number of sexual partners in the past 12 months				
1	Referent			
2 or more	1.4	0.7	2.6	0.362
Reported having sex with a non-marital, non-cohabiting partner in the past 12 months				
No	Referent			
Yes	1.5	0.6	3.4	0.369
Condom use at last sexual intercourse in the past 12 months				
Used condom	Referent			
Did not use condom	0.8	0.5	1.3	0.385
Paid for sexual intercourse in the past 12 months				
No	Referent			
Yes	1.5	0.5	4.6	0.483
HBV				
Tested negative	Referent			
Tested positive	1.5	0.7	3.2	0.310
Syphilis				
Tested negative	Referent			
Tested positive				
Past infection	2.4	1.1	5.2	0.022
Recent infection	3.4	1.8	6.3	<.0001

919 WITHDRAWN

920 HIV PREVALENCE AMONG WOMEN WHO EXCHANGE SEX RECRUITED IN 4 US CITIES, 2016

Senad Handanagic[1], Brooke Hoots[1], Kristen Leigh Hess[1], Emily Higgins[2], Paige Padgett[3], Sarah L. Braunstein[4], Sara N. Glick[5], Dita Broz[1], Gabriela Paz-Bailey[1], Cyprian Wejnert[1], Lina Nerlander[1]

[1]CDC, Atlanta, GA, USA, [2]Michigan Department of Health and Human Services, Lansing, MI, USA, [3]University of Texas at Houston, Houston, TX, USA, [4]New York City Department of Health and Mental Hygiene, Long Island City, NY, USA, [5]University of Washington, Seattle, WA, USA

Background: Women who exchange sex have a high HIV prevalence in many countries, but limited data are available in the United States. In 2016, sampling for National HIV Behavioral Surveillance (NHBS) among heterosexuals focused on women who exchange sex for money or drugs in 4 of 22 cities (Chicago, Detroit, Houston and Seattle). We compared the HIV prevalence from this survey to women of low socioeconomic status (LSES) who did not exchange sex recruited as part of the 2013 NHBS cycle among heterosexuals, and to women in the general population of the included cities based on data from the National HIV Surveillance System (NHSS) for 2015.

Methods: NHBS participants were recruited via respondent-driven sampling (RDS), interviewed and offered HIV testing. Women with valid HIV results were included in analysis. NHBS data in 2013 were limited to the 4 cities included in 2016. We applied RDS weights to estimate the aggregated HIV prevalence in 2016 among women who exchange sex, and in 2013 among women of LSES who do not exchange sex. HIV prevalence in the general population was calculated using census and NHSS data. We used prevalence ratios to compare the HIV prevalence in 2016 among women who exchanged sex to women of LSES who did not exchange sex and women in the general population.

Results: In total, 1,440 women who reported exchange sex in 2016 and 671 women of LSES who did not report exchange sex in 2013 were included in the analysis. More than 80% of women who reported exchange sex in the past 12 months were living below the federal poverty line, homelessness ranged from 41.9% in Detroit to 65.3% in Seattle, and injection drug use from 3.8% in Houston to 61.4% in Seattle. Aggregated HIV prevalence for women who exchanged sex was 4.9% (CI 2.7%-7.1%), for women of LSES who did not exchange sex was 1.6% (CI 0.3%-2.8%), for women in the general population was 0.56% (CI 0.55%-0.58%). HIV prevalence among women who exchange sex was 3.1 times (CI 1.6-5.9) as high as among women of LSES who do not exchange sex, and 8.7 times (CI 6.9-10.9) as high as among women in the general population.

Conclusion: A high proportion of women who exchanged sex in this survey were homeless and lived in poverty. Their HIV prevalence was significantly higher compared to women in the general population and women of LSES who do not exchange sex. There is a need for further research of the role of exchange sex and LSES in the vulnerability for HIV among women and development of tailored interventions addressing these factors.

921 TRANSACTIONAL SEX MEASUREMENT AND ASSOCIATION WITH HIV INCIDENCE AMONG WOMEN

Mary K. Grabowski[1], Virginia Burke[1], Gertrude Nakigozi[2], Fred Nalugoda[2], Robert Ssekubugu[1], Larry W. Chang[3], Godfrey Kigozi[2], Deanne Kerrigan[1], David Serwadda[4], Betty Nantume[2], Darix K. Ssebagala[2], Ronald H. Gray[1], Joseph Kagaayi[2], Maria Wawer[1], Caitlin E. Kennedy[1]

[1]Johns Hopkins University, Baltimore, MD, USA, [2]Rakai Health Sciences Program, Kalisizo, Uganda, [3]Johns Hopkins Hospital, Baltimore, MD, USA, [4]Makerere University, Kampala, Uganda

Background: Transactional sex (TS) has been defined as "an exchange of money, favors, or gifts for sexual relations" and may overlap with sex work, but is often considered distinct and less formal. However, no population-based studies have documented the prevalence of TS among women in sub-Saharan Africa and its relationship with HIV incidence. We sought to compare reporting of TS using different survey measures, and assess the association between TS and HIV infection.

Methods: We compared trends in reporting TS over time among sexually active women ages 15-49 in the Rakai Community Cohort Study, a longitudinal open cohort in Rakai, Uganda. From 1999-2013, women were asked if they had ever exchanged money or gifts for sex with any partner (global measure). Beginning in 2014, women were asked if they had ever exchanged money, gifts, or favors with each of their four most recent sexual partners (partner-specific measure). We then used 2014-16 data to assess the association between the partner-specific measure and HIV prevalence and incidence using Poisson regression with and without adjustment for demographics.

Results: Reporting of TS among 19,155 women (58,414 woman-visits) in 30 continuously surveyed communities increased significantly with use of the partner-specific questions, from 0.5% to 8.9% of visits (p<0.001). Among 11,138 women surveyed in 2014-16, TS was reported at 13% (2,102/16,245) of visits. Only 4 women (0.03%) reported their occupation as sex workers. Women reported TS with husbands at 8% (952/11,667) of visits compared to 20% (1,150/5,631) for non-marital partners. There were 179 incident HIV cases identified, including 31 among women reporting any TS. Women reporting TS with marital partners had somewhat higher HIV prevalence (adjPRR=1.12, 95%CI:1.00-1.25) but not incidence compared to women not reporting TS with marital partners. Among women with non-marital partners, TS was also associated with higher prevalence regardless of community (adjPRR:1.10, 1.01-1.21). HIV incidence increased only among women who reported TS with non-marital partners in fishing communities (11 vs. 6 per 100 woman-years), but this association was not statistically significant after adjustment (adjIRR=1.65, 0.92-2.98).

Conclusion: Asking about TS using a partner-specific measure may elicit more accurate reporting than a global measure. TS may modestly correlate with HIV, but there is a need for more nuanced understanding of what dimensions of social relationships and HIV risk this measure captures.

Table: Association between transactional sex (TS) and HIV prevalence/incidence among 11,138 women in 38 communities surveyed between 2014-16 (16,245 woman-visits)

	HIV prevalence (N=11,138 women)			HIV incidence (N=5,513 women***)		
	HIV-positive/ woman-visits (%)	PRR (95% CI)	adjPRR** (95% CI)	Incidence per 100 woman-years (95%CI)	IRR (95% CI)	adjIRR (95% CI)
All communities						
*Marital partners**						
No TS	2251/10715 (21)	Ref.	Ref.	0.89 (0.72-1.08)	Ref.	Ref.
TS	246/952 (26)	1.23 (1.09-1.38)	1.12 (1.00-1.25)	0.69 (0.24-1.43)	0.75 (0.31-1.84)	0.58 (0.23-1.43)
Non-marital partners						
No TS	1366/4481 (30)	Ref.	Ref.	2.39 (1.89-2.96)	Ref.	Ref.
TS	398/1150 (35)	1.14 (1.03-1.25)	1.10 (1.01-1.21)	3.84 (2.54-5.54)	1.61 (1.03-2.51)	1.25 (0.79-1.98)
Fishing communities (hyperendemic; average HIV prevalence: 40%)						
Marital partners						
No TS	1057/2427 (44)	Ref.	Ref.	2.75 (1.97-3.70)	Ref.	Ref.
TS	134/296 (45)	1.04 (0.91-1.19)	1.05 (0.92-1.20)	1.24 (0.21-3.83)	0.45 (0.11-1.87)	0.47 (0.11-1.94)
Non-marital partners						
No TS	498/1034 (48)	Ref.	Ref.	5.76 (3.82-8.27)	Ref.	Ref.
TS	213/379 (56)	1.17 (1.04-1.31)	1.17 (1.05-1.30)	11.1 (6.40-17.7)	1.93 (1.02-3.65)	1.64 (0.84-3.20)
Non-fishing communities (average HIV prevalence: 12%)						
Marital partners						
No TS	1194/8288 (14)	Ref.	Ref.	0.60 (0.45-078)	Ref.	Ref.
TS	112/656 (17)	1.19 (0.98-1.43)	1.23 (1.01-1.48)	0.51 (0.13-1.32)	0.85 (0.26-2.70)	0.65 (0.20-2.11)
Non-marital partners						
No TS	868/3447 (25)	Ref.	Ref.	1.84 (1.34-2.39)	Ref.	Ref.
TS	185/771 (24)	0.95 (0.83-1.10)	1.04 (0.91-1.20)	2.02 (1.05-3.47)	1.10 (0.58-2.10)	0.99 (0.51-1.97)

TS=Transactional sex; PRR=Prevalence risk ratio; IRR=Incidence rate ratio; adjPRR=adjusted prevalence risk ratio; adjIRR=adjusted incidence rate ratio; CI: Confidence interval; Ref: Reference group; *Marital partners includes long-term cohabitating consensual unions; **Models were adjusted for age, educational attainment, marital status, and residence in a fishing community (overall analyses only); ***HIV incidence was calculated among the 5,513 HIV-negative women with follow-up data.

922 VIOLENCE AND HIV RISK FACTORS AMONG WOMEN WHO EXCHANGE SEX FOR MONEY OR DRUGS

Christine Agnew-Brune[1], Lina Nerlander[2], Dita Broz[1], Zaida Lopez[3], Stephanie Schuette[4], Vivian Griffin[5], Alexis Rivera[6], Sara N. Glick[7], Gabriela Paz-Bailey[1]
[1]CDC, Atlanta, GA, USA, [2]European Centre for Disease Prevention and Control, Stockholm, Sweden, [3]Houston Health Department, Houston, TX, USA, [4]Chicago Department of Public Health, Chicago, IL, USA, [5]Southeastern Michigan Health Association, Detroit, MI, USA, [6]New York City Department of Health and Mental Hygiene, Long Island City, NY, USA, [7]University of Washington, Seattle, WA, USA

Background: Violence among women who exchange sex is pervasive and has been associated with risk for HIV infection. Client-perpetrated violence (CPV) and intimate-partner violence (IPV) introduce vulnerability that place women at higher risk of sexual and drug-use behaviors associated with HIV and may affect their ability to seek healthcare services. Despite the importance of violence and HIV risk among women who exchange sex, data for prevention efforts in the US is lacking. We used data from CDC's National HIV Behavioral Surveillance to examine violence experienced by women who exchange sex and estimate associations between violence and behaviors known to increase risk for HIV.

Methods: In 2016, women who exchanged sex for money or drugs in the prior 12 months were recruited via respondent-driven sampling and interviewed in five cities (Chicago, Detroit, Houston, New York City, and Seattle). Using log-linked Poisson regression, we calculated separate adjusted prevalence ratios (aPR) for associations between 4 violence measures and 2 past-year behavioral outcomes: condomless sex (vaginal or anal) and injection drug use. The violence measures included physical (e.g., slapped, punched, kicked) or sexual (forced or pressured vaginal, oral or anal sex) perpetrated by clients or intimate partners (boyfriend, spouse, or other sex partner). Models were adjusted for city and age.

Results: Of 1,790 women sampled, most were black (65%) or Latina (13%) and the median age was 46. Injection drug use was reported by 26% of women and 43% reported condomless sex. Over 85% visited a healthcare provider in the past year and 83% had health insurance. Physical CPV was reported by 10% of women, sexual CPV by 13%, physical IPV by 32%, and sexual IPV by 29%. Sexual CPV and sexual IPV were associated with injection drug use (aPR=1.47, confidence interval [CI]: 1.16–1.86; aPR=1.26, CI: 1.04–1.53, respectively) while physical violence were not. Physical and sexual CPV were associated with condomless sex (aPR=1.28, CI: 1.08–1.51; aPR=1.19, CI: 1.01–1.39, respectively) as were physical and sexual IPV (aPR=1.25, CI: 1.10–1.41; aPR=1.25, CI: 1.11–1.41, respectively).

Conclusion: Among sampled women who exchange sex, CPV and IPV were prevalent and associated with sexual and drug use HIV risk factors. Most women sampled were engaged in healthcare, suggesting an opportunity for provider-initiated routine screening for violence and integration of services to address HIV risk in this population.

923 SEXUAL PARTNER TYPE AND INCIDENT HIV-INFECTION AMONG ADOLESCENT GIRLS IN HPTN 068

Nadia Nguyen[1], Kimberly A. Powers[1], Annie Green Howard[1], William C. Miller[2], Carolyn T. Halpern[1], Yaw Agyei[3], Catherine MacPhail[4], Kathleen Kahn[5], Audrey Pettifor[1]
[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]The Ohio State University, Columbus, OH, USA, [3]Johns Hopkins University, Baltimore, MD, USA, [4]University of Wollongong, Wollongong, Australia, [5]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa

Background: Sexual partners play a critical role in HIV transmission, but efforts to study and target sexual partner types for HIV prevention have been stymied by current measurement approaches, which have not shown clear associations with HIV acquisition, and do not provide clear guidance on the design of specific, targeted interventions to prevent HIV acquisition across different sexual partner types and contexts.

Methods: This secondary analysis examined the sexual partners of 1034 sexually active, adolescent girls and young women (AGYW), ages 13-20, enrolled in a 3-year randomized controlled trial of cash transfers for HIV prevention (HPTN 068) in Mpumalanga Provence, South Africa. AGYW were tested for HIV infection annually and reported the following 10 indicators for each sexual partner (up to three partners per visit): partner age, school enrollment, children with AGYW, children with other women, cohabit with AGYW, sex only one time, always use condoms, partner HIV-status, partner concurrency status, and transactional sex with partner. We used these indicators to identify sexual partner types using Latent Class Analysis (LCA), and estimated risk ratios (RR) and 95% confidence intervals (CI) for the association between LCA-identified sexual partner type and incident HIV-infection using generalized estimating equations with a robust variance estimator and exchangeable correlation matrix, controlling for confounders.

Results: Over the course of 2140 AGYW-visits, 1034 AGYW reported 2968 sexual partners, and 63 AGYW become HIV infected. We identified six, distinct sexual partner types: only one partner type was older, two were not enrolled in school, condom use was low across all but one type, while transactional sex was present in all but one type (Table 1). Compared to AGYW with "monogamous" partners, AGYW with "older" partners had more than 3 times the risk of HIV infection (RR: 3.35, 95% CI: 1.43, 7.85), while AGYW with "unprotected" partners had more than 2 times the risk of HIV infection (RR: 2.45, 95% CI: 1.11, 5.44). AGYW with "casual protected" or "anonymous" partners were at increased risk of infection, while AGYW with "cohabiting" partners were at decreased risk compared to AGYW with "monogamous" partners (results not statistically significant).

Conclusion: Partner types based on explicit, reported partner characteristics predict incident HIV-infection among AGYW, and offer an alternative approach for measuring and targeting specific partner types for HIV research and intervention.

Table 1. Sexual partner types among South African adolescent girls and young women

Sexual partner type	N (% of reported partners)	Defining characteristics of sexual partner type
Monogamous HIV-negative peer partners ("monogamous")	1226 (41%)	• Less than 5 years older (89%; mean age difference 2.5 years) • No children with other women (92%) • No concurrent sexual partners (72%) • Inconsistent condom use with AGYW (87%) • Sex more than one time (92%) • HIV negative (96%)
Unprotected peer partners ("unprotected")	527 (18%)	• Less than 5 years older (96%; mean age difference 2.1 years) • HIV positive (15%), unknown HIV status (44%) • Have concurrent sexual partners (30%), unknown concurrency status (42%) • Inconsistent condom use with AGYW (93%)
Casual protected peer partners ("casual protected")	508 (17%)	• Less than 5 years older (95%; mean age difference 2.0 years) • Enrolled in school (76%) • HIV negative (80%) • Sex only one time (60%) • Always use a condom with AGYW (68%) • No transactional sex (92%)
Older out-of-school partner ("older")	321 (11%)	• 5 or more years older (97%; mean age difference 6.1 years) • Not enrolled in school (85%) • Children with AGYW (31%) • Children with other women (28%) • Have concurrent sexual partners (28%), unknown concurrency status (28%) • Inconsistent condom use with AGYW (82%)
Anonymous out-of-school peer partners ("anonymous")	246 (8%)	• Less than 5 years older (74%; mean age difference 3.5 years) • Not enrolled in school (73%) • Children with other women unknown (61%) • Unknown concurrency status (74%) • Unknown HIV status (57%) • Inconsistent condom use with AGYW (82%)
Cohabiting with kids peer partners ("cohabiting")	140 (5%)	• Less than 5 years older (78%; mean age difference 3.1 years) • Enrolled in school (64%) • Live with AGYW (84%) • Children with AGYW (70%) • Children with other women (51%) • Have concurrent sexual partners (31%) • Inconsistent condom use with AGYW (97%) • Transactional sex (82%)

924 AN AGE-STRATIFIED RISK SCORE TO PREDICT HIV ACQUISITION IN YOUNG SOUTH AFRICAN WOMEN

Emma K. Burgess[1], **Nonhlanhla Yende-Zuma**[2], Delivette Castor[1], Quarraisha Abdool Karim[2]
[1]*United States Agency for International Development, Washington, DC, USA,* [2]*CAPRISA, Durban, South Africa*

Background: Prioritizing high-risk women in HIV hyperepidemic settings is important for optimized introduction and scale of new prevention methods (e.g., oral PrEP). We assessed the performance of a risk score derived from the VOICE cohort using the CAPRISA 004 dataset and modified the score for age-specific prediction.

Methods: The initial risk score (IRS) included 7 items: age; HSV-2 serostatus; partner exclusivity; marital/co-habitation; partner's financial support; alcohol use, and STIs. We developed an age-stratified modified risk score (MRS) and public health use risk score [(PHRS) excludes non-routine HSV serotesting] and evaluated risk prediction according to the area under the curve (AUC), sensitivity, specificity, and un/adjusted hazard ratios (aHR). Given the effect of the tenofovir gel, only participants in the CAPRISA 004 placebo arm (n=444) were used in this analysis.

Results: There were 60 HIV infections over 660.7 person-years of follow-up (incidence=9.08/100 person-years (PY); 95%CI 7.05, 11.7). Women with IRS scores of <8 had a significantly lower HIV incidence of 5.95/100 PY (95%CI 3.88, 9.12) compared to those with scores ≥8 (12.83/100 PY; 95%CI 9.29, 17.7). This cut-off had a sensitivity of 64% and specificity of 57% (Figure 1). The AUC was 0.66. Among the 7 IRS items, only 3 were significantly associated with HIV acquisition in this dataset; age <25 years (aHR=2.47; 95%CI 1.24, 4.89), responding "don't know" and "yes" that your partner has other partners (aHR=4.02; 95%CI 1.22, 13.3 and 3.77; 95%CI 1.07, 13.3), and being HSV-2 positive (aHR=2.10; 95%CI 1.19, 3.68). The age stratified MRS showed the most predictive score for women <25 years included HSV-2, casual partnerships and partner exclusivity (AUC: 0.70). The PHRS had an AUC of 0.62, and women <25 years with scores <3 vs. ≥3 had incidences of 1.57 (95%CI 0.22, 11.16) and 12.6/100 PY (95%CI 9.17, 16.44), respectively.

Conclusion: The ability of the IRS to predict incident HIV infections was comparable to previous validations. However, a cut-off where women were at a substantially low risk of HIV infection could not be determined. Exploratory analyses show the MRS and PHRS to be simpler tools that can be used for PrEP counselling, increasing risk perception and to focus interventions on modifiable risk factors. Yet, relatively lower risk women still had high HIV incidence suggesting further modification to the tool or the need to offer PrEP to any at-risk young woman in hyperepidemic settings.

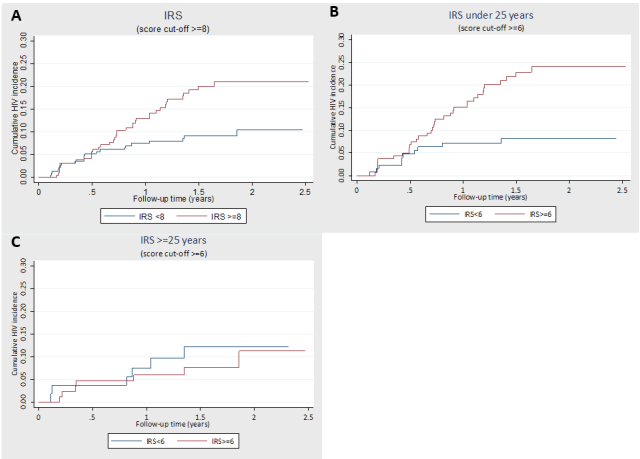


Figure 1. Cumulative HIV incidence over study time at risk score cut offs of ≥8 for IRS (A), ≥6 for IRS applied to those under 25 years old with the 2 possible points for young age removed (B) and ≥6 for IRS applied to those ≥25 years old. (C)

925 SEROSORTING FOR CONJUGAL RELATIONSHIP FORMATION IN HETEROSEXUAL COUPLES, SOUTH AFRICA

Hae-Young Kim[1], Alain Vandormael[1], Andrew Tomita[1], Till Bärnighausen[2], Frank Tanser[1]
[1]*Africa Health Research Institute, Mtubatuba, South Africa,* [2]*Heidelberg University, Heidelberg, Germany*

Background: Serosorting can have potential benefits including reduction in HIV incidence and better ART adherence and retention. Although serosorting behavior has been reported among high risks groups such as men who have sex with men, its role is largely unknown in heterosexual couples in a high HIV endemic setting in sub-Saharan Africa.

Methods: Data from a population-based open cohort between January 2003 and December 2016 in KwaZulu-Natal, South Africa was used. Individuals with known HIV status, not currently in stable conjugal relationship (CR), were included for the analysis. Competing-risks survival regression was used to estimate the incidence of conjugal relationship formation with known HIV seropositive partners by participants' HIV status, where formation with known seronegative or unknown serostatus partners was fitted as the competing risks. HIV status was used as a time-varying exposure. Hazard ratios (HR) and 95% confidence intervals (CI) are reported.

Results: A total of 24,232 HIV-negative and 10,384 HIV-positive individuals including 3,345 who seroconverted were followed over 166,686 person-years (PY) follow-up time. We observed 68 (0.4 per 1000 PY) CR formation with known HIV seropositive, 193 (1.2/1000 PY) with known seronegative and 385 (2.3/1000 PY) with unknown serostatus partners. The average median age at the time of CR formation was 27 (IQR:21-36). HIV-positive individuals had 2.17 (95% CI: 1.29-3.64) times higher hazard of CR formation with a HIV-positive partner, compared to HIV-negative individuals. The adjusted HR was 2.26 (95% CI: 1.29-3.96) after adjusting for age, sex, education, household asset, and the number of partners in the past 12 months. When stratified by participants' age at <30 vs. 30+ years, the association became only significant in those aged 30+ years (HR=4.11; 95% CI: 1.93-8.73).

Conclusion: Positive serosorting was observed among HIV-positive individuals in older heterosexual couples in rural KwaZulu-Natal, South Africa. Such behavior might be due to increased knowledge for HIV and access to antiretroviral therapy (ART) care and may lead to better long-term health outcomes.

926 SELF-REPORTED RISKY SEXUAL PRACTICES AMONG ADOLESCENTS AND YOUNG ADULTS IN BOTSWANA

Unoda A. Chakalisa[1], Kathleen Wirth[2], Kara Bennett[3], Etienne Kadima[1], Kutlo Manyake[1], Tendani Gaolathe[1], Pamela J. Bachanas[4], Tafireyi Marukutira[5], Scott Dryden-Peterson[6], Mompati O. Mmalane[1], Joseph Makhema[1], Molly Pretorius Holme[2], Max Essex[2], Shahin Lockman[6], Kathleen M. Powis[7]
[1]*Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana,* [2]*Harvard University, Cambridge, MA, USA,* [3]*Bennett Statistical Consulting, Inc, New York, NY, USA,* [4]*CDC, Atlanta, GA, USA,* [5]*Monash University, Melbourne, VIC, Australia,* [6]*Brigham and Women's Hospital, Boston, MA, USA,* [7]*Massachusetts General Hospital, Boston, MA, USA*

Background: An estimated 1700 adolescent and young adults (15-24) acquire HIV daily, accounting for over a third of new HIV cases. Understanding sexual practices of this high-risk group is critical in designing HIV prevention programming.

Methods: We sought to examine the sexual practices, regardless of HIV status, of adolescents and young adults aged 16-24 years participating in the Botswana Combination Prevention Project (BCPP), an ongoing pair-matched, cluster-randomised trial of 30 communities. Information on age of sexual debut, number of sexual partners, condom and alcohol use during sex, intergenerational sex (intercourse with a partner 10 or more years older), and transactional sex (receiving money, transport, food, drink or other goods in exchange for sex) were collected at enrollment. Modified Poisson estimating equations were used to obtain prevalence ratios comparing engagement in different sexual practices according to gender, adjusting for community-level clustering.

Results: Among the 12,610 BCPP participants, 3,380 were 16-24 years-of-age. Of these 2,311 (68%) reported being sexually active with significantly more females reporting ever being sexually active compared with males (65% vs 35% respectively; p<0.0001). Sexually active individuals reported significantly higher levels of poverty, indicated by lack of television (44.2% vs 37.5%; p=0.0004) or refrigeration (56% vs 46%; p<0.0001), and reliance on a communal stand pipe for water (26% vs 20%; p<0.0001). Compared to males, sexually active females were significantly more likely to report inconsistent condom use (PR: 1.61; 95% CI: 1.44-1.80), intergenerational sex (PR: 9.00; 95% CI 5.84-13.88), and transactional sex (PR: 3.46; 95% CI 2.07-5.77). [Table 1] In contrast, women were significantly less likely to engage in sex before age 15

years (PR: 0.59; 95% CI: 0.41-0.85), use alcohol around time of intercourse (PR: 0.59; 95% CI: 0.45-0.76), or have ≥2 partners in the last 12 months (PR: 0.65; 95% CI: 0.57-0.74).

Conclusion: Self-reported risky sexual practices of adolescents and young adults in Botswana differed significantly between males and females. Economic stress was strongly associated with increased risk behavior in females and interventions targeting this vulnerability (income transfer, pre-exposure prophylaxis) have promise in Botswana. Programs targeting episodic risk, particularly around alcohol, could be more effective in young males.

Table 1. Risky Sexual Practices among Sexually Active Adolescents and Young Adults by Sex

Risky Sexual Practice (n)	N (%) Males (N=815)	N (%) Females (N=1,496)	Univariable prevalence ratio (95% CI)	P-value
Sexual debut before age 15 years (n=2,311))	119 (15%)	129 (9%)	0.59 (0.41-0.85)	0.005
Alcohol use by respondent, partner or both during intercourse (n=2,308)	93 (11%)	100 (7%)	0.59 (0.45-0.76)	<0.0001
Inconsistent Condom Use (n=2,012)	237 (29%)	742 (50%)	1.61 (1.44-1.80)	<0.0001
Two or more Sex Partners in Last 12 Months (n=2,247)	332 (41%)	395 (26%)	0.65 (0.57-0.74)	<0.0001
Intergenerational Sex with Older Partner (n=2,028)	21 (3%)	373 (25%)	9.00 (5.84-13.88)	<0.0001
Transactional Sex (n=2,048)	18 (2%)	122 (8%)	3.46 (2.07-5.77)	<0.0001

927 HIGH PREVALENCE OF CONCURRENT SEXUAL PARTNERSHIPS IN A LARGE POPULATION SURVEY

Etienne Kadima[1], Kathleen Wirth[2], Kara Bennett[3], Tendani Gaolathe[1], Jean Leidner[4], Unoda A. Chakalisa[1], Erik VanWidenfelt[1], Pamela J. Bachanas[5], Refeletswe Lebelonyane[6], Mompati O. Mmalane[1], Joseph Makhema[1], Molly Pretorius Holme[2], Shahin Lockman[2], Max Essex[2], Sikhulile Moyo[1]
[1]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [2]Harvard University, Cambridge, MA, USA, [3]Bennett Statistical Consulting, Inc, New York, NY, USA, [4]Goodtables Data Consulting, Norman, OK, USA, [5]CDC, Atlanta, GA, USA, [6]Botswana Ministry of Health, Gaborone, Botswana

Background: Multiple and concurrent sexual partnerships (MCP) are considered a driver of new HIV infections in Sub-Saharan Africa. Understanding predictors of MCP could help design prevention strategies to reduce HIV incidence. We investigated predictors of MCP and the association between MCP and recent HIV infection in a large household-based cluster-randomized HIV prevention trial (BCPP) in 30 Botswana communities from Nov 2013–Nov 2015.

Methods: In BCPP, we used structured questionnaires to evaluate for MCP over the prior 12 months via: a) standard UNAIDS-recommended method in which MCP was defined as having at least 2 active and overlapping sexual partners in the past 12 months, and b) a direct question regarding whether concurrent sexual relationships existed at the same time. MCP was defined as present if either method indicated MCP. Recent HIV infection was determined using an algorithm including the Limiting-Antigen Avidity Assay, as well a time of less than 2 years between the last documented negative HIV test to first documented positive HIV test. We estimated prevalence ratios and 95% confidence intervals for factors associated with MCP, adjusting for clustering, age and gender.

Results: Data were available from 11,965 (94.9%) of 12,610 participants. Among 9,364 who were sexually active in the past 12 months, 2,878 (30.7%; 95%CI: 29.8–31.7) had multiple sexual partners. Among 9,363 with recent partner data, 2,770 (29.6%, 95%CI: 28.7–30.5) had MCP. Those reporting MCP were more likely to be male (prevalence ratio [PR]=1.6; 95%CI: 1.5-1.7), and of median age 32 years (Q1, Q3: 25,41). After adjusting for age and gender, MCP was significantly associated with being employed (PR=1.3; 95%CI: 1.3–1.5), transactional sex (PR=1.7;95%CI:1.5–2.1), intergenerational sex (PR=1.2; 95%CI:1.1–1.3), and high alcohol consumption (PR=1.5; 95%CI:1.4–1.6). MCP was not significantly associated with recent or prevalent HIV infection. Participants who knew their HIV-positive status were less likely to have MCP (PR=0.9;95%CI:0.8-0.96). Among those who believed their partners had other partners during the course of their relationships in the past year, 49.9% were in MCP (PR=2.0;95% CI:1.97-2.2).

Conclusion: Despite efforts to reduce MCP behaviors , they were still common particularly among men. MCP was not associated with recent or prevalent HIV infection. Knowledge of positive HIV status was associated with lower MCP rates. Multiple socio-behavioral HIV prevention strategies are needed to reduce MCP.

928 ARE FISHERFOLK AT HIGHER RISK THAN THEIR NEIGHBORS: FINDINGS FROM WESTERN KENYA, 2015

Emily Zielinski-Gutirrez[1], Sifunjo F. Odongo[2], Daniel Kwaro[2], Kennedy Mutai[2]
[1]US CDC Nairobi, Nairobi, Kenya, [2]Kenya Medical Research Institute, Kisumu, Kenya

Background: Counties bordering Lake Victoria have the highest adult HIV prevalence in Kenya. Within the region, fisherfolk (FF) who catch, sell, or process fish and their spouses are considered a priority population in HIV transmission. We asked if FF differ from their immediate non-fishing neighbors (non-FF) in terms of HIV prevalence, risk behaviors and health service utilization in Siaya county, western Kenya.

Methods: A cross-sectional bio-behavioral household survey was conducted at beaches and adjacent villages in the Kenya Medical Research Institute Health and Demographic Surveillance System from August 2014-March 2015. The survey collected demographics, HIV risk behavior and service utilization and offered HIV testing. Bivariate comparisons were used to examine factors of interest, evaluated by Pearson's chi-square, with stratification by sex as appropriate.

Results: Of 3462 participants aged 15-64 years, 940 (27.2%) were FF. Of 3344 respondents with HIV status, 17.1% were HIV positive; prevalence was higher among FF (24.1%) than non-FF (14.7%), p<.001. Most HIV-positive respondents (77.0%) self-reported their status. HIV prevalence was significantly higher among women (20.1%) than men (11.8%, p<.001), with a greater difference by sex among non-FF. HIV prevalence was highest among FF aged 30-49 years (34.4%) with a similar pattern among non-FF, peaking at 28.4% among the same age group. More non-FF men were circumcised than FF men (61.9% vs. 51.9%, p<.001). Among the sexually active, FF men were more likely than no-FF men to report two or more sexual partners in the past 12 months (34.9% vs. 25.9%, p<.006), and all FF were more likely to report no condom use with at least one sexual partner in past 12 mos. (77.2% FF vs. 46.8% non-FF, p<.001). Most respondents had previously tested for HIV (95.2% FFX vs. 92.2% non-FF, p<.001). Among 446 total respondents self-reporting as HIV positive, 78.0% reported taking anti-retroviral therapy (ART), with no significant difference by FF status. When accounting for all HIV positives, ART coverage was 56.9% among FFX and 62.9% among non-FF.

Conclusion: HIV prevalence was higher among FF than among non-FF. FF reported higher HIV-related risk such as non-circumcision, more sexual partners and sex without condoms. While ever-testing rates were high, just over half of FF were on ART, suggesting that aggressive scale-up of testing, treatment and prevention interventions targeted for FF are required to meet the needs of this priority population.

929 NATIONAL TRENDS IN HIV PREVALENCE IN 3 KEY POPULATIONS IN UKRAINE

Kostyantyn Dumchev[1], Yana Sazonova[2], Tetiana Salyuk[2], Olga Varetska[2]
[1]Ukrainian Institute on Public Health Policy, Kyiv, Ukraine, [2]Alliance for Public Health, Kyiv, Ukraine

Background: Once recognized as the most severe in Europe, the HIV epidemic in Ukraine is concentrated among people who inject drugs (PWID), men who have sex with men (MSM) and female sex workers (FSW). Integrated bio-behavioral surveys (IBBS), as a part of the second generation surveillance, are used to monitor HIV infection and risk behaviors in key populations since 2002. This analysis focused on HIV prevalence trends in four latest nationally-representative rounds of IBBS in Ukraine.

Methods: Each of the four IBBS studies in 2008-9, 2011, 2013, and 2015 covered all 27 regions of Ukraine, and used respondent-driven sampling to recruit PWID and MSM, and time-location sampling for FSW. HIV seropositivity was determined by a single rapid test. Sociodemographic, HIV risk behavior and drug use characteristics were assessed using an anonymous questionnaire. Chi-square test was used to detect differences between rounds, Mantel-Haenszel test was used to assess significance of the overall trend.

Results: Sample sizes and HIV prevalence in total samples, age group younger than 25, and MSM and FSW subgroups who ever injected drugs are presented in Table 1. Over the four rounds, HIV prevalence has decreased significantly

in PWID and FSW, all young subgroups, and drug injecting MSM and FSW. In between-round comparison, there was a significant almost two-fold increase between 2013 and 2015 in MSM (from 4.3% to 7.8% overall, p<0.001 1.9% to 4.3% in young subgroup, p<0.001) while there was an insignificant decrease in drug-injecting MSM (from 16.1% to 11.4, p=0.227). Prevalence increased in 2015 in all PWID (from 18.1% in 2013 to 22.0%, p<0.001), but not in younger subgroup (from 4.29% in 2013 to 4.27% in 2015, p=0.974). There were no significant changes between 2013 and 2015 in FSW.

Conclusion: The pooled analysis of four nationally-representative IBBS surveys in Ukraine has confirmed the decreasing trend in HIV prevalence in PWID and FSW. Prevalence in younger subgroups, commonly used as a proxy indicator for incidence, has decreased markedly in all three populations. The change in PWID may be explained by the effect of the massive harm reduction program supported by the Global Fund, covering more than 60% of estimated PWID nationally. The decreases in MSM and FSW, covered by prevention to a lesser extent, may be driven by the decline in PWID. The recent increase in MSM, especially the younger subgroup, may indicate a new wave of non-injection related transmission, which is correlated with other studies.

Table 1. HIV prevalence in three key populations in four rounds of integrated bio-behavioral surveys in Ukraine.

		2008-9		2011		2013		2015		p-value
		N (% of N)	HIV prev.	N (% of N)	HIV prev.	N (% of N)	HIV prev.	N (% of N)	HIV prev.	for trend
PWID	Total	6,458	**24.2%**	9,069	**22.6%***	9,496	**18.1%***	9,405	**22.0%***	<0.001
	Age <25 y.o.	(25.2%)	**10.3%**	(16.5%)	**8.1%***	(14.5%)	**4.3%***	(10.2%)	**4.3%**	<0.001
MSM	Total	2,302	**8.5%**	5,950	**6.4%***	8,004	**4.3%***	4,550	**7.8%***	0.099
	Age <25 y.o.	(36.8%)	**7.8%**	(41.1%)	**4.5%***	(39.3%)	**1.9%***	(35.1%)	**4.3%***	<0.001
	Ever drug injecting	(1.7%)	**18.4%**	(2.5%)	**25.7%**	(1.8%)	**16.1%***	(3.9%)	**11.4%**	0.004
FSW	Total	3,282	**13.6%**	5,023	**10.5%***	4,806	**5.6%***	4,262	**6.3%**	<0.001
	Age <25 y.o.	(41.4%)	**8.9%**	(37.4%)	**3.7%***	(31.2%)	**1.7%***	(29.2%)	**1.4%**	<0.001
	Ever drug injecting	(21.0%)	**39.0%**	(9.4%)	**41.9%**	(7.9%)	**21.8%***	(10.9%)	**23.8%**	<0.001

* p-value for change from previous round <0.05

930 TRENDS IN HIV INFECTION AMONG AMERICAN INDIANS/ALASKA NATIVES, US 2010–2014

Andrew J. Mitsch[1], Xiao Wang[2], Dean Seneca[1], Sonia Singh[1], Donald Warne[3]
[1]CDC, Atlanta, GA, USA, [2]ICF International, Atlanta, GA, USA, [3]North Dakota State University, Fargo, ND, USA

Background: During 2010-2014, American Indians/Alaska Natives (AIs/ANs) were among the two racial/ethnic groups that experienced increasing annual rates of diagnoses of HIV infection. At year-end 2014, one in five AIs/ANs living with HIV were unaware of their infection. The objective of this analysis was to describe trends among AIs/ANs in annual diagnoses and prevalence by subgroup and variations by place for the purpose of guiding HIV prevention efforts among this population.

Methods: Using National HIV Surveillance System (NHSS) data, we determined the number of HIV diagnoses reported to CDC from 2010 through 2014, and through year-end 2014 for prevalence, among US residents with diagnosed HIV infection classified as AI/AN, aged ≥ 13 years. We measured trends in annual diagnoses during 2010-2014 using arithmetic change and for 2014, we calculated diagnosis rate ratios for sex, age group, transmission category, and place of residence at diagnosis. We also measured trends in prevalence during 2010–2014 using estimated annual percent change (EAPC) with 95% confidence intervals (CI), overall and for transmission category and jurisdiction.

Results: During 2010–2014, the overall rate of annual diagnoses of HIV infection among AIs/ANs increased by 17.3%. Annual diagnosis rates increased among male AIs/ANs by 25.5%, those aged 13-34 years by 28.0%, in the South by 37.7% and in large metropolitan areas by 16.3%. For 2014, the male to female diagnosis rate ratio was 4.1 and 9.3 for those aged 13-34 years as compared to those aged ≥ 55. In addition, AIs/ANs were 1.6 times as likely to have their HIV infection diagnosed in the West as compared to the Northeast and 3.4 times as likely to have their HIV infection diagnosed in a large metropolitan area as compared to a nonmetropolitan area. Overall prevalence increased, (EAPC 3.2, 2.1-4.3) as did the prevalence among men who have sex with men (EAPC 3.9, 1.6-6.3). Prevalence rates increased in 2 jurisdictions, were stable in 27, decreased in none and could not be calculated in 22 due to small cell sizes.

Conclusion: Increasing trends among AIs/ANs suggest growing vulnerability to HIV. Prevention efforts should be strengthened for all AIs/ANs-particularly for men who have sex with men, those aged 13-34 years, and those residing in urban areas and the West. The increasing trend in the South represents an emerging threat.

931 COMPLEX HIV EPIDEMIC DYNAMICS IN MIGRANTS IN EUROPEAN UNION/ ECONOMIC AREA (EU/EEA)

Julia Del Amo[1], Inma Jarrin[1], Victoria Hernando[1], Cristina Moreno[1], Belen Alejos[1], Anastasia Pharris[2], Teymur Noori[2]
[1]Institute of Health Carlos III, Madrid, Spain, [2]European Centre for Disease Prevention and Control, Stockholm, Sweden

Background: We aim to understand the impact of migrants from sub-regions within Sub-Saharan Africa (SSA), Europe, and Latin America/the Caribbean (LAC) to HIV epidemic dynamics in the EU/EEA.

Methods: HIV Surveillance data from 30 EU/EEA countries from 2004 till 2015 were analysed. Cases in migrants (defined as cases with different country of origin to that of report) from SSA were divided into Western, Central, Eastern and Southern Africa UN sub-regions; those from Europe into Eastern (EE), Central (CE) and Western Europe (WE); and those from LAC into Central (CA), Andean (AA), South-America (SA) and Caribbean (Cb). Differences in CD4 counts at HIV diagnosis were analyzed using multivariate median regression.

Results: Of 375,743 reports, 18% were from SSA [35% Western SSA, 31% Eastern, 22% Central, 5% Southern SSA, 7% unknown], 7% were European migrants [48% WE, 31% CE and 21% EE] and 5% from LAC [31% unknown LAC sub-region], 27% Cb, 24% SA, 9% AA and 9% CA]. In migrants from SSA, 86% acquired HIV heterosexually and 3.5% through sex between men (MSM). Absolute and relative HIV declines (2014 vs 2004 to lessen reporting delay) were -98 (-5%), -1750 (-61%), -705 (-40%), -274 (-63%) for Western, Eastern, Central and Southern SSA, respectively. Increases were seen in MSM from SSA. In migrants from Europe, 74% and 57% of reports from WE and CE, respectively, were in MSM and 34% of reports from EE in persons who inject drugs (PWID). Absolute (+833) and relative (+139%) increases in HIV diagnoses in migrant MSM from Europe were observed. For heterosexually transmitted cases, absolute (+429) and relative (+257%) increases from CE and EE were reported. For PWID, absolute (-63) and relative (-52%) declines in WE and absolute (+54, + 47) and relative (+357%, +62%) increases in HIV diagnoses from CE and EE were observed. In migrants from LAC, 53% were MSM. Absolute and relative +679 (+167%) increases in HIV diagnoses in MSM and corresponding -215 (-27%) declines in heterosexually transmitted cases were reported. CD4 count at diagnosis increased over time for SSA and WE migrants and were higher in women and MSM.

Conclusion: Declines in heterosexually transmitted HIV are observed in migrants from Central and Eastern SSA, the Caribbean and WE, together with striking increases in migrant MSM from all regions. Rising CD4 counts reflect more HIV testing in most migrant groups. Migration flows changes from UN-sub regions into EU/EEA are likely to shape these trends.

	Migrants from SSA Median difference (95%CI)			Migrants from LAC Median difference (95%CI)				Migrants from Europe Median difference (95%CI)		
	WA	CA	EA	AA	SA	CA	Cb	WE	CE	EE
2004	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2005	-26(-66,4)	17(-14,47)	-1(-17,15)	-17(-154,120)	-20(-100,60)	34(-71,138)	2(-60,63)	18(-21,56)	-42(-125,419	-75(-171,21)
2006	-20(-50,10)	11(-21,43)	6(-12,23)	34(-99,168)	-34(-110,42)	14(-94,121)	28(-36,92)	35(-5,75)	-64(-146,18)	-80(-175,16)
2007	1(-29,31)	30(-3,63)	17(-1,34)	7(-133,147)	-48(-120,24)	38(-42,138)	16(-47,79)	18(-23,58)	-31(-81,75)	-98(-192,4)
2008	9(-18,36)	40(12,68)	20(2,38)	-46(-168,76)	-48(-117,21)	84(-10,177)	34(-24,92)	42(5,79)	-19(-94,56)	-97(-185,9)
2009	18(-9,45)	43(15,71)	28(10,46)	25(-96,146)	-24(-93,45)	73(-19,164)	-3(-60,54)	35(-3,73)	-6(-80,68)	-42(-129,45)
2010	21(-5,47)	43(14,71)	33(14,52)	-2(-117,113)	6(-59,71)	40(-130,51)	-8(-64,48)	65(28,102)	18(-54,90)	-73(-156,11)
2011	14(-11,39)	50(21,78)	37(17,56)	-7(-121,107)	-7(-71,57)	-40(-130,51)	42(-15,99)	67(30,104)	-5(-76,66)	-112(-196,-28)
2012	30(5,55)	54(25,82)	40(18, 61)	-1(-115,113)	-16(-81,49)	48(-40,136)	24(-33,80)	76(39,113)	-4(-75,67)	-95(-176,-14)
2013	30(4,56)	72(43,101)	65(42,88)	27(-86,140)	13(-81,49)	-15(-110,80)	31(-15,90)	95(59,131)	41(-30,110)	-97(-179,-15)
2014	41(15,67)	63(34, 92)	51(27,74)	29(-83,141)	53(-11,117)	43(-47,134)	14(-45,73)	117(81,153)	33(-38,104)	-93(-175,-11)
2015	34(6,62)	62(30, 94)	79(55,102)	33(-79,145)	42(-23,107)	15(-81,111)	34(-28,96)	119(82,156)	27(-44,98)	-104(-187,-21)
Male	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Women	61(51,71)	21(8,33)	22(12,31)	67(0,134)	46(-0,92)	80(31,129)	36(8,63)	65(39,91)	30 (3,57)	38(6,70)
Hetero	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
MSM	100(72, 128)	48(15, 81)	111(85,136)	154(98,210)	109(68, 150)	156(109,202)	97(68, 126)	123(101,146)	140(114,166)	143(103,183)
PID	-	-				-		-4(-36,28)	24(-12,60)	-25(-60,10)

*Analyses are adjusted by age

932 HIV TESTING AND US ACQUISITION AMONG AFRICAN IMMIGRANTS LIVING WITH HIV IN THE US

Roxanne P. Kerani[1], Amanda Lugg[2], Baiba Berzins[3], Oumar Gaye[4], Lauren Lipira[1], Camille Bundy[3], Helena Kwakwa[4], King Holmes[1], Matthew R. Golden[1]
[1]University of Washington, Seattle, WA, USA, [2]African Services Committee, New York, NY, USA, [3]Northwestern University, Chicago, IL, USA, [4]Philadelphia Department of Public Health, Philadelphia, PA, USA

Background: African immigrants in the U.S. are more likely to have a late HIV diagnosis than U.S.-born people, potentially leading to onward transmission of HIV. We sought to determine the proportion of African-born people living with HIV (APLWH) who 1) had HIV tested prior to diagnosis, and 2) likely acquired HIV in the U.S.

Methods: We interviewed APLWH in King County, WA, New York City, Philadelphia, and Chicago from February, 2014- August, 2017. Participants

were recruited through medical clinics, public health agencies, or community-based organizations. We obtained clinical information from medical or case management records, and estimated location (U.S. vs. outside the U.S.) of HIV acquisition based on clinical data, testing history, dates of immigration and first positive/last negative HIV test, and sexual behaviors before/after immigration. We identified predictors of having >1 previous negative HIV test and U.S. HIV acquisition with log binomial regression.

Results: Of 164 participants, 106 (65%) were women. Median age was 43 years (range: 18-72). Fifty-nine (59/159, 37%) reported HIV diagnosis prior to immigration, although this varied by year of arrival (25% before 2010 vs. 49% in 2010 or later, p=0.04). Among 98 persons diagnosed in the U.S., median time from arrival to diagnosis was 2.6 years (range 29 days-31 years). Among all APLWH, 43% (67/156) had >1 negative HIV test prior to diagnosis. Having a college degree compared to < a high school education was associated with a previous test (prevalence ratio [PR]:1.39, 95% CI:1.04-1.87), adjusting for sex, income, childhood family income, and year of diagnosis. Data were sufficient to estimate place of HIV acquisition for 132 (80%) participants (table); 23% definitely or probably acquired HIV in the U.S., while 72% probably or definitely acquired HIV in Africa. Among persons with definite or probable acquisition outside the U.S., median time from immigration to diagnosis was 274 days, and CD4 counts at diagnosis were lower than for others. APLWH who arrived before 2010 (PR: 5.26, CI:1.93, 14.4) and with high childhood family income (vs. low income, PR: 2.93, CI:1.06-8.07) were more likely to be categorized as probably or definitely acquiring HIV in the U.S., adjusted for sex and education.

Conclusion: Most cases of HIV among APLWH in the US are acquired in Africa and are diagnosed shortly after arrival in the U.S. However, almost a quarter acquire HIV in the US, highlighting the need for prevention efforts focused on APLWH in the U.S.

	Estimated Location of HIV acquisition				
	Definitely Africa	Probably Africa	Probably U.S.	Definitely U.S.	Inadequate information
N, (%) N=164	88 (54)	7 (4)	13 (8)	24 (15)	32 (20)
Percent of total excluding those with inadequate information	67	5	10	18	--
Diagnosed in the U.S. (%)	31	100	100	100	100
Median CD4 at diagnosis*	135	206	274	409	313
Median time in U.S. to diagnosis* (years)	0.54	1.41	1.51	5.00	3.29
Concurrent HIV and AIDS diagnosis*	55	100	45	26	48

* Among those diagnosed in the U.S.

933 NO CHANGE IN THE FREQUENCY OF AGE DISPARATE RELATIONSHIPS OR IMPACT ON HIV STATUS

George Mwinnyaa[1], Oliver Laeyendecker[2], Kate Grabowski[3], Joseph Ssekasanvu[3], Anthony Ndyanabo[4], Robert Ssekubugu[4], Joseph Kagaayi[4], Godfrey Kigozi[4], Gertrude Nakigozi[4], David Serwadda[4], Ronald H. Gray[3]
[1]The Johns Hopkins University, Baltimore, MD, USA, [2]NIAID, Baltimore, MD, USA, [3]Johns Hopkins University, Baltimore, MD, USA, [4]Rakai Health Sciences Program, Kalisizo, Uganda

Background: Age disparate relationships (≥5 years) are associated with increased HIV prevalence. We assessed age differences between never married women and their male sexual partners over time and the risk of HIV infection in Rakai, Uganda.

Methods: 10,061 never married women, aged 15-49 in the Rakai Community Cohort Study (RCCS) provided information on the age of their male sexual partners from 1997 to 2013. Logistic regression was used to assess trends in age difference and associations with HIV prevalence.

Results: 2 ,992 women (30%) had a male partner ≥ 5 years older with a median age difference 7 years (IQR 5, 12). Women in an age disparate relationship were older (median age 22 [IQR 15, 26]) compared to those not in such a relationship (median age 19 [IQR 15, 30]). There was no change in the frequency of age disparate relationships over time. In 1997, 29% (95% CI 25, 33) of women were in an age disparate relationship, compared to 33% (95% CI 30, 37) in 2013. The prevalence of HIV was higher among women in an age disparate relationship (14.0%) than those with partners 0-4 years older (9.8%), but this was not statistically significant after adjustment (adjOR= 1.03, 95%CI 0.89, 1.19; see table). In young women <25 HIV prevalence was higher among women in an age disparate relationship (8.3%) than those with partners 0-4 years older (5.6%), but this difference was not statistically significant after adjustment (adjOR=1.14, 95% CI 0.91, 1.41). Young women had increased odds of HIV infection if they had multiple partners and reported inconsistent condom use. Young women had lower odds of HIV infection if they were more educated (secondary education adjOR=0.32, 95%CI 0.16, 0.62 or tertiary (adjOR=0.27, (95% 0.09, 0.77 vs. no education).

Conclusion: The frequency of age disparate relationships among never married women has not changed over a 15-year period and was not associated with increased risk of HIV infection in Rakai, Uganda.

Table 1. The odds of being HIV positive among 10,061* never married women from Rakai, Uganda (1997-2013).

	Unadjusted OR	95% CI	Adjusted OR	95% CI
Age difference				
0-4 years	Ref	--	Ref.	--
5+ years	1.50	1.31, 1.71	1.03	0.89, 1.19
Number of sex partners				
1	Ref	--	Ref.	--
2	1.32	1.11, 1.57	1.81	1.50, 2.20
3+	2.05	1.53, 2.74	3.29	2.38, 4.53
Year of survey				
1997	reference	--	Ref.	--
1999	0.72	0.51, 1.00	0.89	0.62, 1.26
2000	0.77	0.56, 1.08	0.89	0.63, 1.27
2001	0.62	0.44, 0.85	0.69	0.49, 0.98
2003	0.61	0.43, 0.87	0.63	0.44, 0.92
2004	0.76	0.54, 1.06	0.76	0.53, 1.08
2005	0.72	0.53, 0.99	0.67	0.48, 0.94
2007	0.77	0.56, 1.05	0.74	0.53, 1.03
2008	0.59	0.42, 0.83	0.54	0.37, 0.78
2009	0.69	0.50, 0.96	0.65	0.46, 0.93
2013	0.72	0.51, 1.09	0.63	0.43, 0.92
Education				
No education	Ref	--	Ref.	--
Primary	0.63	0.41, 0.97	1.02	0.64, 1.62
Secondary	0.45	0.29, 0.69	0.68	0.43, 1.09
Tertiary	0.96	0.56, 1.65	0.78	0.44, 1.38
Location				
Urban	Ref	--	Ref.	--
Rural	0.78	0.68, 0.89	0.85	0.74, 0.97
Condom use				
Never	Ref	--	Ref.	--
Inconsistent	0.97	0.84, 1.13	1.61	1.12, 1.56
Always	0.66	0.56, 0.77	1.10	0.92, 1.32
Age groups				
15-19	Ref	--	Ref.	--
20-24	3.38	2.76, 4.15	3.61	2.93, 4.46
25-29	8.16	6.62, 10.1	9.46	7.58, 11.8
30+	10.25	8.31, 12.6	12.63	10.1, 15.9

CI=confidence intervals, OR=odds ratio, *out of 10,061 women, HIV data was available for 9,625 (96%)

934 HIGH INCIDENCE AND BURDEN OF HIV INFECTION IN EAST LONDON, SOUTH AFRICA

Bhakti Hansoti[1], Anna Eisenberg[2], David Stead[3], Nomzamo Mvandaba[4], Eshan U. Patel[1], Andy Parrish[3], Madeleine Whalen[5], Reinaldo Fernandez[1], George Mwinnyaa[1], Steven J. Reynolds[2], Andrew D. Redd[2], Stewart Dandorf[1], Richard Rothman[1], Oliver Laeyendecker[2], Thomas C. Quinn[2]
[1]The Johns Hopkins University, Baltimore, MD, USA, [2]NIAID, Baltimore, MD, USA, [3]Frere Hospital, East London, South Africa, [4]Walter Sisulu University, Mthatha, South Africa, [5]Johns Hopkins Hospital, Baltimore, MD, USA

Background: To define the scope of the current HIV epidemic in East London, South Africa, HIV incidence and burden of disease was evaluated in patients attending the Emergency Department (ED) at Frere Hospital.

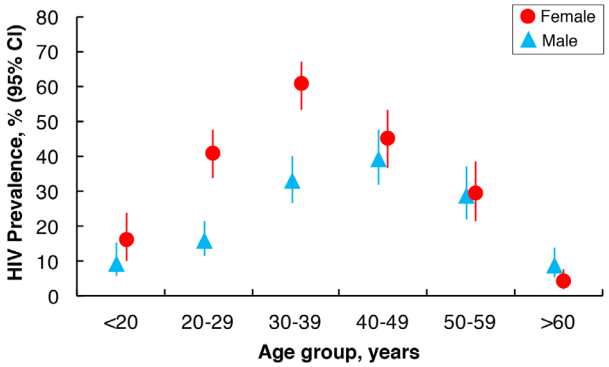
Methods: A cross-sectional, identity-unlinked serosurvey was conducted between September and November of 2016 to determine HIV seroprevalence and incidence at the Frere Hospital ED in East London, South Africa. HIV viral load (VL) testing was performed using the Abbott RealTime m2000sp-rt platform (limit of detection of 640 copies/mL). The CDC-validated multi-assay algorithm that is currently used by the Public Health Indicator Surveys was applied to estimate incidence. This algorithm includes a Limiting-Antigen avidity assay (<1.5 normalized optical density units) and a viral load <1000 copies/mL were applied to identify recently infected HIV positive individuals. Prevalence ratios (PR) and 95% confidence intervals (CI) of HIV prevalence and HIV viral suppression (VL<1000 copies/mL) were estimated by log-binomial regression.

Results: HIV prevalence was 26.9% (565/2100) overall, 21.9% (230/1049) among males and 32.2% (321/998) among females. HIV infection significantly

varied by age group among males and among females (Figure), with the highest prevalence observed among females in the 30-39 age group (60.3% [114/189]). HIV prevalence was significantly higher among females compared to males in the 20-29 year age group (PR=2.55 [95%CI: 1.78-3.63]) and 30-39 year age group (PR=1.84 [95%CI: 1.45-2.32]; though near identical at the older age groups. The frequency of viral suppression (<1000 copies/mL) was 48.8% and similar among males (45% [99/220]) and females (51.5% [160/311]; age-adjusted PR=1.14 [95%CI: 0.94-1.37]). The incidence testing algorithm identified 4 males (of 220 HIV+ tested) and 11 females (of 311 HIV+ tested) as recently infected, yielding an overall annual HIV incidence estimate of 2.9% (95%CI=1.4-4.3). HIV incidence was higher among females (4.7 [95%CI=1.9-7.6]) in comparison to males (1.4% [95%CI=0.0-2.9]).

Conclusion: These results demonstrate a high burden and incidence of HIV infection among males and females in East London. In addition, the prevalence of HIV viral suppression in this population is substantially lower than 90-90-90 goal of 73%. Together these data support an expanded outreach in East London to identify, test, and treat these untreated HIV infected individuals with the ED serving as a promising point-of-contact for this underserved population.

Figure. HIV Prevalence in the Frere Hospital Emergency Department.



935 ARE HIV PREVALENCE ESTIMATES FOR WESTERN KENYA TOO HIGH?

Peter W. Young[1], Emily C. Zielinski-Gutierrez[1], Daniel Kwaro[2], Martien W. Borgdorff[3], Joshua Gitonga[4], Joyce Wamicwe[5], Samuel M. Mwalili[1], Rachel Joseph[6], **Kevin M. De Cock**[1]

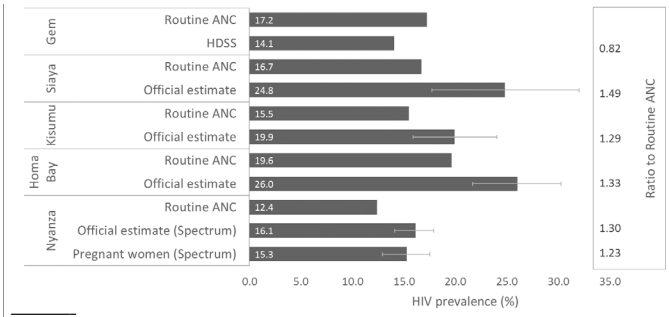
[1]US CDC Nairobi, Nairobi, Kenya, [2]Kenya Medical Research Institute, Kisumu, Kenya, [3]University of Amsterdam, Amsterdam, Netherlands, [4]National AIDS Control Council, Nairobi, Kenya, [5]National AIDS and STD Control Programme, Nairobi, Kenya, [6]US CDC Kisumu, Kisumu, Kenya

Background: The Nyanza region comprises six counties bordering Lake Victoria in Western Kenya including the three highest HIV prevalence counties in Kenya of Siaya, Homa Bay and Kisumu. Together, these three counties account for 27% of all patients on antiretroviral treatment (ART) and 31% of estimated unmet need for ART in Kenya. The UNAIDS-supported Spectrum model is used to generate HIV incidence and prevalence estimates for Kenya which are distributed from regions to counties using a workbook method, resulting official estimates are used to set county HIV testing and treatment targets. We triangulated these estimates with routine antenatal care (RANC) HIV testing results and population-based HIV prevalence estimates from a health and demographic surveillance system (HDSS).

Methods: We compiled annual official HIV prevalence estimates for 2014-2015 for Nyanza, and RANC prevalence from monthly facility reports from 2014-2016 submitted to the national health information system, and HIV prevalence from a community-based HIV sero-surveillance activity that screened 15,627 persons aged 15-49 years in the HDSS in Gem sub-County, Siaya County in 2016. We compared RANC to population-based HIV prevalence within the HDSS catchment area, and to official estimates.

Results: In 2015, official estimates were higher than pooled RANC HIV prevalence (14.8% vs. 12.4% for the six county Nyanza region, 24.8% vs. 16.7% for Siaya, 26.0% vs. 19.6% for Homa Bay, 19.9% vs. 15.5% for Kisumu); the ratio in adults ranged from 1.29 to 1.49 (Figure). The ratio between Spectrum estimates for pregnant women and RANC for Nyanza was 1.23 (15.3% vs. 12.4%). Gem RANC was slightly higher than Siaya RANC as a whole (17.2% vs. 16.7%). In Gem, HDSS-based prevalence estimates were lower than RANC (ratio 0.82) in 2016; both were notably lower than the official prevalence estimate of 24.8% for Siaya. Ratios between official and RANC HIV prevalence were similar in 2014 and 2015.

Conclusion: Results from Gem HDSS indicate RANC may over-estimate HIV prevalence in adults, and recent official estimates are consistently higher than RANC, suggesting Spectrum may over-estimate true adult HIV prevalence in Nyanza. Over-estimation would result in apparent under-achievement of the first and second 90% fast-track targets for knowing HIV status and overall ART coverage among persons living with HIV in Nyanza. This analysis illustrates the importance of triangulating all available data to monitor the HIV epidemic and guide the response.



Notes: HDSS = Health and Demographic Surveillance System. ANC = Antenatal care. Spectrum/official estimates and routine ANC HIV prevalence and ratios between them are for 2015 while Gem routine ANC and Health & Demographic Surveillance System HIV prevalence estimates and ratio are for 2016. The Nyanza region includes six counties: Siaya, Homa Bay and Kisumu (shown here) as well as Kisii, Nyamira and Migori (not shown). Error bars show spectrum-generated 95% plausibility bounds for Nyanza which are generated by Monte Carlo simulation and reflect uncertainty in Spectrum assumptions; bounds were calculated for official county estimates by computing a regional sample size and distributing to each county, which was then used to generate plausibility bounds for the counties.

936 ASSOCIATION OF MOBILITY WITH HIV RECENT INFECTIONS AND VIREMIA IN BOTSWANA

Mompati O. Mmalane[1], Sikhulile Moyo[1], Baraedi W. Sento[1], Jean Leidner[2], Kara Bennett[3], Thandie Phindela[4], Kutlo Manyake[1], Ernest Moseki[1], Tendani Gaolathe[1], Joseph Makhema[1], Molly Pretorius Holme[5], Janet Moore[6], Max Essex[5], Shahin Lockman[5], Kathleen Wirth[5]

[1]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [2]Goodtables Data Consulting, Norman, OK, USA, [3]Bennett Statistical Consulting, Inc, New York, NY, USA, [4]Botswana Ministry of Health, Gaborone, Botswana, [5]Harvard University, Cambridge, MA, USA, [6]CDC, Atlanta, GA, USA

Background: Mobility may create opportunities for risky behavior in the context of diminished societal controls, constrain health-seeking behavior, and has been associated with higher HIV prevalence. We examined associations between mobility, recent HIV infection, and detectable HIV-1 RNA in Botswana, a country with a highly mobile population.

Methods: As part of the Botswana Combination Prevention Project (BCPP), an ongoing cluster-randomized HIV prevention trial, consenting persons aged 16-64 years from a random 20% household sample in 30 peri-urban/rural communities were surveyed. All participants without documentation of positive HIV status underwent HIV testing, and HIV-1 RNA was measured in all HIV-infected participants, regardless of treatment status with >400 copies/mL considered viremic. Recent HIV infection was assessed cross-sectionally using HIV testing and treatment history and Limiting-Antigen Avidity Assay (LAg) data. Mobility was defined as self-reported absence from the community ≥1 night during the past year. Modified Poisson generalized estimating equations were used to obtain crude and age- and gender-adjusted prevalence ratios (PR) and 95% confidence intervals (CI) accounting for the clustered design.

Results: Among 12,583 participants with mobility data, 6,783 (54%) met the criteria for mobility; of these 26% were HIV-positive compared to 32% of non-mobile persons. One-third of sexually-active mobile persons reported concurrent partnerships during the past year compared to 25% of non-mobile persons (Table 1). Forty-two participants had recent HIV infection and 26% of all infected persons were viremic. Similar proportions of mobile (0.4%) and non-mobile (0.3%) participants were recently-infected (adjusted P=0.11). In contrast, HIV-positive persons who spent ≥1 night outside the community had a 20% higher probability of being viremic compared to those who reported no overnight travel (adjusted PR: 1.2; 95%CI: 1.1–1.4). A lower proportion of HIV-positive mobile participants knew their HIV status (P=0.001) or were on antiretroviral treatment (P=0.02) compared with non-mobile individuals.

Sensitivity analyses of varying mobility definitions (e.g. away >3 weeks/year) did not change findings qualitatively

Conclusion: Mobile individuals were significantly more likely to be viremic, a primary risk factor for HIV transmission. Health systems may need to better accommodate more mobile populations, to achieve high treatment and viral suppression targets.

Table 1. Summary of outcomes, demographics, and behavioral characteristics of participants in the Botswana Combination Prevention Project, 2013-2015, overall and by mobility status.

Characteristic (*n* with data)	Overall (N=12,583)	Mobility status, N (%): No nights spent away from community (N=5,800)	Mobility status, N (%): ≥1 night spent away from community (N=6,783)
Outcomes of interest			
Recently infected with HIV (*n*=12,546)[a]	42 (0.3%)	15 (0.3%)	27 (0.4%)
HIV RNA >400 copies/mL (*n*=3,584)[b]	930 (26%)	414 (23%)	516 (29%)
Other covariates			
Age, in years (*n*=12,583)[c]	33.0 (24.3, 45.4)	34.3 (24.6,47.3)	32.2 (24.1, 43.7)
Male gender (*n*=12,583)	4,549 (36%)	1,909 (33%)	2,640 (39%)
HIV-positive (*n*=12,548)	3,594 (29%)	1,838 (32%)	1,756 (26%)
Prior knowledge of HIV-positive status (*n*=3,594)	2,993 (83%)	1,568 (85%)	1,425 (81%)
Currently receiving ART (*n*=2,993)	2,615 (87%)	1,389 (89%)	1,226 (86%)
Number of partners, past 12 months (*n*=11,945)			
None	2,596 (22%)	1,385 (25%)	1,211 (19%)
1 partner	6,473 (54%)	3,015 (55%)	3,458 (53%)
2 or more partners	2,876 (24%)	1,070 (20%)	1,806 (28%)
Concurrent partners, past 12 months (*n*=9,348)[d]	2,768 (30%)	1,025 (25%)	1,743 (33%)

ART, antiretroviral therapy
[a] Recent infect has defined by either identified as recent by the Lag assay or provided documentation of a negative HIV test at the survey visit within 24 months prior
[b] Proportions calculated among HIV-infected participants with a non-missing viral load measurement.
[c] Median (25th, 75th percentile)
[d] Proportions calculated among sexually active participants.

937 NEW METHOD FOR RAPID DETECTION OF HIV TIME-SPACE CLUSTERS FOR PUBLIC HEALTH ACTION

Laurie Linley, Arthur Fitzmaurice, Meg Watson, Chenhua Zhang, Riuguang Song, **Anne Marie France**, Alexandra M. Oster
CDC, Atlanta, GA, USA

Background: CDC has not previously developed systematic methods to use HIV diagnosis data in real time to detect possible outbreaks of HIV. We sought to determine whether we could apply methods of time-space cluster detection to U.S. HIV surveillance data and identify possible clusters of increased diagnoses to focus high-impact prevention efforts.

Methods: We developed a systematic method for determining increased numbers of HIV diagnoses above expected baselines ("alerts") in a given geographic area, as these might represent possible transmission clusters or outbreaks. Using National HIV Surveillance System data reported through December 31, 2016 from 51 jurisdictions (50 U.S. states and the District of Columbia), we compared the number of cases reported in 2016 to the previous 3-year baseline period by jurisdiction and county, both 1) for all diagnoses and 2) for those with a transmission risk category of injection drug use (IDU). An alert for a given area was generated when two criteria were met: a statistically greater number of cases for the most recent year (by 2 standard deviations) than the 3-year mean of the baseline period, and an increase of more than 2 diagnoses over the baseline mean. To improve sensitivity given possible reporting delays, the analyses were performed with and without lags of up to 3 months.

Results: In analyses of all diagnoses by jurisdiction, alerts occurred for 12 (24%) of the 51 jurisdictions, of which 4 alerted without lags. At the county level, alerts occurred for 265/3,142 (8%) counties (143 without lags). The median and mean were 4 and 6 county alerts per jurisdiction, respectively. A higher percentage of counties with alerts than counties without alerts were located in the South (Table). For cases with IDU as a risk, alerts occurred for 7/51 (14%) jurisdictions, and 39/3,142 (1%) counties. Compared with counties without IDU alerts, a higher percentage of counties with IDU alerts were in the Northeast. Alerts were found in counties with low (<3), medium (3–9), and high (10+) baseline burden of HIV diagnoses (Table).

Conclusion: This method of time-space cluster detection identifies significant increases in annual HIV cases across all regions and for counties with varying levels of disease burden. Use of this tool in near real time to provide systematic automated detection of possible increases in diagnoses that merit further investigation can serve to prioritize and focus prevention efforts in local areas for maximal public health impact.

Table. Characteristics of counties with time-space clusters of diagnoses of HIV, 50 U.S. states and the District of Columbia, 2016

	Total	Region				Baseline Average Annual HIV Diagnoses, 2013 - 2015		
All diagnoses		Northeast	Midwest	South	West	<3	3 to 9	10+
Counties with alerts	265	30 (11%)	44 (17%)	158 (60%)	33 (12%)	91 (34%)	83 (31%)	91 (34%)
Counties with no alerts	2,877	187 (6%)	1,011 (35%)	1,264 (44%)	415 (14%)	2,089 (73%)	453 (16%)	335 (12%)
Diagnoses with IDU transmission category								
Counties with alerts	39	7 (18%)	9 (23%)	17 (44%)	6 (15%)	23 (59%)	14 (36%)	2 (5%)
Counties with no alerts	3,103	210 (7%)	1,046 (34%)	1,408 (45%)	443 (14%)	2,157 (70%)	522 (17%)	424 (14%)

938 EPIDEMIOLOGICAL STUDY OF TRANSMISSION CLUSTERS IN A LOCAL HIV-1 COHORT

Carmen M. González Domenech[1], Isabel Viciana-Ramos[1], Gabriel Sena-Corrales[2], Laura Mora Navas[1], Guillermo Ojeda[1], Enrique Nuño[1], Encarnación Clavijo[1], Rosario Palacios[1], Jesus Santos[1]
[1]Hospital Virgen de la Victoria, Málaga, Spain, [2]Hospital Regional Carlos Haya, Malaga, Spain

Background: Integration of molecular, clinical and demographic data represents a powerful tool to understand the dynamics of local transmission HIV-1 chains (TCs). The aim of our study was the phylogenetic analysis of the TCs within a HIV-1 cohort and the description of the relevant patients´ data within a TC.

Methods: We performed a phylogenetic analysis of 757 sequences from newly HIV-1 diagnosed patients in Málaga (Southern Spain) during the period 2004-2015. We used the partial pol gene sequence in a preliminary phylogeny by Neighbour Joining method (MEGA v6.06 program) and after eliminating all those branches with bootstrap values<80%, we constructed a new phylogeny by Maximum likelihood method (FastTree program). We consider a TC any cluster with bootstrap values≥90%. Patients within and out TCs were compared. Resistance mutations in PR and RT sequences were analyzed by Stanford algorithm.

Results: 451 out of 757 patients (59.6%) were grouped into 53 TCs, 17 of them with five or more subjects. The largest number of patients associated within a TC was 90. Patients younger than 40 years (OR 1.75, 95%CI 1.2-2.4, p=0.002), MSM (OR 2.14, 95%CI 1.3-3.2, p<0.0001), non-Spanish (OR 1.48, 95%CI 1.0-2.1, p=0.038), with a non-B subtype HIV-1 (OR 3.12, 95%CI 2.0-4.8, p<0.0001), and presenting primary resistance mutations (OR 14.1, 95%CI 3.1-62.6, p=0.001), were more likely to be associated within a cluster. 94 out 118 patients (79.6%) with transmission resistance mutations were included in some TC. The most frequent mutations associated with clusters were T69D/N, L210W and K219E/Q, for NRTIs, K103N and G190A/S for NNRTIs, and the I54L/M and L90M mutations for PIs. The prevalence for resistance to NNRTIs in TCs was 13.7%. There were two TCs of peculiar non-B subtypes: CRF19_cpx, with 21 individuals, 16 of them (76.2%) with mutation G190A; and CRF51_01B with 39 patients, 20 of them with the K103N mutation.

Conclusion: About 60% of newly HIV-1 diagnosed patients were included in a TC. Younger patients, MSM, non-Spanish, with non-B subtype HIV-1 and primary resistance mutations possessed more probability of belonging to a cluster. NNRTIs mutations were the most frequent ones among patients in TCs. We observed two TCs represented by infrequent non-B subtypes in our area, like CRF19_cpx and CRF51_01B, both of them associated to the transmission of primary resistances.

939 AGE-DEPENDENT RACIAL/ETHNIC DISPARITIES IN LONGITUDINAL HIV CARE INDICATORS

Fidel A. Desir[1], Catherine R. Lesko[1], Richard D. Moore[1], Michael J. Silverberg[2], Peter F. Rebeiro[3], Michael A. Horberg[4], Mari Kitahata[5], Stephen Crystal[6], Angel Mayor[7], Marina Klein[8], Amy C. Justice[9], Michael John Gill[10], Keri N. Althoff[1]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]Kaiser Permanente Northern California, Oakland, CA, USA, [3]Vanderbilt University, Nashville, TN, USA, [4]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [5]University of Washington, Seattle, WA, USA, [6]Rutgers University, Newark, NJ, USA, [7]Universidad Central del Caribe, Bayamon, Puerto Rico, [8]McGill University Health Centre Research Institute, Montreal, QC, Canada, [9]VA Connecticut Healthcare System, West Haven, CT, USA, [10]University of Calgary, Calgary, AB, Canada

Background: Maximizing the amount of time spent in care, on antiretroviral therapy (ART), and with viral suppression (VS) after linkage to HIV care is critical to improving the health of persons with HIV. Although racial/ethnic disparities in these HIV care indicators have been described, the effect of age

is less understood, particularly among men who have sex with men (MSM). We examined the impact of age on the magnitude of racial/ethnic disparities in longitudinal HIV care indicators among MSM newly linked to HIV care.

Methods: Adult MSM who successfully linked to care (i.e., ≥2 HIV care visits in ≤12 months) for the first time between 2004-14 in 11 US clinical cohorts in the NA-ACCORD were followed from HIV care linkage until 5 years after linkage, 31 December 2014, or death, whichever occurred first. We added and subtracted cumulative incidence curves for ART initiation, disengagement from care (i.e., not having ≥1 HIV care visit, CD4 count, or HIV RNA measure in ≤12 months), re-engagement in HIV care, VS (HIV RNA ≤200 c/mL), and loss of VS. We then integrated the area between the curves to estimate the mean percentage of person-time spent 1) in care, 2) on ART, and 3) with VS in the first 5 years after linkage, by race/ethnicity and age group. Analyses were adjusted for age (to reduce confounding within age groups), history of injection drug use, site, CD4 count, and HIV RNA at linkage.

Results: A total of 11,003 MSM were included. MSM of most racial/ethnic and age groups spent on average >70% of person-time engaged in care and >50% of person-time on ART during the first 5 years after linkage to care (Table). Black MSM ≥40 years of age and Hispanic MSM ≥50 years of age spent less time in care, on ART, and with VS than white MSM in the same age range. Hispanic MSM <50 years of age spent more time in these stages than white MSM in the same age range, although most differences were not statistically significant. The magnitude of the black-white and Hispanic-white disparity generally increased with increasing age for these outcomes.

Conclusion: The magnitude of racial/ethnic disparities in the HIV care continuum after inital HIV care linkage increases with increasing age. Clinical initiatives designed to reduce racial/ethnic disparities in engagement in care, early ART initiation, and VS among MSM with HIV should especially focus on minority MSM from older age groups.

Table. Racial differences among MSM in the average percentage (%, [95% CI]) of person-time spent in HIV care, on ART, and VS in the first 5 years after HIV care linkage, by age, NA-ACCORD, 2004-2014.

	Age, y	Black %	Hispanic %	White %	% Difference: Black vs. White	% Difference: Hispanic vs. White
In care	18 - 29	74.2 (72.6, 75.7)	73.5 (70.1, 77.3)	71.8 (69.8, 73.8)	2.3 (-0.3, 4.8)	1.7 (-2.3, 6.1)
	30 - 39	74.4 (71.9, 77)	77.6 (74.3, 80.7)	72.8 (71.1, 74.6)	1.6 (-1.5, 4.8)	**4.8 (1.2, 8.5)**
	40 - 49	75.6 (72.7, 78.7)	77.2 (71.1, 83.6)	76.4 (74.4, 78.2)	-0.8 (-4.5, 2.7)	0.8 (-5.7, 7.8)
	≥50	75 (70.5, 79.7)	76.9 (69.9, 83.8)	80 (77.1, 82.9)	-4.9 (-10.3, 0.7)	-3.1 (-11.2, 4.3)
On ART	18 - 29	54.4 (52.4, 56.4)	52.6 (47.7, 57.3)	48.7 (46.1, 51.3)	**5.7 (2.6, 9)**	3.9 (-1.5, 9.2)
	30 - 39	54.1 (51, 57.2)	58.6 (53.9, 62.8)	52 (49.8, 54.1)	2.1 (-1.8, 5.9)	**6.6 (1.5, 11.3)**
	40 - 49	52.8 (49, 56.5)	61.1 (54.9, 67.1)	58.6 (56.3, 60.7)	**-5.8 (-10.1, -1.4)**	2.5 (-4.3, 8.9)
	≥50	54 (47.7, 59.8)	52.9 (40.9, 63.9)	66.3 (62.8, 69.6)	**-12.3 (-19.6, -5)**	**-13.4 (-26.1, -2)**
VS	18 - 29	40.8 (38.9, 42.7)	42.8 (38.4, 47.3)	38.7 (36.4, 41.2)	2.1 (-0.9, 5.2)	4.1 (-1.1, 9.4)
	30 - 39	38.7 (35.5, 41.7)	48.4 (43.8, 52.4)	41.6 (39.5, 43.7)	-2.9 (-6.7, 1)	**6.7 (1.8, 11.4)**
	40 - 49	38 (34.7, 41.5)	50.5 (43.4, 57.2)	46.8 (44.5, 49)	**-8.7 (-13, -4.7)**	3.7 (-3.4, 10.8)
	≥50	44.9 (38.7, 50.8)	44.8 (33.1, 55.4)	55.3 (52.1, 58.7)	**-10.4 (-17.6, -3.5)**	-10.6 (-22.6, 0.2)

Abbreviations: MSM, male-to-male sexual contact; CI, confidence interval; ART, antiretroviral therapy; VS, virally suppressed

Bold denotes statistical significance.

Legend: ≤-12% | -12% to -9% | -9% to -6% | -6% to -3% | -3% to 0% | 0% to 3% | 3% to 6% | 6% to 9% | 9% to 12% | ≥12%

940 HIV VIRAL SUPPRESSION ASSESSED BY TWO METRICS IN NORTH CAROLINA DURING 2016

Manuela Bullo[1], Erika Samoff[2], Nicole Dzialowy Adams[2], Brad Wheeler[2], Kimberly A. Powers[1], Anna Cope[3]

[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]North Carolina Division of Public Health, Raleigh, NC, USA, [3]CDC, Atlanta, GA, USA

Background: To maximize HIV clinical outcomes and reduce onward transmission, durable viral suppression (DVS) is needed among people living with HIV/AIDS (PLWHA). However, most viral suppression analyses are based on measures that consider only a single viral load (VL) and thus cannot indicate durability. We sought to compare viral suppression prevalence using a single viral suppression (SVS) and DVS measure, and to assess disparities in both measures by age and race, among PLWHA in North Carolina (NC) during 2016.

Methods: The NC Division of Public Health (DPH) maintains a registry of all PLWHA in an electronic surveillance system. Since 2013, all HIV care labs (VL and CD4 counts) are reportable to the NC DPH by law. We considered all PLWHA who were diagnosed between 2006 and 2015, were alive and resided in NC in 2016, and were ≥18 years old at diagnosis. We measured: a) prevalence of SVS, defined as VL ≤200 copies/ml at most recent measure in 2016; and b) DVS, defined as at least two separate VLs ≤200 copies/ml and with no VL >200 copies/ml during 2016. Eligible PLWHA with no VL recorded in 2016 were included and assigned to not having either outcome. We used univariable log-binomial models with each outcome to estimate prevalence ratios (PRs) and 95% confidence intervals (CIs) according to key demographic variables.

Results: Overall, 13,628 persons were eligible for analysis. Most were male (75.6%), men who report sex with men (MSM) (62.6% among males), African American (61.8%), and had ≥1 VL reported during 2016 (76.6%). The median age at diagnosis was 35.4 years (IQR 26.0-45.8). A total of 8859 (65.1%) PLWHA exhibited SVS and 6,004 (44.1%) exhibited DVS during 2016. Differences in both SVS and DVS were observed by age (>35 vs ≤35 years: SVS PR 1.23, 95% CI 1.20-1.26 and DVS PR 1.41, 95% CI 1.35-1.46) and race/ethnicity (African American vs White: SVS PR 0.88, 95% CI 0.85-0.90 and DVS PR 0.83, 95% CI 0.79-0.86; Hispanic vs White: SVS PR 0.83, 95% CI 0.79-0.88 and DVS PR 0.89, 95% CI 0.83-0.96).

Conclusion: Nearly two-thirds of all PLWHA in NC achieved SVS in 2016, but fewer than half achieved DVS. Differences by age and race were apparent with both measures, suggesting that either approach may be useful in identifying disparities to be addressed; however, the SVS measure, which does not reflect the durable suppression needed for optimal clinical and prevention benefits, may provide an overly optimistic view of viral suppression in the population.

Table 1: Prevalence of single viral suppression (SVS) and durable viral suppression (DVS) by demographic characteristics, NC in 2016

			SVS			DVS		
		Total	Prevalence (per 100)	Prevalence Ratio	95% CI	Prevalence (per 100)	Prevalence Ratio	95% CI
Total		**13,628**	**65.1**			**44.1**		
Sex	**Female**	3321	**65.8**	1.02	0.99-1.05	**44.8**	1.02	0.98-1.07
	Male	10297	**64.8**	REF	-	**43.8**	REF	-
Age at diagnosis	**>35 years**	6919	71.5	1.23	1.20-1.26	**51.4**	1.40	1.35-1.46
	≤35 years	6699	58.3	REF	-	**36.6**	REF	-
Race/ Ethnicity	**African American**	8414	**62.8**	0.88	0.85-0.90	**41.4**	0.83	0.79-0.86
	White	3403	**71.6**	REF	-	**50.0**	REF	-
	Hispanic	1181	**59.6**	0.83	0.79-0.88	**44.7**	0.89	0.83-0.96
	Other	620	**69.4**	0.97	0.92-1.02	**46.9**	0.94	0.86-1.03
MSM (among Males only)	**MSM**	6692	**67.2**	1.11	1.08-1.15	**44.9**	1.08	1.03-1.13
	non-MSM	3,605	**60.4**	REF	-	**41.8**	REF	-

941 UNDISCLOSED ANTIRETROVIRAL DRUG USE IN BOTSWANA – IMPLICATIONS FOR NATIONAL ESTIMATES

Sikhulile Moyo[1], Simani Gaseitsiwe[1], Kathleen M. Powis[2], Terence Mohammed[1], Comfort Maphorisa[1], William Abrams[3], Liziwe Chebani[4], Kutlo Manyake[1], Molly Pretorius Holme[5], Tendani Gaolathe[1], Joseph Makhema[1], Shahin Lockman[5], William Clarke[6], Max Essex[5], Vlad Novitsky[5]

[1]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana, [2]Brigham and Women's Hospital, Boston, MA, USA, [3]CDC Botswana, Gaborone, Botswana, [4]Ministry of Health, Gaborone, Botswana, [5]Harvard University, Cambridge, MA, USA, [6]Johns Hopkins Hospital, Baltimore, MD, USA

Background: Undisclosed ART use may affect national estimates and confound results of clinical trials. We assessed ARV traces among virologically suppressed individuals participating in the Botswana Combination Prevention Project (BCPP) who self-reported no prior ARV use.

Methods: Plasma from 134 BCPP participants who reported no ART use and had undetectable HIV-1 RNA (£400 copies/mL) was screened for ARVs by high-throughput liquid chromatography coupled with Q-Exactive high-resolution mass spectrometry using data-dependent fragmentation and selected reaction monitoring at resolution of 17,500 (Marzinke et al. 2014 *Clinica Chimica Acta* 433:157-68). To obtain qualitative results, each specimen was compared to positive and negative controls for each drug (Abacavir, Amprenavir, Atazanavir, Darunavir, Efavirenz, Emtricitabine, Indinavir, Lamuvidine, Lopinavir, Maraviroc, Nelfinavir, Nevirapine, Raltegravir, Rilpivirine, Ritonavir, Saquinavir, Stavudine, Tenofovir, Tipranavir, and Zidovudine).

Results: Among 3,596 HIV-positive participants enrolled in a household survey in BCPP, 953 (27%; 95% CI 25-28%) self-reported no prior use of ART, 135 (14%, 95% CI 12-17%) of whom had HIV-1 RNA£400 copies/mL. Plasma ARV traces were tested in 134 of these 135 individuals, 52 (39%, 95% CI 31-48%) of whom had detectable ARVs. Traces of 3 ARV drugs were found in 42 participants, 2 drugs in 9 participants, and one participant had traces to a single drug (EFV). The most commonly identified ARVs (EFV/NVP, FTC, TDF) represented regimens in Botswana's national ART program. The overall proportion of HIV-infected

people who have undetectable HIV-1 RNA increased from 70.2% (Gaolathe et al. 2016 *Lancet HIV* 3:e221-30) to 71.7%, after taking into account undisclosed ARV use.

Conclusion: Among household survey participants in Botswana who had HIV-1 RNA<400 copies/mL but who reported not being on ART, undisclosed ART use was found in 39%. The overall proportion of virologically-suppressed HIV-infected adults increased by 1.5% after accounting for undisclosed ART. National estimates of treatment coverage should include methods that account for undisclosed ART use, to more accurately reflect achievement against 90-90-90 targets. Testing for ARV traces in those without detectible virus should supplement self-report of ART use in population surveys.

Table 1: Prevalence of NRTI, NNRTI and PI Drug Resistance Mutations Across Botswana

NRTI mutations		NNRTI mutations		PI mutations	
M41L	0.48%	K101E/P	0.53%	D30N	0.17%
K65R	0.31%	K103N/S	1.68%	M46I/L	0.56%
D67N	0.31%	V106M	0.31%	F53Y	0.04%
K70R/E	0.26%	Y181C/I/V	0.66%	G73S	0.35%
L74I	0.04%	Y188L/C	0.18%	V82A/S	0.30%
V75M/S	0.13%	G190A	0.79%	I85V	0.04%
Y115F	0.04%			N88S	0.04%
M184V/I	2.12%				
T215Y/F/S/D	0.35%				
K219E/R	0.22%				
Any NRTI	**2.90%**	**Any NNRTI**	**3.20%**	**Any PI**	**1.20%**

942 CONCOMITANTLY SUPPRESSED SYSTEMIC AND IMBALANCED MUCOSAL IMMUNITY INCREASE HIV RISK

Charles S. Morrison[1], **Raina Fichorova**[2], Pai-Lien Chen[1], Sophie Gao[1], Cynthia Kwok[1], Hidemi Yamamoto[2], Sharon Anderson[3], Christopher Bukowsky[2], Robert Barbieri[2], Anna Wald[4], Tsungai Chipato[5], Robert Salata[6], Gustavo Doncel[7]
[1]FHI 360, Durham, NC, USA, [2]Brigham and Women's Hospital, Boston, MA, USA, [3]Eastern Virginia Medical School, Norfolk, VA, USA, [4]University of Washington, Seattle, WA, USA, [5]University of Zimbabwe, Harare, Zimbabwe, [6]Case Western Reserve University, Cleveland, OH, USA, [7]CONRAD, Arlington, VA, USA

Background: We found previously that women in Uganda and Zimbabwe had different individual biomarkers of altered cervical immunity associated with progestin-only (DMPA) versus combined oral contraceptive use; however, only one cervical marker – higher RANTES - altered in DMPA use was associated with subsequent HIV seroconversion. Here we expand the analysis to examine concomitantly altered systemic and cervical immunity as a risk factor for HIV.

Methods: Ten cervical and four systemic immune biomarkers were measured in 2347 cervical and serum specimen pairs at quarterly visits from 218 HIV seroconverters (median 4.4 months prior to seroconversion) and 784 matched controls. Biomarker activation/suppression was defined as Box-Cox transformed levels above/below the median of all HIV-negative visits. Odds ratios (OR) and 95% confidence intervals were calculated for likelihood of HIV seroconversion with biomarker activation.

Results: In multivariable modeling subsequent HIV seroconversion was associated with 5 of the 14 individual biomarkers: suppressed systemic CRP (OR=0.63, 0.51-0.79, p<0.001), cervical SLPI (OR=0.63, 0.49-0.80, p<0.001) or cervical VEGF (0.71, 0.54-0.94, p=0.016), or activated cervical IL-1β (OR=1.38, 1.07-1.78, p=0.012) or IL-6 (OR=1.35, 1.02-1.79, p=0.036). Additional significant patterns emerged when concomitantly suppressed systemic immunity biomarkers (CRP, IL-6 and IL-7) were combined with activated RANTES (OR=1.47, 1.09-1.98, p=0.013), activated cervical IL-1β and IL-6 (OR=1.92, 1.29-2.83, P=0.001), or with suppressed cervical immunity, measured by suppressed SLPI (OR=1.56, 1.13-2.15, =0.007), IL-1RA (OR=1.66, 1.20-2.29, p=0.002) or VEGF and ICAM-1 (OR=1.99, 1.29-3.06, p=0.002). Systemic sCD14 activation, a possible sign of subclinical endotoxin exposure, combined with the same patterns of activated/suppressed cervical biomarkers resulted in similarly increased risk of HIV.

Conclusion: Suppressed systemic immunity (low CRP, IL-6 and IL-7) concomitant with cervical inflammation (high primary proinflammatory cytokines IL-1β and IL-6, or low anti-inflammatory mediators IL-1RA) or low cervical innate immunity (e.g., SLPI, VEGF, ICAM-1) indicated vulnerability to HIV infection. Understanding the combined effects of systemic and mucosal innate immunity on susceptibility to acquire HIV is an essential step in preventing new infections.

943 RELATIONSHIP BETWEEN DEPRESSION AND RISK BEHAVIORS IN A US MILITARY HIV COHORT

Brandon W. Carney[1], James White[2], Xiaohe Xu[2], Thankam Sunil[2], Colton Daniels[2], Morgan Byrne[3], Anuradha Ganesan[3], Robert Deiss[3], Grace E. Macalino[3], Brian K. Agan[3], Jason Okulicz[1]
[1]San Antonio Military Medical Center, San Antonio, TX, USA, [2]University of Texas at San Antonio, San Antonio, TX, USA, [3]Infectious Disease Service, San Antonio, TX, USA

Background: Previous studies have suggested links between psychological symptoms, such as depression and anxiety, and sexual risk behaviors. We evaluated the multifaceted relations between depression trajectories, depression diagnosis, and risk-taking behaviors among participants in the US Military HIV Natural History Study.

Methods: Participants with risk behavior survey data and either a coded diagnosis of depression (including anxiety, dissociative, and somatoform disorders) or available self-reported Center for Epidemiological Studies Depression (CES-D) measure were included (n=646) to explore ties between depression trajectories, depression diagnoses, and sexual risk behaviors. Latent class analysis was employed to create 3 classes of depression trajectories from 1988-2016, namely low depression (LD, n=369), recent-onset depression (ROD, n=166), and high depression (HD, n=111) trajectories. The latent class was further dummy-coded with the LD trajectory class serving as the reference.

Results: Overall, participants with clinically diagnosed depression were less likely to report often/always using condoms with new sexual partners in the past 3 months than those who have never been clinically diagnosed with depression (OR 0.15, 95% CI 0.49-2.53; p<.001). Participants with both ROD (OR 0.52, 95% CI 0.28-0.97; p<.05) and HD (OR 0.48, 95% CI 0.24-0.96; p<.05) trajectories were less likely to report often/always using condoms with new sexual partners in the past 3 months than those with LD trajectories. Moreover, those with either ROD (OR 2.13, 95% CI 1.19-3.80; p<.01) or HD (OR 2.74, 95% CI 1.43-5.24; p<.001) trajectories were more likely to have had sex with ≥2 new sexual partners in the last 3 months than those with LD trajectories. Furthermore, participants with HD trajectories (OR 4.07, 95% CI 2.09-7.96; p<.001) were more likely to have one or more anonymous male sexual partners in the last 3 months than those with LD trajectories. Regression models also indicated that the cumulative odds of using alcohol was higher for those with ROD (OR 1.61, 95% CI 1.15-2.25; p<.01) than for whose with LD trajectories.

Conclusion: Persons with HIV infection and ROD or HD trajectories were more likely to engage in greater sexual risk behaviors than those with LD trajectories. Educational efforts targeting those with known mental health disorders are warranted to reduce sexual risk behavior in this high-risk population of HIV-infected persons.

944 ARE REAL-TIME PHYLOGENY GUIDED INTERVENTIONS FEASIBLE? A LONGITUDINAL ANALYSIS

Larissa V. Mulka[1], Manon Ragonnet-Cronin[2], Jaime Vera-Rojas[1], Jackie Cassell[1], Anna Tostevin[3], David Dunn[3], Andrew Leigh Brown[2]
[1]Brighton and Sussex Medical School, Brighton, UK, [2]University of Edinburgh, Edinburgh, UK, [3]University College London, London, UK

Background: The use of real-time HIV phylogenetics to guide public health interventions is an area of growing interest, but questions remain over how this technology may be applied in a way that is both of public health benefit and acceptable to patients. A previous phylogenetic analysis found no likely transmitter for 74% of recent HIV infections (RHI) within the studied population in Brighton, UK. Brighton has the highest prevalence of HIV outside London and the cohort is predominantly composed of men who have sex with men (MSM). We aimed to identify sources of RHI more accurately within this cohort, to determine whether real-time phylogenetic reconstruction is a feasible component of intervention within this population.

Methods: Subtype B sequences were retrieved from the Brighton population, diagnosed 1981-2015 (n=1,840) alongside the most similar UK and global sequences from the UK HIV Drug Resistance and Los Alamos databases. Maximum likelihood trees were built in RAxML (GTR + Γ), and dated phylogenies reconstructed in BEAST. Demographic and clinical data available for Brighton patients included CD4 counts, viral loads, sexually transmitted infections, AIDS diagnoses and antiretroviral history. RHI were identified by testing history and

serological markers. Likely transmitters to RHI were identified according to an algorithm considering phylogenetic and clinical data at transmission. Chronic infections linked to, but diagnosed after a RHI were considered potential transmitters.

Results: 389 RHI were identified, for which a likely transmitter was identified for 186 (48%). 176 (95%) transmitters were male, 168 (90%) were white. 173 (93%) transmissions were between MSM. 110 (59%) infections were acquired from the local population, 75 (40%) from elsewhere in the UK; 30 from the nearest major city (London), and one from the USA. 22 (20%) transmitters were diagnosed shortly after the estimated transmission date. A further 142 RHI (37%) were linked to a potential transmitter, 108 being undiagnosed at the time of transmission. 61 RHI (16%) had no potential source.

Conclusion: We identified a transmission source for 48% of RHIs, suggesting phylogenetically guided interventions may be feasible within this population. We are exploring the application of a structured coalescent model to explore the potential of transmission sources as a target for intervention. In parallel we are developing an ethical framework to ensure patient acceptability of phylogeny-based interventions.

945 DYNAMICS OF THE CRF01AE EPIDEMICS IN THE CITIES OF SHANGHAI, SHENZHEN AND SHENYANG

Xiaoxu Han[1], Antoine Chaillon[2], Ping Zhong[3], Jin Zhao[4], Bin Zhao[1], Haibo Ding[1], Junjie Xu[1], Yi Lin[3], Yile Xue[3], Xuqin Wang[3], Min Zhang[1], Lin Wang[1], Davey M. Smith[2], Hong Shang[1]

[1]China Medical University, Shenyang, China, [2]University of California San Diego, La Jolla, CA, USA, [3]Shanghai Municipal Center for Disease Control and Prevention, Shenzhen, China, [4]Shenzhen Center for Disease Control and Prevention, Shenzhen, China

Background: China is experiencing a large increase of HIV infections among men who have sex with men (MSM) and migrants who flow between cities to seek better living conditions. This increase may fuel and reshape local epidemics in large industrialized cities. Here, we evaluated the dynamics and geospatial mixing of rapidly evolving HIV CRF01AE epidemics in three of the largest cities in China.

Methods: HIV-1 CRF01AE pol sequences generated from 3,071 individuals diagnosed in Shanghai (n=884), Shenyang (n=1,719) and Shenzhen (n=568) between 2002-2016 were analyzed for clustering. Optimal genetic distance threshold (GDT) were determined by sensitivity analyses designed to provide the highest resolution. Bayesian analyses were performed to assess the dynamics and transmission rates (TR) among clusters. Viral gene flow between the 3 cities was estimated using a Bayesian phylogeographic diffusion model and a Slatkin-Maddison (SM) approach after adjusting for sampling heterogeneity between sites.

Results: A total of 3,071 individuals predominantly MSM (85.2%) with a median age of 31 years (IQR:26-40) were included. Individuals from Shanghai were exclusively MSM and significantly younger (median age=28, p<0.001). A similar optimal GDT of 0.5% was determined for all cohorts and revealed a higher clustering rate in Shanghai (42.2%) compared to Shenyang (37.3%) and Shenzhen (36.1%). Overall, 38.4% of the sequences were linked (1,178/3,071) into 276 distinct clusters (range: 2-123 seqs/cluster, 149 non-dyad clusters). Clustering individuals were more likely to be younger MSM and diagnosed in Shanghai. Bayesian methods revealed high TR among the 12 largest clusters (range 11-123 seqs/cluster) with a median TR of 20.6/100 person-years (IQR 17-24). Overall, 87.7% (1,895/2,160) linkages were between individuals diagnosed in the same city and 35/276 (12.7%) clusters were spatially heterogeneous clusters (i.e. individuals from 2 cities) (Fig. 1A). Phylogeographic and SM analyses confirmed high gene flow between the three large cities with predominant migration from the central and most populated city of Shanghai toward Shenyang and Shenzhen (Fig 1B).

Conclusion: This study revealed similar dynamics of the CR01AE HIV local epidemics in the 3 cities of China and high clustering rate among young MSM. Network inferences across these cities and spatial dispersal suggest that Shanghai likely serves as hub for HIV dispersal among young MSM. Such results could inform public health efforts among young MSM in large cities.

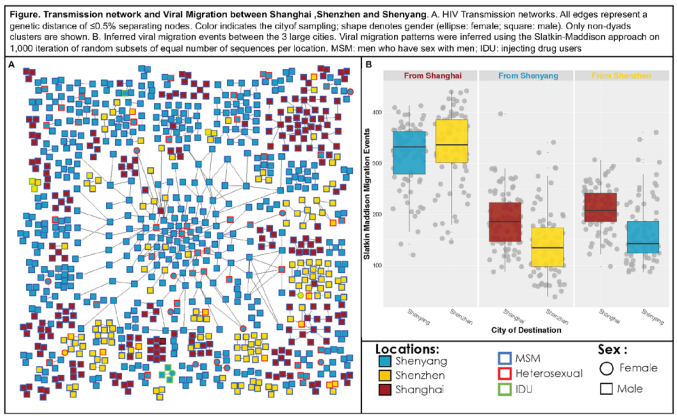


Figure. Transmission network and Viral Migration between Shanghai ,Shenzhen and Shenyang. A. HIV Transmission networks. All edges represent a genetic distance of ≤0.5% separating nodes. Color indicates the city of sampling; shape denotes gender (ellipse: female; square: male). Only non-dyads clusters are shown. B. Inferred viral migration events between the 3 large cities. Viral migration patterns were inferred using the Slatkin-Maddison approach on 1,000 iteration of random subsets of equal number of sequences per location. MSM: men who have sex with men; IDU: injecting drug users

946 PHYLODYNAMIC FEATURES OF ACTIVE LARGE CLUSTERS FUELING THE HIV EPIDEMIC IN QUEBEC MSM

Bluma G. Brenner[1], Ruxandra-Ilinca Ibanescu[1], Irene Vrbik[1], Michel Roger[2], Isabelle Hardy[2], David Stephens[1]

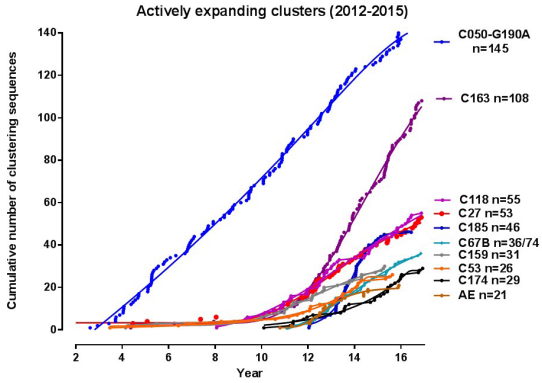
[1]McGill University, Montreal, QC, Canada, [2]Centre de Research du Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada

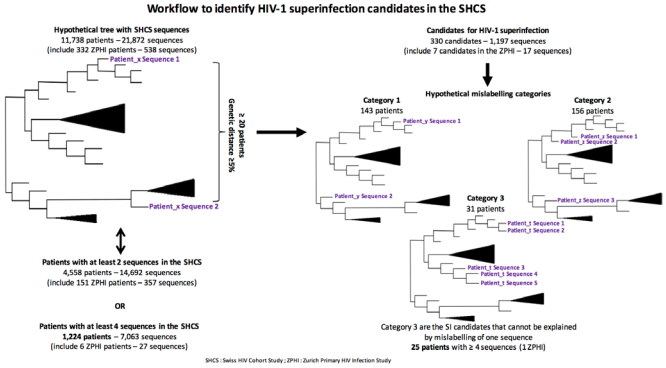
Background: An understanding of the dynamics of onward spread of HIV is essential to the design and optimization of long-term prevention strategies to control epidemics among Men having Sex with Men (MSM). Our studies used Pol sequence datasets from the Quebec genotyping program and phylogenetic modelling strategies to map transmission networks and deduce factors implicated in the expansion of HIV among MSM in Quebec.

Methods: Our data comprise 4051 time-stamped HIV Pol sequences taken from the male subtype B infections excluding mixed gender and IDU/HET clusters. Expanding on previous work, 34 large clusters having 20+ distinct members were identified, having high bootstrap support (>90) and sufficient genetic similarity (<0.05 maximum pairwise patristic distance). We applied a birth-death SIR (BDSIR) model available in the phylodynamic add-on for BEAST2 version 2.4.3 and Richard's five parameter asymmetric dose response curves to model growth trajectories. Genotyping across the viral integrase and V3 loop was performed on representative infections within clusters. Epidemiological and demographic data from the genotyping and Montreal primary HIV cohort deduced risk correlates implicated in clustering.

Results: Phylogenetics revealed two patterns of HIV-1 spread among MSM. While half of the HIV epidemic was ascribed to small self-limiting clusters (size 1-4), thirty-two viral strains contributed to micro-epidemics (cluster size 20-145) disproportionately rising from 13%, 25%, and 42% of new diagnoses in 2004-2007, 2008-2011, and 2012-2015, respectively. BDSIR plots deduced early, active and dying phases of expansion for individual clusters. Ten to twelve 20+ clusters fueled spread of HIV in each quadrennial period. Epidemiological and virological data deduced factors contributing to the expansion of the ten active strains from 2012-2016. Clusters were concentrated in the Montreal area with cluster 67B reflecting a second-wave epidemic in Quebec City. Belonging to 20+ clusters was associated with primary/recent infection and being under 30 years of age (odds ratio 3.7 and 3.3, respectively). Clusters over the 2012-2015 quadrennial period arose in significantly younger populations. The heightened transmissibility of strains belonging to distinct 20+ clusters were related to increased viral replicative fitness and/or dual tropism.

Conclusion: HIV-1 continues to spread among MSM with an alarming shift towards large cluster outbreaks, emphasizing the need for improved prevention paradigms.





947 HIV-1 SUPERINFECTION IN THE SWISS HIV COHORT STUDY: A LARGE SCALE SCREEN

Sandra E. Chaudron[1], Karin Metzner[1], Alex Marzel[1], Jürg Böni[2], Sabine Yerly[3], Thomas Klimkait[4], Matthieu Perreau[5], Roger Kouyos[1], Huldrych F. Günthard[1]
[1]University Hospital Zurich, Zurich, Switzerland, [2]University of Zurich, Zurich, Switzerland, [3]University Hospitals of Geneva, Geneva, Switzerland, [4]University of Basel, Basel, Switzerland, [5]University of Lausanne, Lausanne, Switzerland

Background: HIV-1 superinfection (SI) is the infection of HIV-1 infected individuals by another viral strain. SI has been associated with disease progression, viral recombination and immune escape. Identifying SI remains challenging for various reasons: 1. SI strain may outcompete or be outcompeted by the first strain. 2. SI is difficult to discern from co-infection. 3. SI is difficult to prove within viral subtypes, especially if caused by viruses from similar transmission clusters. 4. Sampling frequencies are too low and systematic screens of large populations to date are missing due to lack of needed longitudinal samples in untreated patients. Here we benefit from historic samples of 2 well characterized longitudinal studies; the Zurich Primary HIV Infection Cohort Study (ZPHI, >360 patients with documented PHI) and the Swiss HIV Cohort Study (SHCS, >19,000 HIV infected individuals).
Methods: Sequences of the HIV-1 pol gene from 11,738 patients in the SHCS drug resistance database were used for phylogenetic reconstruction. Then, patients with ≥2 longitudinal sequences were kept. From the distribution of our dataset; 2 criteria were used to select HIV-1 superinfected patients: 1. a phylogenetic cluster diversity of at least 20 patients for each individual patient's cluster and 2. a genetic distance ≥5% between a patient's sequences. Finally, to address potential samples mislabelling, patients were categorized on their number of longitudinal sequences and the spatial positioning of these sequences in the phylogeny. Category 1 patients have 2 sequences; categories 2 and 3 patients have >2 sequences and respectively 1 sequence or none spatially away from the others.
Results: Of 4,558 HIV-infected individuals with ≥2 sequences, 330 candidates for HIV-1 superinfection (figure) including 7 enrolled in the ZPHI, were found. 111 patients are men having sex with men, 117 heterosexuals and 90 intravenous drug users. In addition, 123 patients show evidence of ≥ 2 viral subtypes. In category 3, mislabelling can be excluded due to patients' sequences clustering pattern corresponding to 31 strong candidates for SI. Based on the 25 patients in category 3 and the 1,224 individuals with ≥ 4 longitudinal sequences, we estimated a minimum rate of SI in our cohorts of 2%.
Conclusion: Our molecular epidemiology approach is the largest screen to identify HIV-1 superinfection using longitudinal samples so far. This work sets the basis to validate and characterize HIV-1 SI using next generation sequencing and our cohorts.

948 GREATER THAN RANDOM HLA-B HOMOGENEITY IN HIV-1 TRANSMISSION CHAINS

Huyen Nguyen[1], Christian Thorball[2], Jacques Fellay[2], Jürg Böni[3], Sabine Yerly[4], Matthieu Perreau[5], Thomas Klimkait[6], Huldrych F. Günthard[1], Roger Kouyos[1]
[1]University Hospital Zurich, Zurich, Switzerland, [2]École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, [3]University of Zurich, Zurich, Switzerland, [4]University Hospitals of Geneva, Geneva, Switzerland, [5]Lausanne University Hospital, Lausanne, Switzerland, [6]University of Basel, Basel, Switzerland

Background: The capacity of HIV to escape immune recognition by Human Leukocyte Antigen (HLA) on cytotoxic T cells is one of the most important and complex components of HIV pathogenesis. Thus, insights into how the individual makeup of HLA class I in HIV-infected patients manifests within transmission chains could have implications for vaccine development.
Methods: Approximately 300 transmission pairs and 400 clusters were identified among participants in the Swiss HIV Cohort Study (SHCS) using HIV pol sequences from the drug resistance database for the 11,000 SHCS patients with viral genome data, in addition to Los Alamos background sequences. HLA class I data, available for 5,000 participants, was compiled at three levels of specificity: four-digit and two-digit alleles, as well as HLA-B supertype. The analysis consisted of two ways to calculate allelic homogeneity. The first looked at the proportion of transmission pairs with at least a single matching HLA allele between the two individuals. The second method was to tabulate the average percentage of HLA allele matches within all clusters (e.g. across 4 individuals in a cluster, the proportion of the 6 possible comparisons between them with a matching HLA allele). These values from the SHCS data were compared to the mean value across 1,000 or 10,000 randomizations (for clusters or pairs, respectively) where the individuals in the clusters or pairs were randomly assorted. The analysis was repeated for the different HLA classification levels and separately for HLA-A, -B, and -C.
Results: In both the cluster and pair analyses, HLA-B showed significantly greater homogeneity, as demonstrated by HLA allelic matching within the clusters/pairs compared to random assortment, at the 2-digit- and supertype-level analyses (Table 1). The HLA-A analyses showed no significantly different results between the randomizations and the actual clusters/pairs. HLA-C was significant for pairs at a 4-digit-level analysis.
Conclusion: HLA class I alleles of the HIV infected individuals in transmission clusters are not randomly distributed, but instead aggregate into significantly more homogenous clusters and pairs compared to random assortment. This indicates that HIV transmission or superinfection may preferentially occur among individuals with similar HLA class I alleles.

HLA-Type	HLA Analysis Level	Pair or Cluster Analysis	Number of Pairs or Clusters (mean cluster size)	Proportion of Pairs Matching	Mean Proportion of Intracluster Comparisons with a Match	Average Value in Randomizations	P-value
A	4-digit	Pair	271	0.369		0.356	0.279
A	2-digit	Pair	271	0.410		0.397	0.281
B	4-digit	Pair	297	0.202		0.172	0.069
B	2-digit	Pair	297	0.283		0.235	**0.022**
B	Supertype	Pair	297	0.646		0.602	**0.024**
C	4-digit	Pair	283	0.329		0.284	**0.034**
C	2-digit	Pair	283	0.431		0.415	0.241
A	4-digit	Cluster	419 (2.63)		0.378	0.369	0.339
A	2-digit	Cluster	419 (2.63)		0.407	0.402	0.376
B	4-digit	Cluster	441 (2.63)		0.204	0.180	0.055
B	2-digit	Cluster	441 (2.63)		0.297	0.248	**0.003**
B	Supertype	Cluster	441 (2.63)		0.640	0.609	**0.033**
C	4-digit	Cluster	426 (2.64)		0.315	0.289	0.078
C	2-digit	Cluster	426 (2.64)		0.429	0.420	0.329

Table 1: Statistical analyses of HLA homogeneity in transmission pairs and clusters. Overview of statistical analyses looking at measure of HLA allelic homogeneity (percent of pairs with at least one matching HLA-allele or average proportion of comparisons within clusters where at least one match exists). Different analyses were done looking at HLA type (A, B, and C), level of HLA classification specificity (4-digit, 2-digit, and supertype), and at either transmissions pairs or clusters. Significant p values of tests (<0.05) denoted by bold font.

949 PREDICTING HIV CLUSTER GROWTH USING PHYLODYNAMIC RECONSTRUCTION IN LOS ANGELES COUNTY

Manon Ragonnet-Cronin[1], Yunyin W. Hu[2], Joel O. Wertheim[1]
[1]University of California San Diego, San Diego, CA, USA, [2]Los Angeles County Department of Health Services, Los Angeles, CA, USA

Background: Genetic clustering approaches are increasingly adopted in Public Health practice to identify groups of HIV-infected individuals potentially arising from rapidly growing transmission clusters. Members of these clusters are candidates for targeted HIV and STD prevention activities such as early treatment initiation and linkage to, and reengagement in, care, and pre-exposure prophylaxis and partner services among at-risk partners. The goal of this study is to identify the most effective computational approaches to detect these rapidly growing clusters.

Methods: The study utilized the earliest HIV pol sequences among 22,398 persons reported in Los Angeles County Molecular HIV Surveillance database from 2000 to 2016. We evaluated five approaches to characterize cluster growth: (i) number of newly identified cluster members in relation to the cluster size [relative growth], (ii) sigmoidal curve fitting, (iii) phylodynamic estimation of the change in effective population size, (iv) phylodynamic estimation of epidemic reproductive number, (v) randomly selected clusters. Clusters for each year in 2008-2015 were identified using HIV-TRACE (pairwise genetic distance threshold of 0.015 substitutions/site). The number of individuals added to the clusters, selected by each approach, over the subsequent 12 months was evaluated to determine the best method for predicting cluster growth.

Results: Of 22,398 persons, 8,133 (36.3%) were linked in 1,722 clusters ranging from 2 to 116 individuals. All approaches predicted cluster growth better than the random method. On average, these four approaches identified a growth rate of 0.3 newly linked persons within 12 months, compared with 0.15 persons in the random method. Although both phylodynamic reconstruction methods could be used to impute non-tested/non-reported cases within a cluster, they did not perform better than relative cluster growth. Notably, phylodynamic analyses of clusters with fewer than 10 cases often failed to converge, (likely due to lack of signal). When we re-analyzed the network focusing only on large clusters (≥10 individuals), none of the methods performed significantly better than targeting large clusters at random.

Conclusion: Past cluster growth is a reliable predictor of future growth. Cluster growth relative to cluster size was as predictive of future cluster growth as phylodynamic reconstruction and was much faster and more reliable to calculate.

950 ASSESSING HIV-1C TRANSMISSION NETWORK IN BOTSWANA AT LOW SAMPLING DENSITY

Vlad Novitsky[1], Melissa Zahralban-Steele[1], Sikhulile Moyo[2], Dorcas Maruapula[2], Baitshepi Mokaleng[2], Tapiwa Nkhisang[1], Mary F. McLane[1], Sally Madiba[1], Erik van Widenfelt[2], Tendani Gaolathe[2], Etienne Kadima[2], Shahin Lockman[1], Joseph Makhema[2], Simani Gaseitsiwe[2], Max Essex[1]
[1]Harvard University, Cambridge, MA, USA, [2]Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana

Background: Phylodynamic assessment of HIV transmission clusters is essential for monitoring the HIV epidemic, better understanding of HIV transmission dynamics, and ultimately controlling the HIV epidemic. The phylogenetic structure of the HIV transmission network remains unknown.

Methods: Near full-length HIV-1C sequences were obtained from blood specimens collected within four Botswana-Harvard AIDS Institute Partnership studies. The genotyping density (the number of analyzed HIV genomes as a proportion of the estimated total number of HIV-infected residents in the targeted area) was under 20%, which we consider as a low sampling density. A total of 3,031 HIV-1C sequences originated from the South (55%), East (30%) and North (15%) of Botswana. Near full-length genome HIV sequences were generated by Sanger sequencing (n=273) and next generation sequencing (n=2,758). Phylogenetic relatedness among analyzed viral sequences was estimated by maximum likelihood using RAxML v.8 and the GTR+Γ4+I model.

Results: We defined an HIV cluster as a viral lineage that gives rise to a monophyletic subtree of the overall phylogeny with bootstrap support of splits 0.80 and median pairwised distance10th quartile of the overall distribution of pairwise distances. We identified 472 phylogenetically distinct HIV-1C lineages circulating in Botswana and 402 of them had predominantly (75%) Botswana sequences. The identified HIV clusters had from 2 to 22 members. The proportion of local viral lineages (community-unique) seen in a single community was 28% (112 of 402). Among HIV-1C lineages spread across multiple communities, 47% (188 of 402) were found in two communities and 25% (102 of 402) were spread across 3 communities. Regional analysis (South vs. East vs. North) demonstrated that 60% (243 of 402) of viral lineages were identified exclusively in the South, East, or North of the country. Among lineages seen in two communities, 99 were identified within, while 89 were spread between geographic regions.

Conclusion: The study revealed an HIV-1C transmission network with a complex structure. A substantial number of circulating phylogenetically distinct HIV-1C lineages were identified, although the genotyping density was relatively low. Twenty-eight percent of viral lineages were local (community-unique), while about half of the identified lineages spread across two communities. The distribution of HIV-1C lineages within vs. between geographic regions split 60% vs. 40%.

951 HIV-1 GENETIC DIVERSITY AND TRANSMISSION DYNAMICS IN FISHING COMMUNITIES OF UGANDA

Nicholas Bbosa[1], Deogratius Ssemwanga[1], Jesus F. Salazar-Gonzalez[1], Rebecca N. Nsubuga[1], Maria Nannyonjo[1], Janet Seeley[1], Noah Kiwanuka[2], Bernard Bagaya[2], Gonzalo Yebra[3], Andrew Leigh Brown[3], Pontiano Kaleebu[1]
[1]MRC/UVRI Research Unit on AIDS, Entebbe, Uganda, [2]Makerere University College of Health Sciences, Kampala, Uganda, [3]University of Edinburgh, Edinburgh, UK

Background: Although fishing communities (FCs) in Uganda are disproportionately affected by HIV-1 (prevalence of 29% and incidence of 6/100 PYAR) relative to the general population (GP), the patterns of viral transmission in this group are not completely understood to guide the implementation of targeted interventions aimed at controlling disease spread. Phylogenetic methods were used to test the hypothesis that HIV-1 transmissions in fishing villages are isolated from networks in the GP.

Methods: In this cross-sectional study, we classified viral subtypes and used Bayesian phylogenetic inference to analyze nucleotide sequences with socio-demographics to identify transmission networks and reconstruct the spatial-temporal dynamics of HIV-1 transmission in 8 FCs (n=255) and 2 neighboring GP cohorts (n=305). Time-resolved trees were generated in BEAST v1.8.3 for phylodynamic and phylogeographic analyses.

Results: Subtype A1 was the prevalent subtype in both the FCs and GP (115, 45.1% and 177, 50.4% respectively) followed by subtype D (84, 32.9% and 121, 34.5%), A1/D recombinants (28, 11% and 37, 10.5%), other recombinants and minor subtypes. 31 linked pairs were found at a maximum genetic distance (GD) of 4.5%, 13 of these were closer than 1.5% but these were significantly more frequent in FCs (Table 1). Confirmation of recent HIV-1 transmission was obtained from phylodynamic analysis (average time to most recent common ancestor and sampling times=6mo). A significant positive relationship between GD and time since most recent common ancestor was observed in this population ($r=0.7$, $p<0.05$), but on an individual level this had low predictive power (positive predictive values at GD thresholds of 1.47 and 4.38 were 52.69% and 29.7% respectively). Phylogeographic analysis showed significant viral diffusion between FCs and the neighboring GP (BF>3) with stronger

support for migration (BF>10) between Rakai, Senyondo and Makungu FCs and Kampala along the Kampala-Masaka highway.

Conclusion: Young adults (average age=35yrs) mainly associated with recent HIV-1 transmission and involved in fishing, farming, bar business and sex work were identified in transmission pairs. The viral dispersal patterns suggest that HIV-1 transmission in FCs along highways is not isolated from networks in the GP. Network-guided interventions targeted at potential HIV transmission hotspots with recurrent viral migration could be useful in preventing disease spread.

Group	No. pairs@ 1.5%-4.5%	No. pairs <1.5%	Total
FF	3	10	13
GP	15	3	18
Total	18	13	31

Fisher's Exact Test p=0.0012

952 PHYLOGENETIC AND GEOGRAPHIC SEPARATION IN HIV-INFECTED PEOPLE IN BRITISH COLUMBIA

David McVea[1], Richard Liang[1], Jeffrey Joy[1], P. Richard Harrigan[1], Art Poon[2]
[1]University of British Columbia, Vancouver, BC, Canada, [2]Western University, London, ON, Canada

Background: Calculating phylogenetic distances between HIV infected individuals can reveal clusters of individuals who share risk factors that may be unknown and otherwise undetected. One clear shared risk factor for infectious diseases is geographic proximity, but the relationship between phylogenetic distance and geographic distance among people with HIV is not well understood. In this study, we describe the geographic distribution of phylogenetic clusters from British Columbia (BC), and compare the geographic and phylogenetic distances separating individuals with HIV.

Methods: Using anonymized genotypes from the BC drug treatment database, the BC phylogenetic monitoring program calculates pairwise tip-to-tip distances between sequences in a phylogenetic tree. Clusters are defined when groups of >5 individuals are separated by short phylogenetic distances. We assigned each individual a geographic location using postal sortation areas centroids of point-of-care locations. We compared geographic and phylogenetic distances by calculating Spearman's correlation with the Mantel test for significance.

Results: Phylogenetic clusters are variably geographically distributed, having members in between 1 and 38 municipalities. The mean pairwise intra-cluster difference ranges from 1 to 440 km (median = 48.4 km, IQR = 19.5-88.6 km). There was no significant correlation between genetic and phylogenetic distances among the most recent 200 individuals added to the drug treatment database ($r^2 = 0.002$). In rapidly growing clusters, the association was variable and ranged from absent to moderate ($r^2 = 0.35$, $p = 1.7 \times 10^{-8}$).

Conclusion: There is no significant association between geographic and phylogenetic distances among recently identified individuals with HIV. This offers support for the use of phylogenetic clusters as an adjunct to traditional methods of outbreak detection, as the shared transmission risks among phylogenetically linked individuals would otherwise be missed. In rapidly growing clusters, there is a variable association among geographic and phylogenetic distances. This likely reflects the differing modes of transmission between clusters and the differently structured contact networks through which HIV infection spreads.

953 PHYLODYNAMIC METHODS OF IDENTIFYING FOCI OF HIV-1 TRANSMISSION

Angela McLaughlin[1], P. Richard Harrigan[2], Jean A. Shoveller[1], Jeffrey Joy[2]
[1]University of British Columbia, Vancouver, BC, Canada, [2]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

Background: Identifying areas that are at a high risk for ongoing HIV transmission is critical for prioritizing targeted public health interventions. Despite advancements in testing and treating, foci of high transmission remain even in developed countries. Measures from phylogenetic trees can be used to identify high rates of transmission. In this study we combine a phylogenetic measure with plasma viral load to develop and employ a new metric, viral load-weighted diversification rate (VLWDR) to identify areas where viral load and transmission rates are simultaneously high among people living with HIV-1.

Methods: We apply this method to 5,190 HIV-1 sequences from 2,853 anonymized patients living in British Columbia, Canada spanning 20 years (mean 2 sequences per patient, range 1-5). The data was split into five 4-year time intervals in order to build five approximate maximum likelihood phylogenetic trees from which the diversification rates were calculated. VLWDR was calculated by combining this data with associated plasma viral loads. To maintain patient confidentiality, census tracts were merged with proximate neighbours until no fewer than five patients resided in that polygon in any time interval. Longitudinal summary statistics were generated for merged census tracts of patient residence and non-parametric Spearman rank correlation tests were used to evaluate associations.

Results: Across British Columbia, the median VLWDR of people living with HIV connected to care decreased from 801 within 1996-1999 to 667 within 2012-2015. Simultaneously, the estimated number of seroconversions decreased from 10.9 per 100,000 people per year within 1996-1999 to 1.26 per 100,000 people per year within 2012-2015. Spearman rank correlations support that the median and sum VLWDR, respectively, correlate with the estimated HIV seroconversion rate in geographic areas during the same time intervals (rho=0.207, p<0.001; rho=0.654, p<0.001). The distribution of median VLWDR and sum VLWDR in individual neighbourhoods in BC over time was mapped.

Conclusion: Our data supports the hypothesis that areas that have simultaneously high viral load and HIV transmission rates as measured by a novel metric, VLWDR, tend to have high rates of seroconversion. Thus, by aggregating data by geographic area, studies of the temporal and spatial distribution of phylogenetic and clinical traits of HIV can identify areas at risk of ongoing transmission that merit additional public health resources.

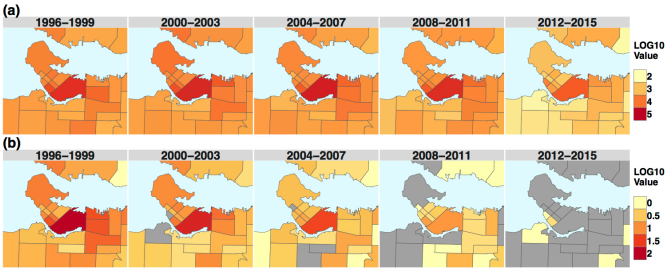


Figure 1. The temporal and spatial distribution of phylogenetic and clinical traits of HIV-1 in downtown Vancouver, British Columbia, between 1996 and 2015. **(a)** The sum viral load-weighted diversification rate is correlated with **(c)** the estimated sum of seroconversions in individual polygons.

954 PHYLOGEOGRAPHIC ANALYSIS SUGGESTS GRAVITY MODEL OF HIV TRANSMISSION IN MEXICO

Antoine Chaillon[1], **Santiago Avila-Rios**[2], Ann M. Dennis[3], Joel O. Wertheim[1], Claudia García-Morales[2], Daniela Tapia-Trejo[2], Sanjay R. Mehta[1], Gustavo Reyes-Terán[2]
[1]University of California San Diego, La Jolla, CA, USA, [2]National Institute of Respiratory Diseases, Mexico City, Mexico, [3]University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: Although Mexico has been highly successful in providing free ART for all HIV infected individuals, HIV detection and prevention efforts are lacking. Understanding the transmission dynamics of HIV across Mexico is key to improve identification of infected individuals and targeting of HIV prevention efforts.

Methods: 4192 HIV-1 subtype B pol sequences sampled from unique individuals from 23 states across Mexico between 2001-2016 were analyzed. Phylogenetic and network analyses were performed to infer putative relationships between HIV sequences. We determined the spatial dispersal and growth rates among the identified clusters. The diffusion of the epidemic across Mexico was inferred using a Slatkin-Maddison approach on 1,000 iterations of random subsets of equal number of sequences per region.

Results: 1389/4192 (33.1%) sequences had a putative linkage with at least one other sequence forming 510 clusters (range: 2-13 individuals). The median cluster growth rate (newly linked sequences) among the six largest clusters (size

range 11-13) was 8.4/100 person-years (IQR 7-9). Of the 1,260 putative links, 942 (74.8%) were between individuals residing in the same state and 116 (9.2%) were between individuals from states with a shared border. 43.3% (221/510) of the clusters spanned multiple states, and two-thirds (147/221,66.5%) included individuals from the Center-South region, which includes Mexico City (Figure 1). Sampled sequences from border states of Baja California and Quintana Roo, and the state of Puebla, with strong migrational links to New York City, were significantly more likely to cluster (OR: 1.57, 1,73 and 1.87 respectively ($p<0.001$). The median distance between linked individuals from different states (based on centroids) was 445 km [IQR:160-834], suggesting regional transmission patterns. Viral migration analysis revealed that the Center-South and East regions, which include the states of Veracruz and Puebla, were main hubs of the epidemic, as significantly more inferred transmissions originated from these regions to the rest of the country.

Conclusion: Viral migration patterns highlight the regional nature of transmission in Mexico, and also demonstrate that the major metropolitan areas of Mexico City, Puebla and Veracruz were important hubs in interstate transmission. Together these results are consistent with a gravity model of transmission, and suggest that focusing prevention resources on major metropolitan hubs may have an enhanced effect on reducing new HIV transmissions.

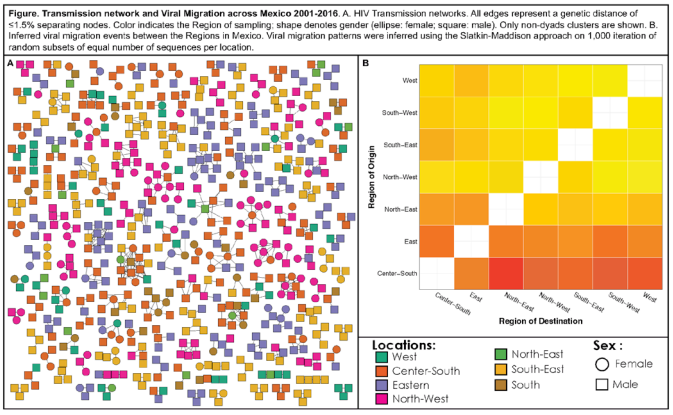


Figure. Transmission network and Viral Migration across Mexico 2001-2016. A. HIV Transmission networks. All edges represent a genetic distance of ≤1.5% separating nodes. Color indicates the Region of sampling; shape denotes gender (ellipse: female; square: male). Only non-dyads clusters are shown. B. Inferred viral migration events between the Regions in Mexico. Viral migration patterns were inferred using the Slatkin-Maddison approach on 1,000 iteration of random subsets of equal number of sequences per location.

955 ASSOCIATION BETWEEN VIRAL SUPPRESSION AND MOLECULAR CLUSTER GROWTH, UNITED STATES

Nivedha Panneer[1], Alexandra M. Oster[1], Cheryl B. Ocfemia[1], Sheryl Lyss[1], Joel O. Wertheim[2], Anne Marie France[1]
[1]CDC, Atlanta, GA, USA, [2]University of California San Diego, San Diego, CA, USA

Background: Molecular clusters identified through analysis of HIV sequences can identify groups of persons among whom HIV is rapidly spreading; these clusters can be prioritized for prevention interventions. Since not all clusters are equally likely to contribute to ongoing transmission, identifying factors predictive of cluster growth is critical for prioritization. As part of an early effort to identify such factors, we assessed whether lack of viral suppression within a small cluster was associated with cluster growth.

Methods: We analyzed HIV-1 *pol* sequences reported to the National HIV Surveillance System through December 2016 for 51,750 persons with HIV diagnosed during 2013–2016. We identified potential transmission pairs at a genetic distance threshold of ≤0.5%. We restricted analysis to clusters of 3 persons with HIV diagnoses during 2013–2015. We categorized as virally suppressed those persons with a reported viral load result of <200 copies/ml during 2015 and, for those with >1 viral load result in 2015, if the most recent was <200 copies/ml. We considered clusters to be incompletely suppressed if ≥1 person in the cluster was not suppressed or completely suppressed if all persons in the cluster were suppressed. We then determined which clusters grew by ≥1 person in 2016.

Results: Of 494 clusters of size three, 84 (17%) grew by ≥1 person in 2016. Cluster growth was identified for 68 (20%) of 347 clusters with incomplete suppression compared with 16 (11%) of 147 clusters with complete suppression. The relative risk of growth among clusters with incomplete versus complete suppression was 1.8 (95% CI: 1.08, 3.00).

Conclusion: Incomplete viral suppression was associated with cluster growth among clusters of 3 persons. We cannot determine whether growth resulted from new transmission or diagnosis of existing infections. Nevertheless, these findings suggest that clusters in which not all persons are virally suppressed could be prioritized for further investigation and intervention. That a substantial portion of clusters with complete suppression continue to grow might represent transmission from unsuppressed persons whose disease is not yet diagnosed or reported. As we explore the use of this novel tool to guide prevention efforts, future analyses of factors associated with growth of clusters will help prioritize the most concerning clusters to maximize the primary and secondary prevention benefits of cluster identification and investigation.

956 HIGH VIRAL LOAD ACROSS STAGE OF INFECTION ASSOCIATED WITH CLUSTERING IN US NETWORK

Joel O. Wertheim[1], Alexandra M. Oster[2], Nivedha Panneer[2], Chenhua Zhang[2], Neeraja Saduvala[3], Ellsworth Campbell[2], Jeffrey A. Johnson[2], William M. Switzer[2], Walid Heneine[2]
[1]University of California San Diego, San Diego, CA, USA, [2]CDC, Atlanta, GA, USA, [3]ICF International, Atlanta, GA, USA

Background: HIV spreads across sexual and injection drug-using partner networks, resulting in clusters of genetically similar viruses. The extent of this clustering is more often associated with risk behavior than viral traits (i.e., viral transmission fitness). Viral load (VL) is a viral trait associated with transmissibility and disease progression. We examined cases diagnosed at different stages of infection to test the hypothesis that VL is associated with transmission fitness (i.e., clustering) in a large U.S. transmission network.

Methods: We analyzed HIV-1 polymerase sequences from 24,028 persons from the U.S. National HIV Surveillance System who were genotyped < 3 months of HIV diagnosis during 2001–2016, received a VL measurement before or within 1 month of genotyping, were treatment-naïve at diagnosis, and had no drug resistance mutations. HIV-TRACE was used to construct a molecular transmission network. We used multiple linear regression analysis to assess the relationship between the $\log_{10}$ earliest VL measurement and clustering in 5,914 cases diagnosed at Stage 1 infection (CD4 cell count ≥500/μL). Birth sex, transmission risk factor, race/ethnicity, age at diagnosis, year of diagnosis, subtype, and CD4 count were included as covariates. Similar analysis was performed on cases diagnosed at Stage 2 (CD4 200−499/μL) and Stage 3 (CD4 <200/μL).

Results: The 2,787 cases diagnosed at Stage 1 that clustered in the network had a mean VL of 70,745 copies/ml, 27% higher than the 3,127 unclustered cases ($p < 0.001$). This finding was robust to the timing of VL measurement, demographic/risk covariates, CD4 count, network structure, genetic distance threshold for assigning partner clustering (0.005 to 0.015 substitutions/site), and inclusion/exclusion of people who inject drugs. Larger clusters (≥5 vs. <5 and ≥10 vs. <10 persons) had increasingly higher VL in cases diagnosed at Stage 1 ($p = 0.01$). Similar patterns of higher VL in clustered cases were observed for those cases diagnosed at Stage 2 (27%; $p < 0.001$) and Stage 3 (7.5%; $p = 0.003$).

Conclusion: Circulating wild type viruses in a large transmission network differ in transmissibility. The robust association between VL and clustering reflects a heritable and durable viral trait maintained throughout infection stages. These findings heighten the importance of interrupting growing transmission clusters comprising cases with high VL through network-assisted targeting of public health interventions.

957 HIV TRANSMISSION CLUSTER DYNAMICS THAT INFORM PUBLIC HEALTH INTERVENTION IN ILLINOIS

Manon Ragonnet-Cronin[1], Joel O. Wertheim[1], Christina S. Hayford[2], Richard D'Aquila[2], Fangchao Ma[3], Cheryl Ward[3], **Nanette Benbow**[2]
[1]University of California San Diego, San Diego, CA, USA, [2]Northwestern University, Chicago, IL, USA, [3]Illinois Department of Public Health, Springfield, IL, USA

Background: Health departments across the US collect HIV sequence data from routine drug resistance tests. HIV sequences from different individuals that are closely related (i.e. clustered) can reveal high-risk groups warranting targeted public health intervention. However, clustering may be indicative of past transmissions, whereas recent cluster growth likely better reflects active transmission.

Methods: We analyzed HIV sequences reported to the Illinois Department of Public Health between 2013-2017 using HIV-TRACE. Transmission clusters were identified at a pairwise genetic distance threshold of 0.015 substitutions/site. A cluster growth statistic was calculated: the number of new cluster members in 2016/2017 divided by the square root of cluster size. We sought epidemiological

and clinical predictors of clustering and cluster growth in the network using multivariate logistic regression (growth statistic ≥1.4 vs. <1.4). We then calculated assortativity for each epidemiological variable.

Results: 2743/8351 (32.85%) sequences clustered, distributed across 643 clusters sized from 2 to 162. The cluster growth statistic varied between 0 and 2.56, and 569 (6.8%) individuals were in high growth clusters. MSM (p<0.05), Hispanic (p<0.001) and white (p<0.05) race/ethnicity, higher CD4 (p<0.01), high viral loads (p<0.01), and incident cases (p<0.01) were associated with clustering. In comparison, when evaluating high cluster growth, race/ethnicity and higher CD4 were no longer significant, but young age at diagnosis (0-20) and current young age (20-30) became predictive (p<0.05). Incident cases (p<0.05), high viral loads (p<0.05) and being an MSM remained significantly associated. The transmission network was highly assortative by race/ethnicity (Assortativity = 0.31, p<0.001), but not strongly assortative for transmission risk group (A=0.13, p<0.01) or age (A=0.12, p<0.01); suggesting individuals linked to others of the same race/ethnicity, but not necessarily the same transmission risk group or age category.

Conclusion: We found that variables associated with high cluster growth in Illinois were different from those associated with clustering. Most notably, younger age stood out as being highly predictive of cluster growth but race/ethnicity did not. Given that the number of individuals in growing clusters is much smaller than the total number of individuals clustered, cluster growth measures should be optimized to best use limited resources to inform and prioritize local public health interventions.

Table 1: Adjusted odds ratios (AOR) for clustering versus cluster growth of patient HIV pol sequences in Illinois, 2013-2017

PREDICTORS	CLUSTERING AOR	HIGH CLUSTER GROWTH AOR
AGE AT DIAGNOSIS		
0 - 20	-	1.51*
20 - 30	REF	REF
30 - 40	0.64**	-
40 - 50	-	-
50 - 60	-	-
60 +	-	-
CURRENT AGE CATEGORY		
0 - 20	-	-
20 - 30	REF	REF
30 - 40	-	0.66*
40 - 50	0.54**	0.44*
50 - 60	-	0.27*
60 +	-	-
RACE/ ETHNICITY		
HISPANIC	1.41***	-
BLACK	REF	REF
ASIAN	0.51*	-
WHITE	1.27*	-
MULTI-RACE	-	-
OTHER	-	-
SEX/ RISK		
FEMALE HETEROSEXUAL	0.66**	0.22***
FEMALE IDU	-	-
FEMALE NO RISK	0.58**	0.32***
FEMALE OTHER	-	-
MSM	REF	REF
MALE HETEROSEXUAL	0.63*	0.40*
MALE PWID OR MSM/PWID	-	-
MALE NO RISK	-	0.65*
MALE OTHER	-	-
LAST CD4 COUNT		
0 - 200	0.59**	-
200 - 500	-	-
500 +	REF	REF
LAST VIRAL LOAD		
0 - 200	REF	REF
200 - 3500	-	-
3500 +	1.36**	1.32*
NEW INFECTION (STAGE 0)		
NO	REF	REF
YES	1.93**	1.68*

***p<0.001 **p<0.01 *p<0.05. Adjusted Odds Ratios (AOR) are only shown for significant variables.

958 A NEW B/CRF02 CIRCULATING RECOMBINANT SPREADING QUICKLY IN PARIS AREA, FRANCE

Marc Wirden[1], Alexandre Storto[2], Magali Bouvier-Alias[3], Karine Grenet[4], Marie-Laure Chaix Baudier[5], Philippe Simon[4], Eric Froguel[4], Thuy T. Nguyen[1], Cathia Soulie[1], Vincent Calvez[1], Diane Descamps[1], Anne-Geneviève Marcelin[1], **Benoit Visseaux**[2]

[1]Pitié-Salpêtrière Hospital, Paris, France, [2]Bichat–Claude Bernard Hospital, Paris, France, [3]Hôpital Henri Mondor, Créteil, France, [4]Groupe Hospitalier de l'Est Francilien, Jossigny, France, [5]Hôpital Saint-Louis, Paris, France

Background: The two majors circulating HIV-1 clades in France, subtype B and CRF02_AG, were originally present in distinct populations, Caucasian and West African population, respectively. However, CRF02_AG is increasing among all HIV populations and several recombinant forms, 7 URF and CRF56_cpx, were already identified. In this study, we describe a new B/CRF02_AG recombinant spreading quickly and forming a recent transmission cluster among an MSM population.

Methods: Main Parisian sequence databases were screened for the new recombinant profile. For each identified patient, available sequences and clinical data were extracted. HIV subtyping was confirmed by phylogenetic analysis for protease (PR-299bps), reverse transcriptase (RT-774bps), integrase (INT-696bps) and envelope (328bps) with the LANL reference sequences dataset and using FastTree 2.1. A first analysis of recombination points was performed on available sequences with RDP4. The time of the most recent common ancestor was estimated from PR-RT using BEAST 1.8.

Results: 30 infected patients were identified so far. PR and INT clustered with CRF02_AG while RT and env clustered with subtype B. This profile and the first recombination point identified, at position 2709 (HXB2), do not correspond to previously described recombinants. No drug resistance mutation was identified. All patients formed a recent transmission cluster in PR-RT (branch support value >99% and maximum genetic distance <2.8%). Patients were diagnosed in 2013 (n=2), 2015 (7), 2016 (11), and 2017 (10). 29/30 are male, 17/18 declared a MSM route of transmission, 8/19 were diagnosed as primo-infections. Median viral loads were at 144,295 [IQR: 58,700-326,829] and 539,808 [IQR: 156,254-3,305,809] copies/mL for non-primo- and primo-infections, respectively. Only 3 patients had CD4 <100 cells/mm^3. Most of these patients are living in the Eastern Paris suburb area. tMRCA analysis estimated the emergence of this cluster in July 2012.

Conclusion: A new CRF02_AG/B recombinant, proposed as CRF94_B02, has been identified. All detected patients so far are included in a single recent transmission cluster and were recently diagnosed, underlying the rapid spread of this strain among MSM in Paris suburb area. A full genome analysis and a research for other patients at a national scale are undergoing.

959 PREDICTIVE MODEL FOR HIV TRANSMISSION CLUSTER GROWTH IN NORTH CAROLINA

Rachael Billock[1], Kimberly A. Powers[1], Erika Samoff[2], Victoria L. Mobley[2], William C. Miller[3], Joseph J. Eron[1], Ann M. Dennis[1]

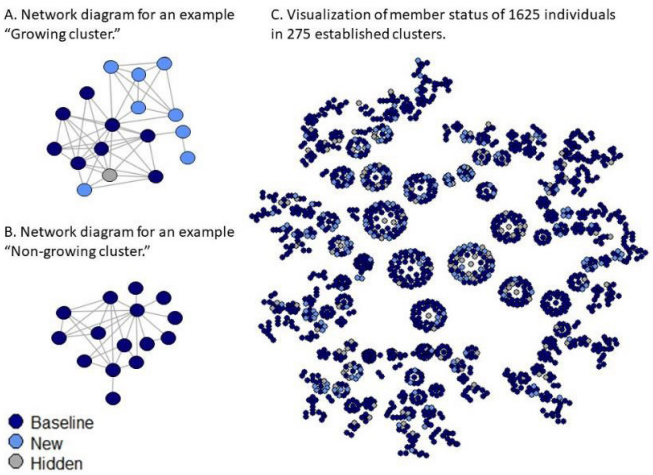
[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]North Carolina Division of Public Health, Raleigh, NC, USA, [3]The Ohio State University, Columbus, OH, USA

Background: HIV transmission cluster identification shows promise as a tool to help prioritize public health intervention. We assessed cluster-level characteristics associated with temporal cluster growth and incorporated these findings into a predictive model for cluster growth in North Carolina (NC).

Methods: HIV-1 pol sequences generated from routine genotypic resistance testing from 11/2010 through 09/2016 in NC (n=8923 persons) were matched to HIV surveillance data and used to identify putative transmission clusters size ≥2 members via pairwise genetic distance differences <1.5%. Of 782 clusters, 275 (35%) were established by 03/2015 and recently active (included any sequences from prior 2 years). Cluster members were categorized as baseline members (sequences prior to 03/2015), hidden members (diagnosed prior to 03/2015 with sequences after 03/2015), and new members (diagnosed after 03/2015) [Figure]. Clusters were retrospectively assessed for growth (any new members) over 18 months (03/2015 – 09/2016). We developed a predictive model for cluster growth incorporating demographic, clinical, and contact tracing characteristics of baseline members and evaluated the model using the area under the receiver operating characteristic curve (ROC AUC).

Results: Of 275 established, recently active clusters (n=1625 persons; size=2-44 persons), 64 (23%) grew over 18 months of follow-up. Growing clusters had a larger median size at baseline than non-growing clusters (6 vs. 2 persons). Persons in growing clusters showed younger median ages (33 vs. 38 years) and were more likely to report male sex (89% vs. 77%), black race (77% vs. 41%), and MSM status (71% vs. 51%) than those in non-growing clusters. Persons in growing clusters had shorter median times to care entry after diagnosis than those in non-growing clusters (45 vs. 71 days) but were less likely to have been in care at the start of follow-up for cluster growth (81% vs. 84%). The final predictive model included terms for cluster size, median time to care entry after diagnosis, median age, and percent with no identified contacts among baseline members, and showed an ROC AUC of 0.85 in the validation sample.

Conclusion: This model has strong predictive ability to forecast new HIV diagnoses in recently active, established genetic clusters in NC and could be adapted to diverse HIV control settings. Identification of HIV transmission clusters that are likely to grow over time could guide prioritization of public health interventions.



960 AGE DISPARITIES IN EUROPEAN HIV TRANSMISSION PAIRS UNCOVERED WITH VIRAL SEQUENCE DATA

Matthew D. Hall[1], Chris Wymant[1], Oliver Ratmann[2], Jan Albert[3], Norbert Bannert[4], Anne-Marte Bakken Kren[5], Marion Cornelissen[6], Kate Grabowski[7], Huldrych F. Günthard[8], Laurence Meyer[9], Kholoud Porter[10], Matti Ristola[11], Guido Vanham[12], Christophe Fraser[1]
[1]University of Oxford, Oxford, UK, [2]Imperial College London, London, UK, [3]Karolinska Institute, Stockholm, Sweden, [4]Robert Koch Institute, Berlin, Germany, [5]Oslo University Hospital, Oslo, Norway, [6]University of Amsterdam, Amsterdam, Netherlands, [7]Johns Hopkins University, Baltimore, MD, USA, [8]University Hospital Zurich, Zurich, Switzerland, [9]INSERM, Le Kremlin-Bicetre, France, [10]University College London, London, UK, [11]Helsinki University Central Hospital, Helsinki, Finland, [12]Institute of Tropical Medicine, Antwerp, Belgium

Background: Viral sequence data provide a powerful tool for investigating closely-related HIV infections, but previous approaches have usually used only one sequence per patient, and have been unable to reconstruct the likely direction of transmission between individuals. With larger within-host genetic datasets now available, methods can be refined to incorporate inference of directionality. We have implemented such an approach in our tool phyloscanner. Here, we use phyloscanner to explore the age disparity between sources and recipients of infection amongst European men who have sex with men (MSM).
Methods: Phyloscanner was used to analyse Illumina short-read sequence data from the BEEHIVE study, sampled from 2892 Europeans living with HIV diagnosed between 1985 and 2015. The results allowed us to assign a measure of confidence to which individuals were involved in transmission pairs and in which direction transmission occurred. We selected a confidence threshold to define probable pairs and examined the distribution of transmitter and recipient ages at the time of recipient seroconversion. We also performed a regression analysis on a richer dataset where no threshold was applied but pairs were weighted by confidence level, and modelled transmitter age as a function of recipient age.
Results: 57 MSM transmission pairs were identified. In 38 (67%), the recipient was older than the transmitter, with a mean age difference of 2.16 years. However, there was marked variation in age disparity with respect to recipient age. In pairs where the recipient was under 30, the transmitter was a mean 6.11 years older. From ages 30 to 39, the mean disparity was not significantly different from zero (0.35 years). In older recipients, the transmitter was a mean 8.41 years younger. The regression model predicts that transmitter age grows by 0.28 years for every increased year of recipient age, with the cross-over to transmitters tending to be younger than recipients occurring at an age of 35.3.
Conclusion: Our results suggest that MSM in their thirties were more likely to be the source of infections in others of all ages. This suggests a trade-off, with MSM under 30 and above 40 both less likely to act as transmitters. In the young, this is likely due to a shorter period of potential exposure, while in the old, it could be due to reduced sexual activity or reduced unsafe sexual activity. This study demonstrates the power brought by large genetic datasets to the investigation of demographic correlates of transmission.

961 RESTART OF THE HIV EPIDEMIC AMONG PWID IN OCCUPIED CRIMEA AND IN THE EAST OF UKRAINE

Marina Kornilova, Yana Sazonova
Alliance for Public Health, Kyiv, Ukraine

Background: Russian military intervention in Eastern Ukraine and occupation of Crimea in March 2014 have caused significant public health consequences. The conflict jeopardized the HIV/AIDS programs and undermined several years of Ukrainian public health efforts aimed at reversing the HIV epidemic in key population. Since 2011 HIV prevalence among people who inject drugs (PWID) in Ukraine has stabilized at approximately 20% (21.9% in the 2015 bio-behavioral survey). The ban on opioid substitution treatment, which was deemed to be illegal in occupied Crimea and self-proclaimed Luhansk and Donetsk People's Republics in the Donbass region, along with limited access to clean needles had affected this population. We analyzed data of two cross-sectional surveys conducted in the occupied Crimea and two biggest cities on the armed intervention zone 1 year before and after the onset of the conflict to measure to what extend the key population was affected.
Methods: We performed the secondary analysis of data obtained through the integrated bio-behavioral surveys among PWID recruited through RDS in 3 main conflict territories in 2013 ad 2015: Simpheropol (Crimea), Donetsk and Luhansk (armed conflict zones). Data analysis was performed in RDS-Analyst taking into account the size of the participants network, with prior adjustments for outliers (imputed visibility procedure) and calculation of 95% CI.
Results: The HIV prevalence among PWID has grown in all three cities from 22.5% (CI 17.6-28.1) in 2013 to 32.2% (CI 26.8-37.9) in 2015 in Simpheropol; from 26.5% (CI 19-35) to 33.5% (28.1 – 38.8) in Donetsk; and from 3.2% (CI 1.7 – 5.4) to 7.5% (2.5 – 13.0) in Luhansk. The coverage with OST decreased from 33.5% in Simpheropol and 23.6% in Luhansk to 0% and from 13.6% to 8.0% in Donetsk. The proportion of PWID who received cleaned needles as part of HIV prevention package in the last 12 month decreased from 79.1% in 2013 to 54.1% in 2015 in Simpheropol, from 49.4% to 31.4% in Donetsk and from 43.7 to 12.0% in Luhansk. The same trend was observed in access to free condoms: from 66.8% in 2013 to 53.8% in 2015 in Simpherolpol, from 49.2% to 30% in Donetsk and from 43.3% to 10.6% in Luhansk.
Conclusion: Russian military intervention in Eastern Ukraine and annexation of Crimea have caused significant public health consequences, the ban on OST and major reduction of HIV prevention programs in the affected territories have re-started the HIV epidemic among PWID. Current behavior trends suggest further desease spread.

962 HIV TESTING AND PREVENTION SERVICES AMONG PERSONS WHO INJECT DRUGS–INDIANA, 2016

Mary Tanner[1], Sharoda Dasgupta[1], Monita Patel[1], Julie O'Donnell[1], Brandon Halleck[2], Joseph Amlung[2], Caitlin Conrad[2], Cameron McAlister[3], Erika Chapman[2], Ayriane Bailey[2], Michael Spiller[1], Dita Broz[1], Philip J. Peters[1], Paul J. Weidle[1], Joan Duwve[3]
[1]CDC, Atlanta, GA, USA, [2]Indiana State Health Department, Indianapolis, IN, USA, [3]Indiana University, Indianapolis, IN, USA

Background: The emergency response to the 2015 HIV outbreak among persons who inject drugs (PWID) in rural Indiana included increased HIV testing, establishment of a syringe services program (SSP), and HIV care services in this underserved area. We assessed uptake of HIV testing and prevention services among PWID one year after outbreak identification.
Methods: PWID in the outbreak area were recruited using respondent-driven sampling between January and February 2016 and interviewed using a structured questionnaire about demographics, HIV testing and diagnosis, and awareness of pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) for HIV. We report percentages and medians with interquartile ranges (IQR) for categorical and continuous variables respectively. We used Fisher's exact test to assess differences in PrEP knowledge based on last HIV test location.
Results: Of 200 participants, 58% were male, 92% were non-Hispanic white, and 92% were heterosexual. Median age was 35 years (IQR: 28, 43). Fifty-nine (30%) persons reported being HIV-positive and 81% of them received the diagnosis in the last year. Only 15 (8%) reported never testing for HIV; most common reasons for not testing were perceived low risk of infection, fear of diagnosis, and other reasons; stigma was not cited as a reason for not testing. Of the 185 persons who ever tested for HIV, 52% had not tested before the outbreak but were tested during/after the outbreak response. Of 182 persons

reporting the location of their last HIV test, 21% tested at the community outreach center/SSP, 15% at jail/prison, 15% were tested by a professional at home, and the remaining persons reported utilizing 1 of 7 other testing options. Sixty-six (33%) and 21 (11%) participants reported having heard of PrEP or PEP, respectively. Of those who had heard of PrEP, 3 were taking it; no one reported taking PEP. Of those reporting the location of their last HIV test, 53% of those who last tested at the SSP expressed knowledge of PrEP, compared to 32% of those whose last HIV test was not at the SSP (p=0.023).

Conclusion: Enhanced HIV testing efforts following an HIV outbreak among PWID in Indiana were associated with increased HIV testing and diagnoses. Awareness and use of PrEP and PEP were low, but PrEP awareness was significantly higher among those whose last HIV test was at the SSP. These findings indicate a need for increased education and access to PrEP and PEP, and suggest that SSPs may offer a useful forum for PrEP/PEP education.

963 AN OUTBREAK OF HIV ASSOCIATED WITH SHARING OPIATE INJECTION PREPARATION EQUIPMENT

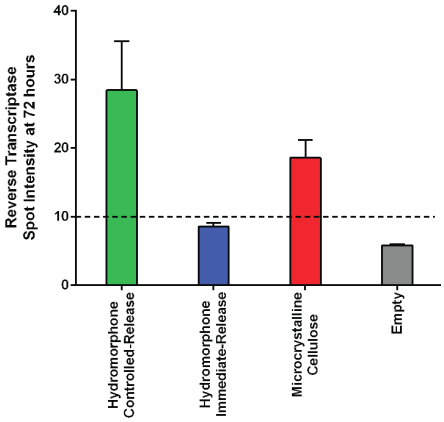
Sharon Koivu, L Ball, K Gupta, C Venner, R Tirona, Eric Arts, B Hallam, Ryan Wong, Klajdi Puka, M Speechley, G Hovhannisyan, **Michael Silverman**
University of Western Ontario, London, ON, Canada

Background: London, Canada is experiencing a HIV outbreak among People Who Inject Drugs (PWID) despite a very extensive needle and equipment distribution campaign, opiate substitution therapy program and local HIV clinic. Hydromorphone hydrochloride time-release capsules (HMC)(Hydromorph Contin®); a controlled release prescription opioid, is the local opiate of choice. Injection of HMC is associated with frequent sharing of injection drug preparation equipment [(IDPE) filters and cookers] with multiple needle insertions into the IDPE.

Methods: We conducted a nested case control study of local PWID. Cases (HIV+) (n=35) and controls (HIV neg)(n=84) completed an extensive questionnaire regarding attitudes and behaviors associated with injection drug use. We assessed the presence of residual HMC or immediate release hydromorphone (IRH) in the IDPE following initial injection, and the effects of heating the preparation (using a cigarette lighter) via liquid chromatography–tandem mass spectrometry. The persistence of HIV reverse transcriptase activity (RT) and Infectivity (Tzm-bl cells) was assessed after adding virus to IDPE in the presence or absence of HMC or IRH.

Results: Logistic regression analysis demonstrated that sharing IDPE in the absence of needle/syringe (NS) sharing was strongly associated with HIV infection [aOR=22.12; p<0.001], sharing both IDPE and NS was also associated with HIV infection [aOR=23.9, p=0.007], while there was no association with sharing only NS [aOR=0.91; p=0.92] (likely due to NS sharing being very infrequent and only with sero-concordant partners vs IDPE sharing being highly repetitive, often several times/day). The belief that heating the HMC preparation in the IDPE was unnecessary or harmful was also associated with HIV infection (p<0.05). We demonstrated that 45% of HMC (but not IRH) remained in the IDPE following initial injection, with no significant change to the quantity of extracted or residual hydromorphone after heating. HIV RT activity and infectivity was preserved in the IDPE by the presence of HMC but not IRH. Heating the IDPE rapidly inactivated HIV even in the presence of HMC.

Conclusion: We demonstrated a high risk for HIV transmission associated with sharing of IDPE. Time released hydromorphone encourages IDPE sharing, and the drug excipients can preserve HIV viability. Messaging "don't share IDPE, but cook it if you do", may be an effective (i.e. reducing infection) and safe (i.e. not contributing to overdose) harm reduction strategy.



964 IDENTIFYING UNDIAGNOSED HIV-INFECTED PWID IN INDIA USING RESPONDENT-DRIVEN SAMPLING

Allison M. McFall[1], Shruti H. Mehta[1], Aylur K. Srikrishnan[2], Santhanam Anand[2], Canjeevaram K. Vasudevan[2], Gregory M. Lucas[1], Sunil S. Solomon[1]
[1]*The Johns Hopkins University, Baltimore, MD, USA,* [2]*YR Gaitonde Center for AIDS Research and Education, Chennai, India*

Background: Globally, people who inject drugs (PWID) have a high HIV burden yet many are not self-referring for HIV testing or engaged by outreach, resulting in awareness levels well below the 90% UNAIDS target. Respondent-driven sampling (RDS), a type of chain-referral sampling, is an efficient way to reach PWID and other hidden populations. We examined if recruiter characteristics could predict recruitment of undiagnosed HIV-infected PWID.

Methods: In 2013, a cross-sectional sample of 14,481 PWID across 15 Indian cities (~1000/city) was accrued using RDS. Each sample was initiated by two well-connected PWID (seeds) with each seed and subsequent recruit given 2 coupons to recruit other PWID. Participants underwent a blood draw, HIV testing, and completed a survey. We evaluated predictive accuracy of combinations of recruiter characteristics in recruitment of undiagnosed HIV-infected PWID by calculating areas under receiver operating characteristic (AUC) from logistic regression models, focusing on easy-to-collect predictors.

Results: Median age was 30 and most were men (94%). 58% injected daily and 20% were HIV-infected, of whom 58% were previously undiagnosed; 40% were HCV-infected. 57% recruited at least one person and 10% recruited an undiagnosed HIV-infected PWID. People with HIV/HCV mono and co-infection were more likely to recruit an undiagnosed PWID (odds ratio [OR] vs. HIV and HCV uninfected, HIV: 1.9 [95% confidence interval CI: 1.5-2.4]; HCV: 1.6 [1.4-1.8]; co-infection: 2.1 [1.8-2.4]; AUC=0.714). Recruiting an undiagnosed PWID was associated with larger network size (OR ≥50 vs. ≤10: 1.7 [1.4-1.9], AUC=0.707) and harm reduction use (OR needle exchange: 1.5 [1.3-1.6]; OR opiate agonist therapy: 1.2 [1.1-1.5]; combined AUC=0.706). Age, gender, marriage, and education were not independently associated and together had an AUC=0.700. HIV/HCV infection with the addition of network size resulted in an AUC=0.718, significantly higher than HIV/HCV infection alone or combined other predictors. Among those with HIV/HCV co-infection and a large network (≥50 PWID), 1 in 5 (22%) recruited an undiagnosed PWID.

Conclusion: Recruitment patterns suggest PWID with HIV/HCV infection and who are central in their network are more likely to recruit PWID with undiagnosed HIV. These easily obtainable characteristics could be used to target an RDS in order to identify undiagnosed infections more efficiently, potentially useful in other high-burden populations or outbreaks when rapid case finding is vital.

Table Predictive accuracy of recruiter characteristics and efficiency in recruitment of undiagnosed HIV-infected people who inject drugs (PWID) via respondent-driven sampling among 14,481 PWID in India

Characteristics	Predictive accuracy (AUC)	AUC 95% Confidence Interval	Efficiency (% recruiting undiagnosed HIV-infected PWID)
At least 40 years old + male + never married + no/primary education (demographics)	0.700	0.687 - 0.713	10.8%
Needle/syringe exchange program (NEP) and opiate agonist therapy (OAT) use in prior 6 months	0.706	0.693 - 0.719	10.9%
Large network size (≥50 PWID)	0.707	0.694 - 0.720	13.1%
HIV/HCV co-infection	0.714	0.701 - 0.726	19.2%
HIV/HCV co-infection + demographics	0.714	0.702 - 0.727	19.4%
HIV/HCV co-infection + injection drug use in prior 6 months	0.714	0.702 - 0.727	19.8%
HIV/HCV co-infection + NEP and OAT use in prior 6 months	0.717	0.704 - 0.729	14.9%
HIV/HCV co-infection + large network size	0.718	0.705 - 0.730	22.4%
HIV/HCV co-infection + NEP and OAT use in prior 6 months + large network size	0.719	0.706 - 0.732	22.3%

AUC= area under receiver operating characteristic

965 HIV TRANSMISSION RISKS AMONG HIV-POSITIVE ADULTS IN MEDICAL CARE WHO MISUSE OPIOIDS

Ansley Lemons, Nicholas DeGroote, Alejandro Pérez, Jason Craw, Margaret Nyaku, Dita Broz, Christine Mattson, Linda Beer
CDC, Atlanta, GA, USA

Background: People living with HIV (PLWH) are prescribed opioids more often and at higher doses for pain than uninfected people and many are at high risk for opioid misuse given their disproportionate risk for substance use disorders. PLWH who misuse opioids may be less adherent to antiretroviral therapy (ART), which increases the likelihood of viral rebound and HIV transmission. Injection opioid misuse increases risk of HIV and HCV transmission and other blood-borne infections. Population-based data on HIV transmission risks among HIV-positive adults who misuse opioids in the US is needed.

Methods: The Medical Monitoring Project (MMP) is a surveillance system that collects sociodemographic, clinical, and behavioral data from a nationally representative sample of adults receiving HIV medical care in the US. We analyzed weighted data collected 6/2009-5/2015 to estimate the proportion and characteristics of people in HIV care who reported opioid misuse (n=975), defined as any self-reported injection or noninjection use of opioid pain relievers for non-medical purposes or heroin in the past 12 months.

Results: In all, 3% of people in HIV care reported opioid misuse and among them, 65% misused pain relievers, 29% used heroin, and 6% used both. Only 32% received drug/alcohol counseling or treatment. People who misused opioids were less likely to be prescribed ART (89%), adhere to ART (78%), and have sustained viral suppression (54%) than people who did not misuse opioids (93%, 88%, and 65%, respectively). People who misused opioids were more likely to have condomless sex while not virally suppressed (Table 1). Among those who misused opioids, 23% reported injecting them, and this group was more likely to engage in distributive syringe/equipment sharing compared to those who injected other drugs (Table 1). Those who injected opioids reported more frequent daily (29%) and weekly (18%) use than those who did not inject (19% and 15%, respectively). Among those who injected opioids, 43% received free sterile needles and 38% received new works.

Conclusion: Persons receiving HIV medical care who misuse opioids face significant risks for poor health outcomes and transmitting HIV. Among PLWH who misused opioids, almost ¼ injected them increasing the potential for HIV to spread rapidly through networks of persons who inject drugs. Because so few received drug/alcohol counseling or treatment, our findings suggest a need for increased delivery of drug treatment, harm reduction services, and behavioral interventions.

Table 1. Association between opioid misuse and factors that influence risk of HIV transmission among adults receiving HIV medical care, Medical Monitoring Project, 2009-2014 (N=28,162)

	Misused Opioids (n=975)		Did Not Misuse Opioids (n=27,187)		
	n[a]	% (95% CI)[b]	n[a]	% (95% CI)[b]	*P* for Rao-Scott Chi square test
Condomless sex with partner of negative or unknown HIV status while not durably virally suppressed[c]					
Yes	100	11.7 (9.2-14.1)	900	3.4 (3.1-3.6)	<.0001
No	813	88.3 (85.9-90.8)	25,212	96.6 (96.4-96.9)	
Distributive syringe sharing[d,e]					
Yes	37	16.6 (10.8-22.4)	31	9.3 (5.4-13.2)	0.0245
No	201	83.4 (77.6-89.2)	322	90.7 (86.8-94.6)	
Distributive sharing of other injection equipment (e.g., cookers, cotton, or rinse water)[d]					
Yes	54	21.2 (14.0-28.3)	22	6.6 (3.6-9.6)	<.0001
No	182	78.8 (71.7-86.0)	329	93.4 (90.4-96.4)	
Shared syringes to divide drugs (backloading/frontloading)[d]					
Yes	75	30.9 (23.3-38.5)	77	18.9 (14.6-23.3)	0.0037
No	161	69.1 (61.5-76.7)	271	81.1 (76.7-85.4)	
Received HIV or STD prevention counseling by an outreach worker, counselor, or prevention program worker					
Yes	405	38.3 (33.5-43.1)	8,829	31.6 (29.1-34.0)	0.0002
No	567	61.7 (56.9-66.5)	18,305	68.4 (66.0-70.9)	
Received HIV or STD prevention counseling by a healthcare provider					
Yes	522	50.7 (46.7-54.6)	13,028	47.0 (44.3-49.7)	0.0578
No	450	49.3 (45.4-53.3)	14,092	53.0 (50.3-55.7)	

HIV, human immunodeficiency virus; CI, confidence interval; STD, sexually transmitted disease; ART, antiretroviral therapy
[a]Numbers are unweighted
[b]Percentages and corresponding CIs are weighted percentages
[c]All viral load measurements documented undetectable or <200 copies/ml. during the past 12 months
[d]Among respondents who injected any opioids among those that misused opioids and any injection drugs among those that did not misuse opioids
[e]Someone using the same needle after the respondent

966 INDICATORS OF INJECTION DRUG USE— INDIAN HEALTH SERVICE, 2010 –2014

Mary Evans[1], Marissa Person[1], Brigg Reilley[2], Jessica Leston[3], Richard Haverkate[2], Michelle Van Handel[1], Michele Bohm[1], Danae Bixler[1], Dita Broz[1], Andrew J. Mitsch[1], Dana Haberling[1], Eyasu Teshale[1], Paul J. Weidle[1], Philip J. Peters[1], Kate Buchacz[1]
[1]CDC, Atlanta, GA, USA, [2]Indian Health Service, Rockville, MD, USA, [3]Northwest Portland Area Indian Health Board, Portland, OR, USA

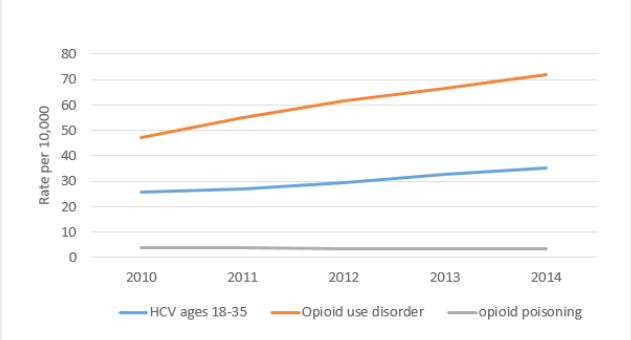
Background: Little is known about the risk of HIV outbreaks linked to injection drug use (IDU) among the American Indian/Alaska Native (AI/AN) population in the United States. We assessed the risk of IDU-related HIV transmission among AI/AN by describing temporal trends in conditions commonly found among persons who inject drugs (PWID) as a proxy for IDU.

Methods: We analyzed 2010-2014 data from the Indian Health Service (IHS) claims database, National Patient Information Reporting System (NPIRS), to include all AI/AN persons eligible for service at an IHS funded or contract outpatient or inpatient facility. As there are no ICD-9-CM codes specific to IDU, we enumerated IDU-related ICD-9-CM codes of hepatitis C (HCV) in 18-35 year olds, arm cellulitis, opioid use disorder (OUD), and opioid poisoning (OP) in ≥ 18 year olds; these could represent new or existing diagnoses. For each outcome, we determined the number of persons with at least one ICD-9-CM code in the year per 10,000 adults. HCV analyses were limited to 18-35 year olds as this group is most likley to have recently acquired HCV. We estimated average annual percentage change in occurrence of the outcomes and determined p-values for trend using Poisson regression. For the 18-35 year olds with HCV during 2010 – 2014, we also assessed co-occurrence of OUD, OP, and arm cellulitis in the same period.

Results: During 2010 – 2014, an average of 1.06 million adults per year were eligible for analysis (median age = 39 years, interquartile range 27-54 years, 46% male). HCV diagnoses increased 9.41% per year from 2010 (25.5 per 10,000, n=1160) to 2014 (35.1 per 10,000, n=1661) ($p < 0.001$); and OUD increased 13.19% per year from 2010 (47.1 per 10,000, n= 4806) to 2014 (72.0 per 10,000, n= 7886) ($p <0.001$), Figure. OP remained constant and arm cellulitis diagnoses decreased 2.97% per year from 2010 (53.3 per 10,000, n= 5435) to 2014 (47.0 per 10,000, n= 5145) ($p <0.001$). Among 4,546 persons aged 18 – 35 years old with HCV during 2010 - 2014, 26% also had OUD, 1% had OP, and 8% had arm cellulitis.

Conclusion: The increasing trend in HCV diagnoses in young AI/AN adults and opioid use disorder among all AI/AN adults is concerning and has important public health implications. Our findings suggest increasing risk for IDU-related HIV outbreaks in this population. These data can be used at a local level to ensure that access to OUD treatment and syringe service programs matches the community's need.

Prevalence of injection drug use indicators per 10,000 persons — Indian Health Service, 2010 – 2014



967 REPORTED DRUG INJECTION BEHAVIORS BEFORE AND AFTER AN HIV OUTBREAK—INDIANA, 2016

Sharoda Dasgupta[1], Mary Tanner[1], Monita Patel[1], Julie O'Donnell[1], Brandon Halleck[2], Joseph Amlung[2], Cameron McAlister[3], Erika Chapman[2], Ayriane Bailey[2], Caitlin Conrad[2], Michael Spiller[1], Dita Broz[1], Philip J. Peters[1], Paul J. Weidle[1], Joan Duwve[3]
[1]CDC, Atlanta, GA, USA, [2]Indiana State Health Department, Indianapolis, IN, USA, [3]Indiana University, Indianapolis, IN, USA

Background: In January 2015, a large HIV outbreak among persons who inject drugs (PWID) was detected in rural Indiana. A syringe services program (SSP) was established during April 2015 to reduce injection-related HIV transmission risk and link persons to prevention and treatment services. We examined injection behaviors before and after outbreak detection and use of the SSP after its establishment.

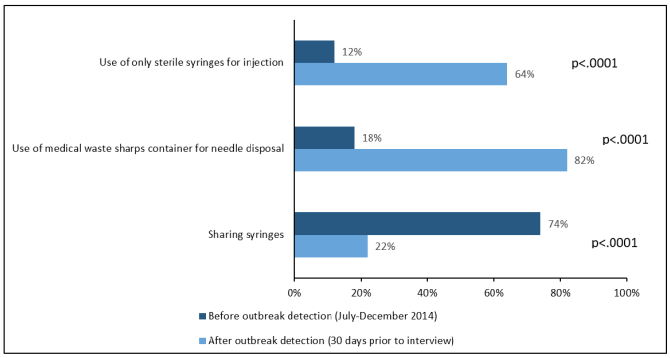
Methods: During January–February 2016, we recruited 200 PWID who injected during the prior 12 months through respondent-driven sampling to collect self-reported information on demographics, injection behaviors, SSP use, and HIV status. We restricted our analysis to persons who injected both before (July–December 2014) and after (30 days prior to interview) outbreak detection. We

assessed demographic characteristics, differences in drug injection behaviors by time period, and use of the SSP overall and by HIV status. Percentages and medians, with interquartile ranges (IQRs), were reported for categorical and continuous variables, respectively. We assessed differences in injection drug behaviors by time period using McNemar's test.

Results: Of the 124 PWID who reported injecting in both time periods, 72 (57%) were male, 115 (93%) were non-Hispanic white, and median age was 35 years (IQR: 28, 43). Self-reported HIV status was HIV-positive for 48 (39%), HIV-negative for 65 (52%), and unknown for 11 (9%) PWID. Compared with before outbreak detection, the percent of persons using only sterile syringes for injection increased from 12% to 64%, using a medical waste sharps container for used syringes increased from 18% to 82%, and sharing syringes decreased from 74% to 22% after outbreak detection. Compared with before outbreak detection, syringe sharing after outbreak detection decreased from 90% to 9% among HIV-positive persons and from 66% to 30% among HIV-negative persons. Overall, 107 (86%) persons used the SSP; 98% of HIV-positive persons and 85% of HIV-negative persons used SSP services. Among those who used the SSP, 85% of HIV-positive and 67% of HIV-negative persons reported never sharing needles after outbreak detection.

Conclusion: High-risk injection practices among a sample of PWID in southeastern Indiana decreased dramatically after detection of an HIV outbreak and establishment of an SSP. Use of the SSP was high, and almost all self-reported HIV-positive persons used the SSP, minimizing HIV transmission risk. The SSP played a key role in decreasing behaviors associated with HIV transmission.

Figure. Changes in injection drug behaviors before and after detection of a large HIV outbreak and establishment of a syringe services program (SSP) among persons who inject drugs—Indiana, 2016.



968 JOINT TRAJECTORIES OF METHAMPHETAMINE USE AND HIV VIRAL LOAD

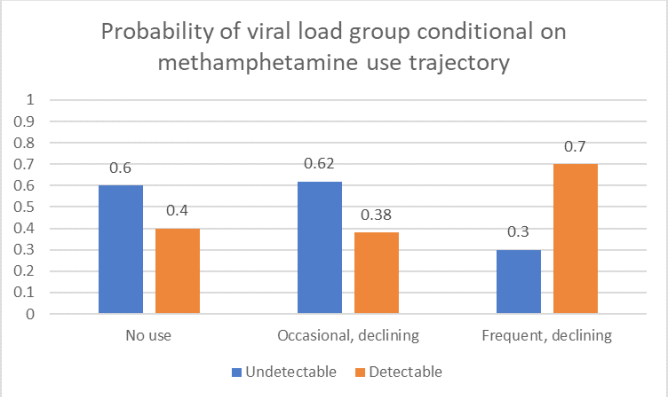
Chelsea L. Shover[1], Heather A. Pines[2], Steven Shoptaw[1], Marjan Javanbakht[1], Robert Bolan[3], Pamina Gorbach[1]
[1]University of California Los Angeles, Los Angeles, CA, USA, [2]University of California San Diego, La Jolla, CA, USA, [3]Los Angeles LGBT Center, Los Angeles, CA, USA

Background: Methamphetamine (MA) is highly addictive, interfering with adherence to HIV treatment and care. To identify effects of use patterns, we characterized the trajectories of MA use and HIV viral load (HVL) over 12 months in a cohort of HIV-positive men who have sex with men (MSM) of color aged 18-45. We hypothesized that there would be a strong association in the trajectories of both having a detectable HVL and MA use.

Methods: The study included 137 HIV-positive men who enrolled in the NIDA-funded mSTUDY cohort between August 2014 and July 31, 2016 and had at least one follow-up visit. MA use and HVL were assessed at baseline and visits every six months. Past six-month frequency of MA use was assessed via computer-assisted self-interview as never, once, less than monthly, monthly, weekly, daily (recoded as 0-5). HVL was assessed via PCR test; under 40 copies/mL defined as undetectable. Group-based trajectory models (GBTMs) were constructed using a censored normal distribution to model trajectories of MA use and a binomial distribution to model trajectories of HVL (detectable vs. undetectable). A joint trajectory model was specified to determine conditional probabilities of membership in the identified groups.

Results: GBTMs identified three MA use trajectory groups: 1) no use (34% of participants), 2) occasional and declining use (25%), and 3) frequent and declining use (42%). A Two HVL trajectory groups were identified: 1) consistently undetectable (53%), with probability of detectable HVL declining from 0.2 to 0.1 over time, 2) consistently detectable (48%), with probability of detectable HVL declining from 0.9 to 0.8 over time. The frequent MA use group's conditional probability of detectable HVL was 0.7 (95% CI: 0.49-0.90), compared to 0.4 (95% CI: 0.21-0.59) in the no MA use group and 0.38 (95% CI: 0.15, 0.61) in the occasional MA use group. GBTM using incomplete 18-month follow-up data suggested a fourth small group with consistent daily MA use, but there was too much missing data for a valid model.

Conclusion: Frequent MA use over time was associated with a longitudinal pattern of detectable HVL. Those who reported occasional MA use had similar HVL trajectories to those who reported no MA use, suggesting that pattern of MA use has ongoing implications for HIV viral load. To improve treatment outcomes for those living with HIV, frequency of use of substances such as MA needs to be addressed.



969 TRANSACTIONAL SEX AMONG MEN WHO HAVE SEX WITH MEN: WHAT'S DRUGS GOT TO DO WITH IT?

Marjan Javanbakht, Amy Ragsdale, Steven Shoptaw, Pamina Gorbach
University of California Los Angeles, Los Angeles, CA, USA

Background: The objective of this study was to examine the prevalence and correlates of transactional sex among men, the role of substance use and sexual risk behaviors, and how transactional sex may impact the use of STI/HIV biomedical prevention strategies.

Methods: Participants included those recruited as part of an NIH/NIDA funded cohort, with 422 participants recruited between August 2014 and May 2017 in Los Angeles, CA. Eligible participants were: (1) ≥18 years of age; (2) male; and (3) if HIV negative reported condomless anal intercourse with a male partner in the past 6-months. By design, half were HIV-positive and half HIV-negative. At baseline and semi-annual visits, computer assisted self-interviews were used to collect information on sexual behaviors and laboratory testing was conducted for current STI/HIV status. Factors associated with transactional sex were evaluated using regression analysis with generalized estimating equations in order to account for within subject correlations.

Results: The average age of participants was 31.4 years with 43% identifying as African American, followed by 36% as Hispanic/Latino. Prevalence of recent transactional sex across the 1,081 study visits was 18% (n=190), with 73% of this group reporting exchanging sex for drugs. Transactional sex was higher among those who reported unstable housing (32% vs. 11%; p value <.01), concurrent sexual partnerships (27% vs. 9%; p value<.01), and transgendered sex partners (38% vs. 16%; p value=0.02). Reciprocal sex work was also high with those who reported receiving money, drugs, or shelter for sex, also more likely to give money, drugs, shelter for sex (76% vs. 11%; p value <.01). HIV viral load was independently associated with transactional sex such that every $\log_{10}$ increase in HIV-1 RNA was associated with a 40% increase in the odds of transactional sex [adjusted odds ratio (AOR)=1.4; 95% confidence interval (CI) 1.1-1.7). Additionally, those testing positive for an STI were nearly twice as likely to report transactional sex as compared to those without STIs (AOR= 1.9; 95% CI 1.0-3.7).

Conclusion: The prevalence of transactional sex among this cohort of high risk HIV-negative and HIV-positive MSM was relatively high. These findings highlight that the intersection of drug use, poverty, and HIV among young LA MSM may require different approaches to HIV prevention and care in order to reduce poorly controlled HIV disease and the practice of HIV transmission behaviors.

970 HIV DIAGNOSES AMONG PEOPLE WHO INJECT DRUGS — UNITED STATES, 2010-2016

Sheryl Lyss[1], Tianchi Zhang[2], Alexandra M. Oster[1]
[1]*CDC, Atlanta, GA, USA,* [2]*ICF, Atlanta, GA, USA*

Background: The number of HIV diagnoses among people who inject drugs (PWID) in the United States declined substantially over the past decade, then increased slightly in 2015, the year of a large HIV outbreak among PWID in Scott County, Indiana. We describe trends in HIV diagnoses among PWID to elucidate the observed increase.
Methods: We used National HIV Surveillance System data reported through June 2017 for diagnoses occurring during 2010-2015 and preliminary data for 2016; missing data were imputed with standard methods. We included persons aged ≥13 years with HIV attributed specifically to injection drug use (IDU) (i.e., those attributed to both IDU and male-to-male sexual contact were not included). To assess the influence of the Scott County outbreak, we examined 2015 diagnoses including and excluding those reported from Scott County.
Results: HIV diagnoses among PWID decreased 35% nationally during 2010-2014 from 3421 to 2229, with annual declines of 14% (2010-2011), 10% (2011-2012), 9% (2012-2013) and 7% (2013-2014) (Table). During 2010-2014, diagnoses declined 35% among both males and females; declines varied across racial/ethnic groups, age groups and U.S. Census regions and were <20% among whites (-10%), those aged 13-34 years (-19%), and in the West (-18%). During 2014-2015, diagnoses among PWID increased by 117 (5%) to 2347 nationally; increases among whites (+233; 32%), those aged 13-34 years (+161; 22%), and in the Midwest (+186; 85%) are consistent with the distribution of the 148 Scott County cases in 2015. Excluding Scott County cases, diagnoses among PWID decreased by 31 (1%) to 2199, but increased among whites (+89; 12%), those aged 13-34 years (+81; 11%), and in the Midwest (+38; 17%). The preliminary number of 2016 diagnoses among PWID is similar to that for 2014.
Conclusion: The national increase in HIV diagnoses among PWID during 2014-2015 followed a slowing decline during 2010-2014. Although the Scott County outbreak was largely responsible for the increase in 2015 cases, without Scott County cases, during 2014-2015 declines stalled nationally, and diagnoses increased in some demographic groups with slower declines during 2010-2014. The extent to which trends in the number and shifting characteristics of HIV diagnoses among PWID reflect a growing number of PWID in the United States, increased testing, increased reporting, or other causes cannot be determined from these data alone. Vigilance is needed so that longstanding gains in preventing HIV among PWID are not reversed.

Table. HIV diagnoses among people who inject drugs, by selected characteristics — United States, 2010–2015*

	2010	2011	2012	2013	2014	2010–2014		2015 (including diagnoses from Scott County)	2014–2015		2015 (excluding diagnoses from Scott County)	2014–2015	
	n	n	n	n	n	Δ	%	n	Δ	%	n	Δ	%
Total	3421	2928	2636	2399	2229	-1192	-35%	2347	117	5%	2199	-31	-1%
Sex													
Male	1987	1666	1489	1396	1297	-691	-35%	1343	47	4%	1262	-35	-3%
Female	1434	1262	1147	1002	933	-501	-35%	1004	71	8%	937	4	0%
Race/ethnicity													
Black/African American	1712	1350	1215	1009	894	-818	-48%	804	-90	-10%	804	-90	-10%
Hispanic/Latino	703	645	568	509	481	-222	-32%	469	-13	-3%	468	-14	-3%
White	817	779	704	741	733	-84	-10%	967	233	32%	822	89	12%
Other	189	155	150	140	120	-68	-36%	108	-13	-11%	105	-16	-13%
Age category at diagnosis													
13–34 years	896	805	788	727	723	-173	-19%	883	161	22%	803	81	11%
35–49 years	1415	1199	971	883	812	-604	-43%	784	-28	-3%	730	-82	-10%
≥50 years	1110	924	877	789	695	-415	-37%	680	-16	-2%	665	-30	-4%
Region of residence													
Northeast	1026	860	788	662	593	-432	-42%	553	-40	-7%	553	-40	-7%
Midwest	355	315	274	281	219	-136	-38%	406	186	85%	257	38	17%
South	1494	1262	1149	1032	967	-527	-35%	939	-28	-3%	939	-28	-3%
West	546	492	425	424	450	-96	-18%	449	-1	0%	449	-1	0%

*Because of statistical adjustment for missing data and rounding, sums of components may vary slightly from the total.

971 CHARACTERISTICS OF HIV INCIDENT INFECTIONS AMONG PERSONS WHO INJECT DRUGS IN THE US

Johanna Chapin-Bardales, Silvina Masciotra, Amanda Smith, Brooke Hoots, William M. Switzer, Wei Luo, S. Michele Owen, Gabriela Paz-Bailey
CDC, Atlanta, GA, USA

Background: Detecting and characterizing recent HIV infections can better describe subpopulations at increased risk of HIV and identify factors that contribute to ongoing HIV transmission. We characterized recent HIV infections among a sample of persons who inject drugs (PWID) from 19 US cities to inform monitoring of the HIV epidemic among PWID.
Methods: PWID aged ≥18 years were interviewed for 2012 National HIV Behavioral Surveillance using respondent-driven sampling. We tested participants' dried blood spot specimens with the CDC-developed Bio-Rad Avidity Index incidence assay (BRAI, mean duration of recency of 240 days). A recent HIV infection was defined as having a reactive HIV screening result, no reported HIV diagnosis ≥12 months before the interview date, a BRAI avidity index ≤30%, and no viral suppression (viral suppression defined as HIV viral load <1,000 copies/mL). In bivariate analyses, we compared recently infected to HIV-negative PWID to evaluate factors associated with recent HIV acquisition. We also assessed differences between PWID with recent infections and PWID with non-recent HIV infections.
Results: Of 9,901 eligible PWID, 50 (0.5%) were recently HIV infected. Compared to HIV-negative PWID, those recently HIV infected were more likely to inject stimulants (p<0.01), have a greater number of sex partners (p=0.02), and have had male-male sex in the past year (p<0.01). PWID who have sex with men had the highest proportion of recent infections (2.0%). Compared to those with non-recent infections, recently infected PWID were more likely to be young (p<0.01), be white (p=0.03), have a high school diploma (p<0.01), not have health insurance (p<0.01), share syringes (p=0.01), have a greater number of sex partners (p=0.01), and have condomless sex in the past year (p<0.01).
Conclusion: Our findings suggest that sexual behavior is associated with recent HIV acquisition among PWID. Promoting not only safe injection practices but also safe sex practices will be key to preventing new HIV infections. Prevention efforts should prioritize PWID who have sex with men, who experienced a higher proportion of recent infections and may be harder to retain on biomedical interventions. Our finding that recently HIV-infected PWID in our study population were more likely to be white and high school graduates, compared to PWID who acquired HIV earlier in the epidemic who were mostly black and who did not graduate high school, suggests a demographic shift in PWID who recently acquired HIV.

972 DISTRIBUTIVE SYRINGE SHARING AND USE OF SYRINGE SERVICES PROGRAMS AMONG PWID

Monica Adams, Qian An, Dita Broz, **Janet C. Burnett**, Cyprian Wejnert, Gabriela Paz-Bailey
CDC, Atlanta, GA, USA

Background: Although syringe sharing is a well-documented risk for HIV transmission among persons who inject drugs (PWID), few studies specifically examined distributive syringe sharing (DSS, i.e., passing on a used syringe to another PWID). Syringe services programs (SSPs) are effective at reducing injection risk behaviors and are important prevention interventions for both HIV-negative and HIV-positive PWID. We examine demographic and behavioral factors that may be associated with DSS and how the effect of SSP use on DSS differs by HIV sero-status.
Methods: PWID aged ≥18 years were recruited in 20 U.S. cities for the 2015 National HIV Behavioral Surveillance using respondent-driven sampling, interviewed and offered HIV testing. Bivariate and multivariable analyses via log-linked Poisson regression with generalized estimating equations were conducted to examine associations between demographic and behavioral variables and DSS. The effect of SSP utilization on DSS by HIV sero-status was assessed by including an interaction between SSP and HIV sero-status in the final model. Multivariable analyses were adjusted for sampling design covariates. Prevalence ratios (PR) and 95% confidence intervals (CI) are presented.
Results: Among 10,402 PWID, 41% reported DSS in the past 12 months. DSS was less likely to be reported among HIV-positive compared to HIV-negative PWID (21% vs. 43%, PR=0.52, CI: 0.45-0.60), and among those who primarily obtained syringes from SSPs versus those who did not (34% vs. 46%, PR=0.82, 95% CI: 0.76-0.88). After adjusting for gender, age, race/ethnicity, homelessness and arrest in the 12 months prior to interview, those who primarily used SSPs were less likely to report DSS than those who did not among both HIV-negative PWID (36% vs. 47%, adjusted PR=0.83, 95% CI: 0.78-0.89) and HIV-positive PWID (12% vs. 27%, adjusted PR=0.53, 95% CI: 0.38-0.73; see Table).
Conclusion: Primary use of SSPs was associated with less DSS among PWID. This effect was greater among HIV-positive PWID, who may unintentionally transmit infection when sharing their used syringes with others. These findings support expansion of SSPs and referrals to SSP programs by service providers working with PWID. Specifically, clinicians providing care and treatment to HIV-positive PWID should consider linkage of these patients to SSPs.

Table. Factors associated with distributive syringe sharing[a] among PWID: NHBS-IDU 2015

Characteristic	Distributitive Syringe Sharing aPR (95% CI)[b]
HIV-positive serostatus and syringe services program (SSP) is most common syringe source[c]	0.53 (0.38-0.73)
HIV-negative serostatus and syringe services program (SSP) is most common syringe source[d]	0.83 (0.78-0.89)
Gender (ref: Male)	
Female	1.13 (1.70-1.20)
Transgender	1.16 (0.84-1.67)
Age (ref: 30 years and older)	1.21 (1.14-1.28)
Race/ethnicity (ref: Black)	
White	1.53 (1.34-1.75)
Hispanic/Latino[e]	1.46 (1.30-1.64)
Other	1.40 (1.19-1.65)
Homelessness[f], past 12 months	1.38 (1.30-1.48)
Arrested, past 12 months	1.23 (1.16-1.30)

[a.] Defined as giving a needle the participant had already used to inject drug with to someone else to inject with

[b.] Log-linked Poisson Regression was generated using generalized estimating equations (GEE) clustered on recruitment chains stemmed from initial recruits ('seeds') in respondent-driven sampling. Prevalence ratios are adjusted (aPR) by recruiter's values on the outcome, IDU network size, and city of interview

[c.] Syringe services program is either the only, or the most common source of syringes, past 12 months. Comparison with HIV-positive serostatus without SSP as most common syringe source.

[d.] Syringe services program is either the only, or the most common source of syringes, past 12 months. Comparison with HIV-negative serostatus without SSP as most common syringe source.

[e.] Hispanics/Latinos can be of any race.

[f.] At any time in during the past 12 months, lived on the street, in a shelter, a single room occupany hotel, or lived in a car

973 NEW DIAGNOSES OF HIV AMONG INJECTING DRUG USERS, NEW YORK CITY 2006-2016

Lucia V. Torian[1], Jasmine Abdelnabi[1], Lisa A. Forgione[1], Joel O. Wertheim[2]

[1]New York City Department of Health and Mental Hygiene, Long Island City, NY, USA, [2]University of California San Diego, La Jolla, CA, USA

Background: Unintentional drug poisoning and overdose deaths in New York City have increased each year between 2010 and 2016. One contributing factor has been the transition of users of medical and non-medical opioid analgesics to non-injection heroin use, with rapid (median 6 months) transition to heroin injection. This has led to concern that a resurgent HIV epidemic among injecting drug users would follow, as has been seen elsewhere in the US.

Methods: We analyzed new diagnoses reported to surveillance to ascertain the trajectory, demographics and risk factors of the HIV epidemic among NYC IDU, focusing on trends among the 2,037 new HIV diagnoses with IDU as a risk factor that occurred in 2006-2016. Pairwise concordance analysis, a genetic distance-based clustering tool, was used to construct transmission networks.

Results: Most injection-related cases in the history of the NYC epidemic have occurred in two distinct waves. The first wave began prior to 1981, is 97% black and Hispanic, 68% aged 40+ at diagnosis, and concentrated in northern Manhattan, the South Bronx, and central Brooklyn. Its survivors occupy genetic transmission networks populated primarily by older diagnosis dates. The second wave is more recent, involves persons with the dual risk of MSM and IDU, and is more evenly distributed by race/ethnicity (40% white) and neighborhood, younger, (47% aged 20-29 and 30% aged 30-39 years), and belongs to transmission networks populated primarily by young, non-injecting, more recently diagnosed MSM. There is minimal overlap between the networks of the two waves. To date, the new heroin injectors, whose numbers and demographics are unknown, have made no discernible impact on HIV rates. In fact, during 2006-2016 new diagnoses declined 88.0% among IDU and 64.6% among MSM/IDU.

Conclusion: Unlike other jurisdictions, NYC has not seen an increase in HIV diagnoses attributable to IDU. However, it has a large population of people living with HIV, including more than 16,000 IDU and more than 2,600 MSM/IDU, and any bridge between the risk sharing networks of new injectors and the survivors of the first and second waves has the potential to spark a third wave of injection-fueled HIV. NYC syringe exchange programs, which reduced incidence in previous waves, as well as New York State legislation that in 2000 legalized over-the-counter syringe sales in pharmacies, may mitigate risk by facilitating safe injection among future new injectors.

974 DRUG OVERDOSE DEATHS AMONG PERSONS WITH HIV IN NEW YORK CITY, 2007-2015

Sarah L. Braunstein, Rebekkah S. Robbins, Demetre C. Daskalakis

New York City Department of Health and Mental Hygiene, Long Island City, NY, USA

Background: Preventable deaths, including those due to drug overdose (OD), are a significant public health concern in New York City (NYC). The rate of unintentional drug OD death in NYC increased 143% between 2010 and 2016; trends in drug OD death among persons with HIV (PWH) in NYC have not been described. Care-seeking by PWH presents an opportunity to avert preventable deaths, including OD deaths.

Methods: We selected PWH from the NYC HIV Surveillance Registry who died during 2007-2015, resided in NYC at death, and died due to OD (classified as accidental (AOD (ICD10 codes X40-X44)) or intentional (IOD (ICD10 codes X60-X64))). We compared the demographics of PWH who died of AOD versus IOD, and analyzed CD4 and viral load (VL) tests from surveillance to evaluate retention in care and viral suppression (VS) (VL≤200 cc/mL) in the 12 months prior to death as markers of care-seeking.

Results: From 2007-2015, 670 PWH died of either AOD or IOD in NYC (Table 1). While the rate of OD deaths in PWH declined during the full period, from 64 per 100,000 in 2007 to 47 per 100,000 in 2015 , it increased from 2013 (36 per 100,000) to 2015 (47 per 100,000). Decedents during 2007-2015 were predominantly male (70.6%), black (37.3%) or Latino/Hispanic (36.3%), aged 40-59 years (74.1%), and persons who inject drugs (PWID) (53.5%). Over three-quarters (76.1%) of decedents were retained in HIV care in the 12 months prior to death, and 51.0% were VS. Of the total, 626 (93.4%) deaths were classified as AOD and 44 (6.6%) as IOD. AOD decedents were also predominantly male (69.2%), black (39.0%) and Latino/Hispanic (37.9%), aged 40-59 years (75.6%), and PWID (48.2%). However, IOD were nearly all male (90.9%), mostly white (70.5%), older (22.7% aged 60+) and men who have sex with men (MSM) (65.9%). Three-quarters of both AOD and IOD decedents were retained in care prior to death, but more IOD decedents were VS (79.5% vs. 49.0%).

Conclusion: A sizeable number of NYC PWH died of OD in the last decade, and OD death rates in recent years increased. Pre-death care patterns reveal frequent interaction with the health care system, underscoring missed opportunities for harm-reduction and suicide prevention interventions for PWH. Differences in the demographic profiles of AOD and IOD decedents warrant further exploration. Interventions for PWID and MSM who are long-term survivors may need to be further tailored to prevent OD-associated mortality in the context of HIV care.

Table 1. Deaths due to drug overdose among people with HIV/AIDS, New York City 2007-2015

	Total		Year of death															
			2007		2008		2009		2010		2011		2012		2013		2014		2015	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total[1]	670	100.0	104	100.0	64	100.0	78	100.0	65	100.0	62	100.0	89	100.0	63	100.0	65	100.0	80	100.0
Age adjusted death rate per 100,000 mid-year			64.3		37.3		43.2		36.3		37.6		52.2		35.5		35.3		47.4	
Type of drug overdose (OD)[2]																				
Accidental OD	626	93.4	97	93.3	60	93.8	74	94.9	57	87.7	57	91.9	83	93.3	59	93.7	61	93.8	78	97.5
Intentional OD	44	6.6	7	6.7	4	6.3	4	5.1	8	12.3	5	8.1	6	6.7	4	6.3	4	6.2	2	2.5
Gender[3]																				
Male	473	70.6	76	73.1	42	65.6	50	64.1	44	67.7	45	72.6	64	71.9	47	74.6	49	75.4	56	70.0
Female	197	29.4	28	26.9	22	34.4	28	35.9	21	32.3	17	27.4	25	28.1	16	25.4	16	24.6	24	30.0
Race/Ethnicity																				
Black	250	37.3	45	43.3	28	43.8	30	38.5	27	41.5	20	32.3	34	38.2	22	34.9	19	29.2	25	31.3
Latino/Hispanic	243	36.3	27	26.0	21	32.8	28	35.9	24	36.9	22	35.5	34	38.2	26	41.3	30	46.2	31	38.8
White	170	25.4	32	30.8	14	21.9	20	25.6	13	20.0	20	32.3	19	21.3	15	23.8	16	24.6	21	26.3
Other[4]	7	1	0	0	1	1.6	0	0	1	1.5	0	0	2	2.2	0	0	0	0	3	3.8
Age group at death (years)																				
0 - 12	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
13 - 19	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
20 - 29	16	2.4	2	1.9	3	4.7	0	0.0	0	0.0	4	6.5	2	2.2	1	1.6	1	1.5	3	3.8
30 - 39	83	12.4	14	13.5	8	12.5	14	17.9	6	9.2	10	16.1	14	15.7	1	1.6	7	10.8	9	11.3
40 - 49	253	37.8	46	44.2	31	48.4	28	35.9	26	40.0	23	37.1	27	30.3	24	38.1	23	35.4	25	31.3
50 - 59	243	36.3	36	34.6	20	31.3	32	41.0	25	38.5	22	35.5	37	41.6	23	36.5	25	38.5	23	28.8
60+	75	11.2	6	5.8	2	3.1	4	5.1	8	12.3	3	4.8	9	10.1	14	22.2	9	13.8	20	25.0
Transmission risk[5]																				
Men who have sex with men (MSM)	131	19.6	18	17.3	9	14.1	21	26.9	9	13.8	11	17.7	18	20.2	13	20.6	17	26.2	15	18.8
Injection drug use history (IDU)	304	45.4	45	43.3	32	50.0	37	47.4	28	43.1	27	43.5	46	51.7	30	47.6	28	43.1	31	38.8
MSM/IDU	54	8.1	9	8.7	6	9.4	3	3.8	3	4.6	6	9.7	8	9.0	5	7.9	4	6.2	10	12.5
Heterosexual contact	82	12.2	12	11.5	5	7.8	10	12.8	11	16.9	8	12.9	10	11.2	7	11.1	4	6.2	15	18.8
Transgender people with sexual contact	2	0.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	3.1	0	0.0
Perinatal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other	3	0.4	0	0.0	1	1.6	0	0.0	1	1.5	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3
Unknown	94	14.0	20	19.2	11	17.2	7	9.0	13	20.0	10	16.1	7	7.9	8	12.7	10	15.4	8	10.0
Retained in care prior to death[7]	510	76.1	80	76.9	47	73.4	57	73.1	50	76.9	49	79.0	71	79.8	52	82.5	46	70.8	58	72.5
Virally suppressed prior to death[8]	342	51.0	38	36.5	23	35.9	37	47.4	31	47.7	33	53.2	52	58.4	37	58.7	42	64.6	49	61.3

[1]Includes people with HIV/AIDS who were living in New York City at death and whose underlying cause of death was drug OD (as indicated by ICD10 codes X40-44 and X60-64 on the death certificate).
[2]Age-adjusted to the US 2000 Standard Population. People newly diagnosed with HIV at death were excluded from the numerator.
[3]Accidental OD includes deaths with ICD10 codes X40-X44 listed as underlying cause of death and intentional OD includes deaths with ICD10 codes X60-64 listed as underlying cause of death.
[4]Transgender men are included in the 'Male' category and transgender women are included in the 'Female' category.
[5]Other race/ethnicity includes Asian/Pacific Islander, Native American, and Multiracial categories.
[6]"Heterosexual contact" includes people who had heterosexual sex with a person they know to be HIV-infected, an injection drug user, or a person who has received blood products. For females only, also includes history of sex work, multiple sex partners, sexually transmitted disease, crack/cocaine use, sex with a bisexual male; probable heterosexual transmission as noted in medical chart, or sex with a male and negative history of injection drug use. "Transgender people with sexual contact" includes people identified as transgender by self-report, diagnosing provider, or medical chart review with sexual contact reported and negative history of injection drug use. "Other" includes people who received treatment for hemophilia, people who received a transfusion or transplant, and children with a non-perinatal transmission risk.
[7]Retention in care is defined as ≥2 CD4 or VL tests ≥90 days apart in the 12 months prior to death.
[8]Most recent viral load in the 12 months prior to death was ≤200 copies/mL.

975 3-YEAR OUTCOMES OF PATIENT NAVIGATION+FINANCIAL INCENTIVES FOR HIV+ SUBSTANCE USERS

Daniel Feaster[1], Carlos del Rio[2], Abigail Matthews[3], Lauren Gooden[4], Tim Matheson[5], Maxine Stitzer[6], Mamta K. Jain[7], Allan Rodriguez[1], Wendy S. Armstrong[2], Gregory M. Lucas[6], Mari-Lynn Drainoni[8], Carmen L. Masson[9], David C. Perlman[10], Petra Jacobs[11], Lisa Metsch[4]

[1]University of Miami, Miami, FL, USA, [2]Emory University, Atlanta, GA, USA, [3]Emmes Corporation, Rockville, MD, USA, [4]Columbia University Medical Center, New York, NY, USA, [5]San Francisco Department of Public Health, San Francisco, CA, USA, [6]Johns Hopkins University, Baltimore, MD, USA, [7]University of Texas Southwestern, Dallas, TX, USA, [8]Boston University, Boston, MA, USA, [9]University of California San Francisco, San Francisco, CA, USA, [10]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [11]National Institute on Drug Abuse, Rockville, MD, USA

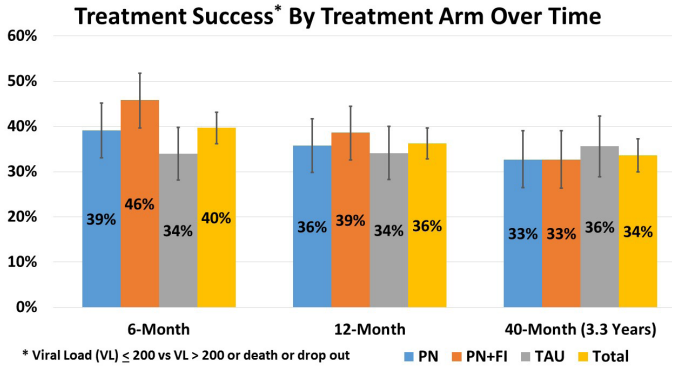
Background: Project Hope (CTN0049), a previously reported 3-arm RCT, tested 6 months of Patient Navigation (PN) and PN+Financial Incentives (PN+FI) versus treatment as usual (TAU) in increasing viral suppression rates in HIV+ substance-using hospitalized patients. Results showed PN+FI had higher rates of viral suppression than TAU at 6 but not 12 months. We report on

the 3-year outcomes of this cohort, the largest group of initially hospitalized HIV+ substance-using individuals with uncontrolled HIV infection followed prospectively.

Methods: Project Hope recruited 801 patients from 11 hospitals in the U.S. from 7/10/2012 until 9/10/2014 and followed for a year. Of the 711 patients alive at 12-months, 686 had consented to contact for long-term follow-up, which was completed between 2/18/2016 and 1/30/2017. Differences by study arm in treatment success (viral suppression) versus failure (non-suppression or death) were tested with mixed models for binary outcomes.

Results: There were 650 of 686 patients located, with 117 of 686 (17%) having died between the last and long-term follow-up and 422 of the 569 alive (74%) enrolled yielding follow-up assessment on 539 of 686 (79%). The median time to the long-term follow-up was 3.3 years [IQR=2.9, 3.6]. There was no difference in the rates of treatment success at long-term follow-up across study arm (PN=33%, PN+FI=33%, TAU=36%, p=.181). Blacks (OR=.42, 95%CI[.23,.77]), those recruited from the South (OR=.27, 95%CI[.16,.47]), and stimulant users (OR=0.43, 95% CI[0.27,0.70]), were all less than half as likely as Whites, those not from the South, and non-stimulant users, respectively, to be virally suppressed. Of 801 patients, 207 (26%) have died since randomization into Project Hope with no differences in rates of deaths across study arm (PN=28%, PN+FI=24%, TAU=25%, p=.681). Rates of viral suppression for those who survived to follow-up were 50%. There were no significant differences in long-term substance use across study arm (PN=71%, PN+FI=70%, TAU=69%, p=.646).

Conclusion: Despite intensive time-limited intervention, the long-term rate of success with hospitalized substance-using patients was only 33%, with lower rates for Blacks, those using stimulants and those recruited in the South. The high rates of death (26%) and high rates of viral non-suppression among survivors (50%) highlight the cost of this public health failure. This coupled with the continued high rates of substance use point to the need for ongoing intervention with this population.



976LB HIV TRANSMISSION POTENTIAL DUE TO INJECTION DRUG USE IN RURAL WEST VIRGINIA, US, 2017

Vicki Hogan[1], Brooke Hoots[2], Christine Agnew-Brune[2], Dawn Broussard[2], Kate Buchacz[2], Bridget Rose[1], Scott Cope[2], Erica Dawson[2], William Hoffman[1], Shacara Johnson[2], Sheryl Lyss[2], Laura Quilter[2], Paul J. Weidle[2], Brunilis White[2], Heather Bradley[2]

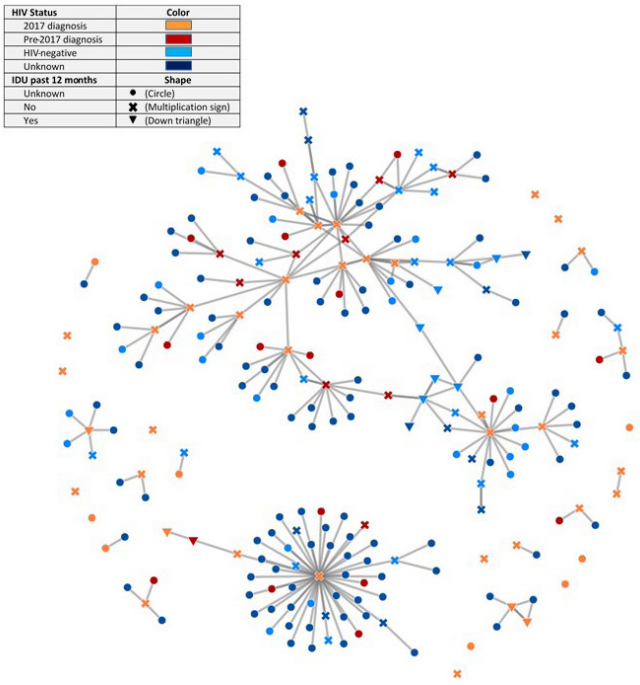
[1]West Virginia Department of Health and Human Resources, Charleston, WV, USA, [2]CDC, Atlanta, GA, USA

Background: In 2017, WV diagnosed 45 HIV infections in 15 largely rural, geographically contiguous counties with historically low HIV prevalence. Based on population characteristics associated with high levels of injection opioid use, CDC identified these counties as highly vulnerable to rapid dissemination of HIV. Nearly all are among the most vulnerable 5% of U.S. counties, and 3 are among the 20 most vulnerable. Initial case review indicated most 2017 diagnoses were attributable to male-to-male sexual contact; we investigated potential for bridging of HIV transmission to persons who inject drugs.

Methods: From October 16–November 9, 2017, we intensified contact tracing efforts in the 15 counties by eliciting an expanded network of contacts and asking detailed questions about current injection drug use (IDU) behavior. First, persons diagnosed in 2017 were interviewed about past year risk behaviors and contacts (sexual, IDU, and social). We then tested their contacts (1st-generation contacts) for HIV and, regardless of their HIV status, assessed risk behaviors and elicited contacts (2nd-generation contacts). We also tested and interviewed 2nd-generation contacts.

Results: Of 45 persons diagnosed in 2017, 87% were male, 60% were 20–29 years old, 67% were white, and 60% likely acquired HIV through male-to-male sexual contact. Only 27% had lab-confirmed viral suppression (<200 copies/mL). Persons diagnosed in 2017 named 190 unique 1st- and 2nd-generation contacts; 14% were diagnosed with HIV before 2017, 27% tested HIV-negative, and 59% had unknown status (Figure 1). We interviewed 84 persons: 38 diagnosed in 2017 and 46 1st- (n=30) or 2nd-generation (n=16) contacts. Overall, 13/84 (15%) injected drugs in the past year, including 4 diagnosed in 2017, 4 1st-generation contacts, and 5 2nd-generation contacts. Among those diagnosed in 2017 who were interviewed and not virally suppressed, 63% (n=17/27) had ≥1 sexual or IDU contact with negative or unknown HIV status. Of those, 3 (18%) injected drugs and shared equipment in the past year, and 2 (12%) others had ≥1 partners who reported injecting drugs and sharing equipment in the past year.

Conclusion: While most 2017 HIV diagnoses in these rural WV counties were attributable to male-to-male sexual contact, we identified potential for HIV transmission through IDU risk behavior. In the context of the rural opioid epidemic in the US, timely public health response to clusters of HIV infection in low prevalence populations is critical to prevent HIV outbreaks.



977 EVALUATING THE USE OF SYPHILIS PARTNER SERVICES FOR HIV CASE FINDING IN MISSISSIPPI

Tigran Avoundjian[1], James Stewart[2], David Peyton[2], Christie Lewis[2], Kendra Johnson[2], Sara N. Glick[1], Matthew R. Golden[1], Christine M. Khosropour[1]

[1]University of Washington, Seattle, WA, USA, [2]Mississippi State Department of Health, Jackson, MS, USA

Background: Mississippi (MS) has one of the highest rates of new HIV infections in the United States. HIV incidence in MS has continued to increase since 2012 despite national decreases. Health departments throughout the US routinely provide partner services (PS) to persons with early syphilis, and many integrate partner HIV testing into those efforts. We evaluated the HIV case-finding effectiveness of syphilis PS in MS.

Methods: We used MS Department of Health (MSDH) STD surveillance data to identify new cases of early syphilis (primary, secondary, and early latent) reported from July 1, 2014 through December 31, 2016, excluding cases with a new HIV diagnosis at the time of syphilis diagnosis. MSDH routinely contacts sexual partners of early syphilis cases to conduct interviews, provide syphilis and HIV testing, and link to treatment. A partner was considered a new case of

early syphilis if their final disposition indicated they had primary, secondary, or early latent syphilis. We defined a partner as a new HIV case if they had a final disposition code for new HIV diagnosis or a positive HIV lab in the MSDH laboratory database within 30 days after being named as a partner and no evidence of a previous HIV diagnosis in MSDH's HIV surveillance database. We calculated the number needed to interview (NNTI) as the number of syphilis index cases interviewed divided by the number of new cases of early syphilis or HIV identified among partners.

Results: We identified 1619 index cases of early syphilis, of whom 1592 (98%) were interviewed for PS. These index cases named 2267 partners, of whom 1868 (82%) were contacted by MSDH. 1508 (81%) partners were tested for syphilis. 745 (56%) of the 1,321 partners who were not previously HIV diagnosed were tested for HIV. PS identified 696 new cases of early syphilis and 25 new cases of HIV. Overall, 64 index case interviews were needed to identify one new case of HIV among partners, and 2 interviews were needed to identify one new case of syphilis among partners (Table). The NNTI for HIV was lowest among index cases who were HIV positive, men who have sex with men (MSM), or Black/African American. Among those tested for HIV, about 1 in 16 MSM partners of syphilis cases tested newly HIV positive.

Conclusion: Syphilis PS allowed MSDH to interact with 1592 MSM over a 30 month period and was effective for identifying new cases of early syphilis and HIV, especially among MSM. Increasing HIV testing among partners of syphilis cases could increase HIV case finding in MS.

Table: Syphilis Partner Services Outcomes by Index Case Characteristics

Index Case Characteristics	Early Syphilis Infections	Partners Tested for Syphilis	New Syphilis Cases (%)[1]	NNTI for Syphilis	Partners Tested for HIV	New HIV Cases (%)[2]	NNTI for HIV
Total	1619	1508	696 (46.15%)	2.29	745	25 (3.34%)	63.68
Gender							
MSM	925	853	412 (48.30%)	2.21	357	23 (6.44%)	39.7
MSW	355	276	119 (43.11%)	2.90	149	1 (0.67%)	345
Women	339	379	165 (43.54%)	2.02	239	1 (0.42%)	334
HIV Status							
Negative/Unknown	1085	1182	527 (44.59%)	2.03	669	11 (1.64%)	97.09
Previous Positive	534	326	169 (51.84%)	3.10	89	14 (15.73%)	37.43
Race							
Black	1257	1162	540 (46.47%)	2.28	576	23 (3.99%)	53.74
White	254	259	123 (47.49%)	2.05	123	2 (1.63%)	126
Other	108	87	33 (37.93%)	3.15	46	0 (0.00%)	-

Abbreviations: MSM = Men who have sex with men; MSW = Men who have sex with women; NNTI = Number needed to interview
[1]Among partners tested for syphilis
[2]Among partners tested for HIV

978 ESTIMATED PRIMARY & SECONDARY SYPHILIS RATES IN MSM BY HIV STATUS – 34 STATES, 2014

Jeremy A. Grey, Elizabeth A. Torrone, Sarah E. Kidd, Kyle T. Bernstein, Hillard S. Weinstock
CDC, Atlanta, GA, USA

Background: Men who have sex with men (MSM) account for the majority of reported cases of primary and secondary (P&S) syphilis in the United States. In 2016, approximately half of MSM diagnosed with P&S syphilis were known to be living with diagnosed HIV infection; however, because MSM population size and HIV prevalence vary by state, comparing case counts without denominators may not accurately reflect the burden of disease. Thus, we present the first estimates of P&S syphilis rates among MSM by HIV status.

Methods: Using national syphilis case report data from 2014, which included information on sex, sex of sex partner(s) and HIV status, we identified the number of reported P&S syphilis cases among MSM by HIV status. We restricted our analysis to 34 states able to classify ≥70% of P&S syphilis cases as women, MSM, or men who have sex with women only. Using state-level population estimates of MSM and estimates of the number of MSM living with diagnosed HIV infection (2014), we calculated state-specific rates of P&S syphilis among MSM living with diagnosed HIV and rates among MSM who are either HIV-negative or who do not know their HIV status. Rate ratios between these two groups were also calculated for each state.

Results: In the 34 states included in the analysis, the rate of P&S syphilis among MSM living with diagnosed HIV infection was 8 times the rate among MSM who were HIV-negative/unknown (1,203 vs. 155 per 100,000 MSM). Rates of reported P&S syphilis were higher among MSM living with diagnosed HIV infection in 33 states; one state reported no P&S syphilis among HIV-positive MSM in 2014 (Table). Ratios of reported P&S syphilis rates ranged from 1.5 to 20.9.

Conclusion: Rates of P&S syphilis were consistently higher among MSM known to be living with diagnosed HIV compared to MSM not know to be HIV-infected; however, the magnitude of the difference varied substantially across states. Observed differences may be a result of increased incidence among HIV-positive MSM, as well as increased case detection through routine syphilis screening among MSM in HIV care. Similarity between HIV-positive and HIV-negative MSM – lower rate ratios – may indicate areas where there is more sexual mixing among individuals of different HIV serostatus. These findings highlight the intersection between HIV and syphilis and the need to examine local epidemiology to inform targeted interventions.

Table. Number and estimated rates of reported primary and secondary (P&S) syphilis cases among men who have sex with men (MSM), by HIV status – 34 states, 2014

State	Number of MSM			Number of Reported P&S Syphilis Cases in MSM, 2014		Estimated Rates of Reported P&S Syphilis Cases in MSM, 2014		Ratio of Estimated Rates of Reported MSM P&S Syphilis Cases, by HIV Status
	Total	Living with Diagnosed HIV Infection	HIV Negative or Unknown HIV Status	Living with Diagnosed HIV Infection	HIV Negative or Unknown HIV Status	Living with Diagnosed HIV Infection	HIV Negative or Unknown HIV Status	
Alabama	44,253 (32,373, 59,162)	6,701	37,552 (25,672, 52,461)	38	34	567.1	90.5 (64.8, 132.4)	6.26 (4.28, 8.75)
Arizona	99,324 (67,450, 140,189)	9,532	89,792 (57,918, 130,657)	194	233	2,035.2	259.5 (178.3, 402.3)	7.84 (5.06, 11.41)
Arkansas	19,039 (12,156, 29,006)	2,994	16,045 (9,162, 26,012)	11	40	367.4	249.3 (153.8, 436.6)	1.47 (0.84, 2.39)
California	712,890 (486,851, 1,002,716)	85,387	627,503 (401,464, 917,329)	995	1296	1,165.3	206.5 (141.3, 322.8)	5.64 (3.61, 8.25)
Colorado	106,583 (70,557, 155,433)	7,692	98,891 (62,865, 147,741)	56	88	728.0	89.0 (59.6, 140.0)	8.18 (5.20, 12.22)
Connecticut	33,324 (17,599, 59,722)	3,202	30,122 (14,397, 56,520)	22	37	687.1	122.8 (65.5, 257.0)	5.59 (2.67, 10.50)
Florida	399,497 (300,885, 512,937)	49,530	349,967 (251,355, 463,407)	650	546	1,312.3	156.0 (117.8, 217.2)	8.41 (6.04, 11.14)
Georgia	143,107 (105,630, 189,181)	26,964	116,143 (78,666, 162,217)	411	256	1,524.3	220.4 (157.8, 325.4)	6.92 (4.68, 9.66)
Hawaii	20,348 (11,870, 33,595)	1,972	18,376 (9,898, 31,623)	14	35	709.9	190.5 (110.7, 353.6)	3.73 (2.01, 6.41)
Illinois	217,082 (136,959, 331,680)	20,687	196,395 (116,272, 310,993)	255	204	1,232.7	103.9 (65.6, 175.5)	11.87 (7.03, 18.79)
Indiana	70,021 (44,284, 107,305)	6,153	63,868 (38,131, 101,152)	58	65	942.6	101.8 (64.3, 170.5)	9.26 (5.53, 14.67)
Iowa	16,898 (9,450, 29,032)	1,375	15,523 (8,075, 27,657)	21	30	1,527.3	193.3 (108.5, 371.5)	7.90 (4.11, 14.08)
Kansas	19,443 (11,714, 30,996)	1,725	17,718 (9,989, 29,271)	9	18	521.7	101.6 (61.5, 180.2)	5.14 (2.90, 8.48)
Kentucky	52,153 (38,374, 69,934)	3,999	48,154 (34,375, 65,935)	46	44	1,150.3	91.4 (66.7, 128.0)	12.59 (8.99, 17.24)
Louisiana	46,638 (34,500, 61,566)	9,004	37,634 (25,496, 52,562)	135	128	1,499.3	340.1 (243.5, 502.0)	4.41 (2.99, 6.16)
Michigan	113,913 (72,341, 173,272)	9,044	104,869 (63,297, 164,228)	131	150	1,448.5	143.0 (91.3, 237.0)	10.13 (6.11, 15.86)
Mississippi	20,054 (12,943, 31,554)	4,522	15,532 (8,421, 27,032)	47	77	1,039.4	495.8 (284.8, 914.4)	2.10 (1.14, 3.65)
Missouri	73,040 (46,203, 111,339)	7,713	65,327 (38,490, 103,626)	96	108	1,244.7	165.3 (104.2, 280.6)	7.53 (4.44, 11.94)
Montana	11,386 (5,998, 21,926)	315	11,071 (5,683, 21,611)	1	3	317.5	27.1 (13.9, 52.8)	11.72 (6.01, 22.87)
Nebraska	11,427 (6,357, 19,669)	1,114	10,313 (5,243, 18,555)	12	18	1,077.2	174.5 (97.0, 343.3)	6.17 (3.14, 11.10)
New Jersey	83,641 (44,342, 148,529)	12,863	70,778 (31,479, 135,666)	67	115	520.9	162.5 (84.8, 365.3)	3.21 (1.43, 6.14)
New Mexico	25,326 (14,892, 41,314)	2,034	23,292 (12,858, 39,280)	22	64	1,081.6	274.8 (162.9, 497.7)	3.94 (2.17, 6.64)
Ohio	148,891 (94,568, 226,187)	12,568	136,323 (82,000, 213,619)	195	138	1,551.6	101.2 (64.6, 168.3)	15.33 (9.22, 24.02)
Oklahoma	41,360 (30,866, 54,564)	3,397	37,963 (27,269, 51,167)	44	55	1,295.3	144.9 (107.5, 201.7)	8.94 (6.42, 12.05)
Pennsylvania	117,658 (63,085, 205,628)	12,742	104,916 (50,343, 192,886)	179	180	1,404.8	171.6 (93.3, 357.5)	8.19 (3.93, 15.05)
Rhode Island	16,778 (8,838, 30,022)	993	15,785 (7,845, 29,029)	13	37	1,309.2	234.4 (127.5, 471.6)	5.59 (2.78, 10.27)
South Carolina	33,912 (22,422, 50,285)	7,588	26,324 (14,834, 42,697)	105	86	1,383.8	326.7 (201.4, 579.7)	4.24 (2.39, 6.87)
South Dakota	4,288 (2,324, 7,665)	189	4,099 (2,135, 7,476)	0	5	0.0	122.0 (66.9, 234.2)	
Tennessee	83,935 (62,938, 108,567)	9,039	74,896 (53,899, 99,528)	69	86	763.4	114.8 (86.4, 159.6)	6.65 (4.78, 8.83)
Texas	466,810 (347,919, 606,839)	45,557	421,253 (302,362, 561,282)	531	499	1,165.6	118.5 (88.9, 165.0)	9.84 (7.06, 13.11)
Utah	31,678 (21,262, 45,469)	1,550	30,128 (19,712, 43,919)	14	13	903.2	43.1 (29.6, 65.9)	20.93 (13.70, 30.51)
Virginia	126,309 (93,937, 165,679)	11,695	114,614 (82,242, 153,984)	116	85	991.9	74.2 (55.2, 103.4)	13.37 (9.60, 17.97)
Washington	132,478 (90,055, 187,533)	7,976	124,502 (82,079, 179,557)	116	133	1,454.4	106.8 (74.1, 162.0)	13.61 (8.98, 19.63)
West Virginia	12,933 (8,309, 19,691)	1,034	11,899 (7,275, 18,657)	5	9	483.6	75.6 (48.2, 123.7)	6.39 (3.91, 10.02)

979 HIGHER RISK AND VULNERABILITY BUT LOWER HIV/SYPHILIS COINFECTION IN THAI TG THAN MSM

Akarin Hiransuthikul[1], Nanthika Prawepray[2], Supab Pengpum[2], Ratchadej Reankhomfu[3], Phubet Panpet[4], Nopparat Mahachokchai[4], Saman Sumalu[5], Pornpichit Brutrat[5], Thanthip Sungsing[1], Jureeporn Jantarapakde[1], Deondara Trachunthong[1], Sutinee Charoenying[6], Praphan Phanuphak[1], Ravipa Vannakit[7], Nittaya Phanuphak[1]
[1]Thai Red Cross AIDS Research Center, Bangkok, Thailand, [2]Sisters Foundation, Chon Buri, Thailand, [3]Caremat Organization, Chiang Mai, Thailand, [4]Rainbow Sky Association of Thailand, Bangkok, Thailand, [5]Service Workers In Group Foundation, Bangkok, Thailand, [6]FHI 360, Bangkok, Thailand, [7]United States Agency for International Development, Washington, DC, USA

Background: Men who have sex with men (MSM) and transgender women (TG) are at increased risk for HIV and sexually transmitted infections (STIs). We aimed to determine the differences in prevalence and associated factors of HIV/syphilis coinfection between HIV-infected MSM and TG.

Methods: Thai MSM and TG adults from 6 community-based organizations in Thailand enrolled into a Test and Treat cohort study and completed a baseline demographic, behavior risk assessment, and HIV/STIs testing. Syphilis testing used a 2-step algorithm with venereal disease research laboratory and if reactive, Treponemal pallidum haemagglutination. Pharyngeal and anal swab, and urine for gonorrhea and chlamydia nucleic acid amplification testing were collected. Logistic regression was used to determine factors associated with HIV/syphilis coinfection.

Results: Among 1862 MSM and 787 TG, 17.8% of MSM and 8.9% of TG were HIV-positive ($p<0.001$), 4.7% of MSM and 0.8% of TG had HIV/syphilis coinfection ($p<0.001$), 13.2% of MSM and 8.1% of TG had HIV infection only ($p<0.001$), 5.2% of MSM and 2.8% of TG had syphilis infection only ($p=0.006$), and 77% of MSM and 88.3% of TG had neither infection ($p<0.001$). Of 402 HIV-positive participants (332 MSM and 70 TG), 87 MSM (26.2% of HIV-positive MSM) and 6 TG (8.6% of HIV-positive TG) had HIV/syphilis coinfection ($p=0.001$). Compared to HIV-positive MSM, HIV-positive TG reported more vulnerability and behavioral risk characteristics: lower educational level (87.1% vs 62.2% with high school or less, $p<0.001$); currently work in entertainment venue (41.8% vs 22.7%, $p=0.001$); had first sexual intercourse at ≤15 year-old (24.3% vs 14%, $p=0.033$); had >3 male sexual partners in the past 6 months (54% vs 36.7%, $p=0.023$); and used non-injected illicit drugs in the past 6 months (49.3% vs 35.5%, $p=0.033$). However, HIV-positive TG had higher mean baseline CD4 cell count compared to MSM (438 vs 377 cells/μL, $p = 0.017$). Factors associated with HIV/syphilis coinfection were being MSM (adjusted odd ratio [aOR] 5.67; 95%CI

1.57-20.43, p=0.008), had group sex in the past 6 months (aOR 2.25; 95%CI 1.01-5.05, p=0.049) and chlamydial coinfection (aOR 2.12; 95%CI 1.12-4, p=0.021).
Conclusion: In this cohort, syphilis coinfection was 3 times higher among HIV-positive MSM than among TG despite TG reported riskier behaviors and higher vulnerability. This suggests that other factors such as sexual networks and biological factors of TG need to be explored to improve the targeting of HIV and STI prevention programs.

980 GAPS IN STI PREVENTION AMONG NIGERIAN MSM ADHERENT TO ART

Rebecca G. Nowak[1], Trevor Crowell[2], Andrew Mitchell[1], Teclaire Ndomb[3], Babajide Keshinro Keshinro[4], Sheila A. Peel[2], Charlotte A. Gaydos[5], Julie Ake[2], William Blattner[1], Stefan Baral[5], Man Charurat[1]
[1]University of Maryland, Baltimore, MD, USA, [2]US Military HIV Research Program, Silver Spring, MD, USA, [3]Institute of Human Virology Nigeria, Abuja, Nigeria, [4]Walter Reed Program–Nigeria, Abuja, Nigeria, [5]The Johns Hopkins University, Baltimore, MD, USA

Background: Once diagnosed with HIV, men who have sex with men (MSM) consistently show a decrease in the potential for onward HIV transmission through modifying sexual practices and engaging in antiretroviral therapy (ART). These health outcomes may also parallel a lower risk of developing bacterial sexually transmitted infections (STIs). Our objective was to evaluate whether engagement in care as quantified by the HIV cascade was associated with fewer incident rectal and urethral STIs among MSM of the TRUST/RV368 cohort study.
Methods: From March 2013-August 2017, all HIV-positive patients were offered ART at baseline and were tested every 3 months for Chlamydia trachomatis (CT) and/or Neisseria gonorrhoeae (NG). Patients with a first negative STI result and a subsequent test result were included in the analysis (n=572) and further categorized by position in the cascade (47 ART-naïve; 365 ART initiated, 160 suppressed). Viral suppression was defined as more than 6 months below the limit of detection (<20copies/ml). STI incidence could occur repeatedly as long as a positive followed a negative diagnosis with incidence rates (IR) per 100-person years calculated using Poisson modelling. Cox proportional hazards modelling estimated hazard ratios (HR) after adjusting for baseline age, time-varying condomless sex, time-varying number of sexual partners, and wave of recruitment.
Results: Median age was 25 years (interquartile range: 22-29). Mean (SD) months of follow-up varied by position in the cascade [ART-naïve: 7.4 (6.4), ART-initiated: 15.7 (9.1), suppressed: 19.9 (9.1)]. Crude incidence rates of rectal NG and CT per 100 person-years (PY) were 3-5 times higher than urethral NG and CT (Table 1). After adjusting for changes in sexual practices, there were no significant differences in the incidence rates of STIs by position in the HIV care cascade. The small amount of observed person-time for those not starting ART may have limited our ability to detect modest differences in the incidence rates between the suppressed and ART-naïve group.
Conclusion: These data suggest that achieving viral suppression among MSM does not parallel a reduction in STI-related risk practices. Considering novel approaches such as increased condom choice, improved lubricants, and potentially presumptive treatment for those at higher risk of STIs may help curtail further transmission.

		Rectal NG	Rectal CT	Urethral NG	Urethral CT
Incidence Rate per 100 PY	Cascade				
	Suppressed	26.55	22.05	3.54	7.13
	ART-initiated	32.38	25.73	3.67	6.06
	ART-naïve	39.94	35.12	6.44	11.99
Crude HR (95% CI)	Cascade				
	Suppressed	Ref.	Ref.	Ref.	Ref.
	ART-initiated	1.2 (0.9-1.6)	1.1 (0.8-1.5)	1.0 (0.5-2.2)	0.8 (0.5-1.4)
	ART-naïve	1.3 (0.6-2.6)	1.3 (0.7-2.6)	1.8 (0.4-9.1)	1.4 (0.5-4.1)
	Age (years)				
	25+	Ref.	Ref.	Ref.	Ref.
	<25	**2.1 (1.6-2.8)**	**1.7 (1.2-2.2)**	1.5 (0.7-3.0)	1.2 (0.7-2.0)
	Condomless sex				
	No	Ref.	Ref.	Ref.	Ref.
	Yes	**1.6 (1.1-2.2)**	1.4 (1.0-2.1)	**2.9 (1.3-6.6)**	0.6 (0.2-1.8)
	No. recent partners				
	0-1	Ref.	Ref.	Ref.	Ref.
	2+	**2.0 (1.5-2.7)**	**1.8 (1.3-2.6)**	2.0 (0.9-4.4)	0.6 (0.3-1.3)
Adjusted HR* (95% CI)	Cascade				
	Suppressed	Ref.	Ref.	Ref.	Ref.
	ART-initiated	1.0 (0.8-1.4)	1.0 (0.7-1.4)	0.9 (0.4-1.9)	0.8 (0.4-1.3)
	ART-naïve	1.0 (0.5-1.9)	1.2 (0.6-2.5)	1.1 (0.2-5.6)	1.4 (0.5-4.1)
	Age (years)				
	25+	Ref.	Ref.	Ref.	Ref.
	<25	**1.9 (1.5-2.6)**	**1.6 (1.2-2.2)**	1.7 (0.8-3.5)	1.1 (0.7-1.9)
	Condomless sex				
	No	Ref.	Ref.	Ref.	Ref.
	Yes	1.1 (0.8-1.6)	1.1 (0.8-1.7)	2.1 (0.9-5.9)	0.7 (0.2-2.3)
	No. recent partners				
	0-1	Ref.	Ref.	Ref.	Ref.
	2+	**1.8 (1.3-2.4)**	**1.5 (1.1-2.1)**	1.7 (0.7-4.4)	0.7 (0.3-1.6)

ART, antiretroviral therapy; CT, *Chlamydia trachomatis*; CI, confidence interval; NG, *Neisseria gonorrhoeae*; No., number; HR, hazard ratio; PY, person-years.
*Andersen-Gill model adjusted for age, condomless sex, number of sexual partners, and wave of recruitment. Covariates for condomless sex and number of sexual partners were stratified as insertive or receptive according to nature of STI (receptive for rectal; insertive for urethral).
Bolding indicates $p<0.05$.

981 HIGH HIV-1 INCIDENCE RATE AMONG ADULTS ATTENDING STI CLINICS IN SOUTHERN MALAWI

Fatima G. Zulu[1], Isaac Singini[2], Dean Soko[3], Treaser Thomas[4], Johnstone Kumwenda[3], **Newton I. Kumwenda**[5]
[1]CDC Malawi, Lilongwe, Malawi, [2]University of Cape Town, Cape Town, South Africa, [3]Malawi College of Medicine-Johns Hopkins University Research Project, Blantyre, Malawi, [4]University of Malawi, Blantyre, Malawi, [5]Johns Hopkins University, Baltimore, MD, USA

Background: Knowing HIV incidence rate in a population is critical to the strategy of "'know your epidemic" for effective planning interventions against the epidemic. The objective of our study was to determine HIV incidence rate and risk factors among adults seeking STI care in three districts in Southern Malawi
Methods: Between 2010 and 2013, HIV negative adults seeking STI care at clinics in Blantyre, Mulanje and Mwanza in Southern Malawi were enrolled in a prospective cohort study. At baseline, after HIV pre and posttest counseling, HIV negative individuals on rapid tests were consented to participate. Venous blood sample was tested for Acute HIV Infection (AHI) using RNA PCR. Data on demographics, sexual behavior, socioeconomic and health status were collected through direct interviews. At follow-up (FU) (every 3 months), venous blood was collected for HIV testing. Rapid test HIV positive results were confirmed using Western Blot (WB). Viral load (VL) was measured by RNA PCR among seroconverters. HIV Incidence rate was calculated by deviding number of HIV seroconversions observed by the follow–up duration in person-years (pys). After univariate analysis and adjustment with multivariate analysis, using the Cox Proportional Hazard model (HR), independent risk factors were identified. Chi-square or Fischer exact test for categorical and t-test for continuous variables were used to test differences among groups.
Results: Preliminary results for Blantyre were previously reported at CROI in 2015. 1055 HIV negative adults were enrolled and followed up, 57% were females, mean age was 28.0 (range18 - 52). Overall, FU duration was 1813 pys and 76 seroconverted, the incidence rate was 4.2 [95%CI; 3.17-5.09] per 100 pys. In Mulanje district, 500 HIV negative adults were followed up for 835 pys and 21 seroconverted, the incidence rate was about 2.51 [95% CI, 1.48-4.38] per 100 pys. In Mwanza, 408 HIV negative adults were followed up for 600 pys, 12 seronconverted and the incidence rate was 1.9 per 100 pys. On multivariate analysis; having more than 2 sexual partners [HR=2.5: (95% CI; 1.3-4.8)], engaging in transactional sex [HR=2.1: 95% CI,1.4-3.2] and reporting ever using a male condom (HR=1.5: 95% CI, 0.9-2.4] were all independently associated

with new HIV infection. However, reporting being married showed to be protective [HR=0.6: 95% CI 0.4-0.9]

Conclusion: HIV incidence rate is high in this population in southern Malawi and special intervention efforts are needed to stem the epidemic in Malawi

982 GAPS ALONG THE PrEP CONTINUUM AMONG STD CLINIC ATTENDING MSM WITH HIGH RISK BEHAVIORS

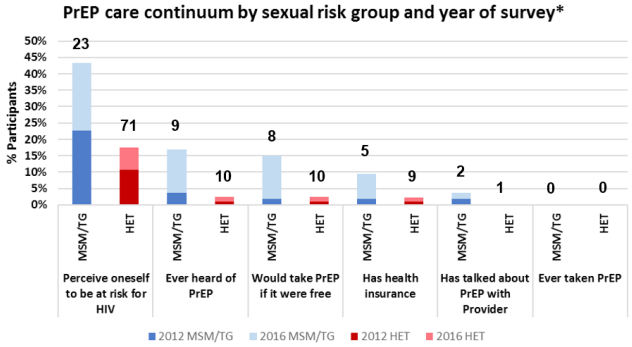
Farah Mouhanna[1], Amanda D. Castel[1], Kerri Dorsey[1], Meredith Haddix[1], Anya Agopian[1], Hannah Yellin[1], Hibo Abdi[1], Michael Kharfen[2], Irene Kuo[1]
[1]George Washington University, Washington, DC, USA, [2]District of Columbia Department of Health, Washington, DC, USA

Background: The Pre-exposure Prophylaxis (PrEP) care continuum is a measurement tool developed to monitor PrEP implementation and identify areas in need of additional scale up. We sought to compare differences in knowledge, attitudes, and use of PrEP among MSM and transgender male-to-females (TG) compared to females and heterosexual males (HET) and trends over time.

Methods: A convenience sample of 460 STD clinic attendees in Washington DC were surveyed in 2012 (n=174) and 2016 (n=286). Demographics, self-reported risk behaviors, and self-perceived risk were measured. Stages of the PrEP continuum were assessed ranging from 'self-perceived HIV risk' to 'have taken PrEP'. Uni-, and bivariate analyses were conducted to assess for differences in populations, risk behaviors, and PrEP continuum outcomes. Multivariate analyses were done adjusting for survey year, race, insurance, income, number of casual partners, HIV tests in the last year, and having heard of and used post-exposure prophylaxis (PEP).

Results: Among 460 participants, 53 (12%) were MSM/TG, 81% were Black, 21% had private insurance, 49% had some college education, and 60% had a regular healthcare provider. Comparing MSM/TG participants to HET, significant differences were observed by race, insurance, and income (all p<0.05). MSM/TG participants had more casual sex partners (OR 1.12; 95%CI:1.06-1.18), and were more likely to be at the STD clinic due to symptoms (OR 2.15; 95%CI:1.01-4.58), or having a partner with an STD (OR 5.07; 95%CI:1.86-13.83), had heard of PEP (OR 5.05; 95%CI:2.79-9.14) and used PEP (OR 11.08; 95%CI:3.33-36.84) compared to HET. In terms of the PrEP continuum, while MSM/TG participants had higher self-perceived risk for HIV (43% vs. 18%, aOR 3.79; 95%CI:1.47-9.82), there were no significant differences in having heard of PrEP (38% vs. 12%, aOR 2.41; 95%CI:1.00-5.83), likelihood of taking PrEP if it were free (68% vs. 54%, aOR 1.84; 95%CI:0.76-4.46), having health insurance (78% vs. 77%, aOR 0.68; 95%CI: 0.24-1.89), having discussed PrEP with a provider (11% vs. 3%, aOR 1.37; 95%CI:0.31-6.16), and having used PrEP (8% vs. 0.7%, aOR 3.06; 95%CI: 0.40-23.32) compared to HET (Figure). PrEP awareness (18% vs. 29%; p=0.0138) and use (0.6% vs. 2.5%; p<0.0001) increased from 2012 to 2016.

Conclusion: PrEP awareness and use was low among both groups, with minor increases over time. PrEP education and risk-reduction programs should be implemented in STD clinics to facilitate high-risk groups' advancement along the PrEP continuum.



*The proportion of MSM/TG and HET in each step of the continuum is contingent upon cumulatively meeting all previous steps of the continuum.
In 2012, of the 174 participants, 21 were MSM/TG and 153 were HET.
In 2016, of the 286 participants, 32 were MSM/TG and 254 were HET.

983 COMMUNITY-BASED SERVICES REACH LARGE VOLUMES OF HIGH RISK MEN IN TANZANIA

Caterina Casalini[1], Dorica Boyee[1], Amasha Mwanamsangu[1], Magnus Ndolichimpa[1], Yeronimo Mlawa[2], Peris Urasa[3], Neema Makyao[3], Erick Mlanga[4], Nelson Rutabanzibwa[1], Benjamin Myovela[1], Anike Akridge[4], Albert Komba[1], Jason Reed[1], Kelly Curran[1]
[1]Jhpiego, Dar es Salaam, Tanzania, United Republic of, [2]EngenderHealth, Dar es Salaam, Tanzania, United Republic of, [3]National AIDS Control Program, Dar es Salaam, Tanzania, United Republic of, [4]USAID Tanzania, Dar es Salaam, Tanzania, United Republic of

Background: Population-based HIV Impact Assessments in African countries show that men are under-represented in the 90-90-90 cascade. In Tanzania, UNAIDS estimates that as of 2016, 70% of PLHIV had been diagnosed, with a smaller proportion of men knowing their HIV status as compared to women (PEPFAR, 2017), increasing the likelihood of transmitting HIV to uninfected women. USAID-funded Tanzania's Sauti Project provides community-based combination HIV prevention, testing and linkage services to key and vulnerable populations including partners of female sex workers (PFSW) and other men at Hotspots (OMHS).

Methods: We analyzed routine program data from Sauti services between August 2015 and July 2017 to determine the volume of tests provided to men and characterize males testing for HIV. Male PFSW were defined as having paid for sex within past 12 months. OMHS were defined as men reached in areas of high HIV transmission risk. Men reporting sex with men were excluded. Binomial logistic regression was used for the analysis.

Results: Nearly half of the 1,026,358 individuals tested for HIV (482,925 or 47.1%) were men: 30.4% were PFSW; 53.4% were ages 20-35 years; 54.6% were married; 37.3% never used condom in the past three vaginal sex acts, 21% reported anal sex, among whom 40.7% never used condom in the last three anal sex acts; 50.7% did not know the HIV status of the current partner(s). Among 477,890 males receiving an HIV test, 219,046 (45.8%) tested for the first time ever. Among first-time testers, 6,095 (2.8%) tested HIV positive, compared to 6,255 (2.5%) testing positive who had been previously tested for HIV or had an unknown HIV testing history. First time HIV testing was associated with age <20 years (RR: 1.66; 95% CI: 1.25-2.21; p<0.001), being single (RR: 1.27; 95% CI: 1.13-1.43; p<0.001), testing HIV positive (RR: 1.31; 95% CI: 1.07-1.60; p=0.009), and reporting inconsistent condom use with regular/permanent partners (RR: 1.24; 95% CI: 1.01-1.52; p=0.041).

Conclusion: Through community based testing platforms that target PFSW and other males congregating in areas of high HIV incidence, it is possible to reach large volumes of high risk behaviors adult men with HIV testing, including first time testing and diagnosis of new cases of HIV, which is imperative to achieving the first 90 of the 90-90-90 goals. Additional innovations such as HIV self-testing and partner notification services may further expand the number of men reached with testing.

Table 1: Binomial logistic regression to determine factors associated with new HIV testing among men accessed Sauti program services from August 2015 to July 2017 (N=468,480)

Characteristic		Total	New Tester's		Adjusted analysis	
		(N)	n	%	RR [95% CI]	P-value
Age group (yrs)	15-19	34,044	22,613	66.4	Ref	
	20-25	96,728	49,116	50.8	0.69 [0.55-0.86]	0.001
	26-30	96,415	42,704	44.3	0.55 [0.40-0.76]	<0.001
	31-35	64,567	26,600	41.2	0.53 [0.35-0.80]	0.002
	36+	176,726	78,013	44.1	0.58 [0.40-0.83]	0.003
Marital status	Single	163,052	86,999	53.4	Ref	
	Married	263,456	112,325	42.6	0.83 [0.72-0.97]	0.018
	Divorced Widowed	37,994	17,912	47.1	0.85 [0.70-1.04]	0.120
Today HIV results	Positive	12,350	6,095	49.4	Ref	
	Negative	456,130	212,951	46.7	0.75 [0.61-0.92]	0.006
Condom use with permanent, regular partners	Always	25,187	10,676	42.4	Ref	
	Sometimes	152,856	71,521	46.8	1.24 [1.01-1.52]	0.041
	Never	161,846	73,132	45.2	1.38 [1.24-1.54]	<0.001

984 MALE AND ADOLESCENT FIRST-TIME HIV TESTERS REACHED BY COMMUNITY HEALTH INITIATIVE

Hong-Ha M. Truong[1], Dancun O. Obunge[2], Mary A. Guzé[1], Esther Wandera[2], Placide Ntawali[1], Eliud Akama[2], Frankline Otieno[2], Elizabeth A. Bukusi[2], Patrick Oyaro[2], Craig R. Cohen[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]Kenya Medical Research Institute, Kisumu, Kenya

Background: Knowledge of HIV status is the entry point for linkage to prevention, and care and treatment, and the first step towards achieving the UNAIDS 90-90-90 target. In Kenya, HIV testing coverage is lower among men than women and lower among adolescents than older adults, a pattern observed in other sub-Saharan African countries. We characterized persons presenting for first-time HIV testing through a community health initiative facilitating testing and linkage.
Methods: HIV testing and linkage to same-day antiretroviral therapy (ART) initiation were offered at multi-disease community health campaigns (CHCs) conducted in western Kenya. Home-based HIV testing was offered to residents not attending the CHCs. Persons age ≥15 years and sexually-active youth <15 years who had not been previously-diagnosed with HIV were eligible. Differences by first-time and repeat testers were assessed by Fisher's exact test and bivariate logistic regression.
Results: The initiative reached 1,230 first-time testers, representing 13% of 9,465 persons accepting HIV testing and 4.3% of 28,460 persons reached overall. Of first-time testers, 634 (52%) were male and 480 (39%) were adolescents aged 10-19 years, including 272 adolescent males. First-time testers were more likely to be male (p<0.01) and younger (p<0.01) than repeat testers. Overall, 0.98% of first-time testers (12 cases) were newly-diagnosed with HIV compared to 1.25% of repeat testers (103 cases). HIV+ proportion was 1.1% among male first-time testers and 0.9% among male repeat testers. Among testers aged 25-34, HIV+ proportion was higher among first-time [6 of 48 (12.5%)] than repeat [(34 of 1,312 (2.4%)] testers (OR=5.36, p<0.01) and male first-time [4 of 30 (13%)] than repeat [(9 of 533 (2%)] testers (OR=8.96, p<0.01). No adolescent first-time testers were newly-diagnosed. Of 10 new cases identified at CHCs, 7 initiated ART the same day as part of the campaign.
Conclusion: The hybrid approach offering HIV testing at CHCs in combination with follow-up home visits is an effective strategy for reaching first-time testers, particularly adolescent males. The yield of newly-diagnosed HIV cases among males and persons aged 25-34 was higher among first-time testers than repeat testers. Innovative approaches that make HIV testing more accessible and acceptable to the community, such as HIV testing as part of a package of health services, may be critical for reaching populations that might otherwise be reticent to take up standard facility-based testing services.

985 DOOR-TO-DOOR HIV TESTING TO INCREASE ANTIRETROVIRAL THERAPY UPTAKE, WESTERN KENYA

Fredrick Miruka[1], Kawango Agot[2], Spala Ohaga[2], Rose Oyoo[2], **Rachel Joseph**[1], Jonathan Mwangi[3], Jesee N. Nakhumwa[2], Isaac Ngere[4], Paul K. Musingila[1], Hellen Muttai[1]
[1]US CDC Kisumu, Kisumu, Kenya, [2]Impact Research and Development Organization, Kisumu, Kenya, [3]US CDC Nairobi, Nairobi, Kenya, [4]Ministry of Health, Nairobi, Kenya

Background: Identifying and initiating persons with HIV infection on antiretroviral therapy (ART) to achieve viral suppression is critical for epidemic control and improved patient outcomes. A national survey in Kenya in 2012 found that 53% of persons with HIV infection were unaware of their HIV status and 16% had never been tested for HIV. Home-based HIV testing services (HTS) aim to increase access to HIV testing and enable linkage to ART. We describe the demographic characteristics and HIV testing uptake among persons reached by door-to-door HTS conducted in Siaya County, Kenya where estimated HIV prevalence was 25%.
Methods: We conducted a retrospective analysis of routine program data collected from home-based HTS in Siaya County in May 2016–April 2017. HTS was offered to residents aged >15 years according to Kenya guidelines. Those with known HIV status (HIV positive or tested negative ≤3 months prior) were ineligible for testing. SAS v.9.3 was used for exploratory analysis and to test for associations between variables using bivariate and multivariable logistic regression.
Results: In total, 206,435 (90%) of 229,143 residents enumerated were found at home. Of these, 23,220 (11%) had known HIV status. The remaining 183,564 (89%) were eligible for HIV testing; 177,559 (97%) were tested, among whom 7% (12,884) had never been tested, 23% (41,186) were tested >12 months prior, and 69% (123,172) were tested <12 months prior. Of the 22,359 residents away from home, 65% (14,502) were males of whom 65% (9,483) were aged >25 years. Among those tested, the median age was 27 (IQR 19-44) years, and 56% were female. Overall, 1,937 (1.1%) of those tested-1.2% of females and 0.9% of males (p-value 0.063)-were newly HIV-positive. The majority (57%) of HIV infections were detected among persons last tested <12 months ago and among those >35 years of age (43%). However, persons whose last test was >12 months vs. ≤12 months prior (aOR 1.54, 95% CI 1.34-1.77) and those aged 25-34 years vs. >35 years (aOR 1.96, 95% CI 1.67–2.30) were more likely to have a positive test. Overall, 76% (1,480/1,937) of newly HIV-positive residents were linked to ART.
Conclusion: Door-to-door testing increased knowledge of HIV status and identification of new HIV positives although positivity was low in spite of high coverage. Strategies for reaching those missed, at highest risk of acquiring HIV, specifically males aged ≥25 years, and linkage of HIV positive individuals to ART are needed.

986 BARRIERS TO HIV TESTING IN SWAZILAND: EFFECT OF FAMILY SUPPORT AND TRAVEL TIME

Harriet Nuwagaba-Biribonwoha[1], Yingfeng Wu[2], Averie B. Gachuhi[2], Margaret McNairy[2], Matthew R. Lamb[2], Sikhathele Mazibuko[3], Zandile Mnisi[4], Veli M. Madau[1], Sean Burke[1], Neena M. Philip[2], Wafaa M. El-Sadr[2]
[1]ICAP at Columbia University–Swaziland, Mbabane, Swaziland, [2]ICAP at Columbia University, New York, NY, USA, [3]Ministry of Health–Swaziland National AIDS Programme, Mbabane, Swaziland, [4]Ministry of Health, Mbabane, Swaziland

Background: HIV testing and awareness of HIV positive (HIV+) status are the gateway to HIV prevention and treatment. We assessed factors associated with HIV testing among participants in Link4Health, a cluster-randomized study evaluating the effect of a combination strategy on linkage to- and retention in-care after an HIV+ test in Swaziland.
Methods: Adults ≥18 years (y), newly tested HIV+ were recruited into the study from Aug-2013 to Nov-2014. We analysed baseline study data for 1) history of prior HIV testing and 2) self-report of awareness of HIV+ status prior to the study baseline HIV+ test. We assessed demographic and structural factors associated with testing e.g. age, sex, family support received, and travel time to clinic. Hierarchical logistic regression models with study sites as random effects were used to generate raw and adjusted odds ratios [AOR, 95% Confidence Intervals] for covariates of HIV testing.
Results: Of 2,196 HIV+ adults [59% female, median age 31y, IQR 26-39], 1183 [53.8%] reported no prior HIV test. The odds of no prior HIV testing were higher among men [AOR 1.7, 1.4-2.0], and among adults who needed more family support [AOR 1.5, 1.2-1.8], versus those who reported needing the same or less family support. Among the 2,196 HIV+ adults, the most common reasons for HIV testing at the study baseline visit were being sick [58%], worry about HIV [34%], and health provider recommendation [15%]. Reasons did not differ by prior HIV testing. Only 248 of 2,196 HIV+ participants [11.3%] were aware of their HIV+ status prior to the study baseline HIV+ test. Men were less likely to be aware of their HIV+ status [AOR 0.7, 0.5-0.9)]. Compared to adults 40-49y, HIV+ youth 18-25y [AOR 0.6, 0.4- 0.95] and older adults 50+y [AOR 0.5, 0.3-0.9] were less likely to be aware of their HIV+ status. Adults who reported needing more family support were less likely to be aware of their HIV+ status [AOR 0.6, 0.5-0.8]. HIV+ participants who lived ≥45 minutes from the clinic were less likely to be aware of their HIV+ status [AOR 0.5, 0.4-0.8], compared to those who lived <45 minutes of the clinic.
Conclusion: About half the HIV+ adults in this study had no history of prior HIV testing and only 1/10 were aware of their HIV+ status. Men, youth, older adults, those needing more family support and those living further from clinics were less likely to be aware of their HIV+ status. Tailored strategies are needed to effectively engage such groups in testing and enable access to relevant services.

987 HIV TESTING IN PRIMARY CARE CLINICS IN SOUTH AFRICA: A MISSED OPPORTUNITY

Bhakti Hansoti[1], Tonderai Mabuto[2], Griffiths Kubeka[2], Salome Charalambous[2], Deanne Kerrigan[1], Chris Hoffmann[1]
[1]Johns Hopkins Hospital, Baltimore, MD, USA, [2]The Aurum Institute, Johannesburg, South Africa

Background: South Africa (SA) has the world's highest burden of HIV infection (approximately 7 million), with the burden of undiagnosed HIV infection

being estimated at 23.5% in women and 31.5% in men. The 2010 national South African HIV testing guidelines mandates the universal offer of testing in all healthcare facilities. Studies have reported that delivery of HIV Testing Services (HTS) struggle due to the requirement of extensive pre-and post-test counselling and a lack of standardized training/supervision.

Methods: A multi-prong approach was use to evaluate the current implementation of HTS in ten primary health care facilities in South Africa (Figure 1). First we conducted patient exit interviews to quantify engagement in HTS services. Second we systematically mapped the flow of individual patients through the clinic. Finally, we audited the clinic documentation of newly diagnosed HIV positive individuals to quantify antiretroviral treatment (ART) initiation.

Results: Of those interviewed 1548 (51.8%) patients reported that they had not received a HIV test in the last 12 months. Overall testing acceptance was high at 84.7% (244) but less then 10% (288) of the patients were offered testing. Female patients were significantly more likely to be offered testing (233, 11.9% vs. 55, 5.8% in males), even though testing acceptance was equal in both sexes (41, 74.6% vs. 203, 87.1%). Value stream mapping revealed that patients undergoing HTS had longer total visit times (160 minutes; IQR 135, 249) compared to those without HTS (119 minutes; IQR 81,197). Patients were usually offered HTS an average of 56 minutes into their care (IQR 27, 82). Accounting for age and gender, patients offered HIV testing had a total visit time of 51 minutes (95% CI: 30-72) more compared to those not offered testing. Of those testing HIV positive, 571 patients (58.8%) had ART initiation documented by 90s days of testing positive, despite a universal test and treat policy.

Conclusion: Despite a national mandate less than 10% of patients were offered HTS in the clinic setting, this represents a missed opportunity especially given that testing acceptance was high. The poor delivery of HTS appears to be due to a failure to recommend HTS and the added time burden placed on those accepting testing. Health system, rather than patient factors need to be addressed to improve HTS delivery.

Figure 1: Facility-based HIV Testing Evaluation Constructs

Location	*In the Clinic*		*ARV Clinic*
Methodology	*Exit Interviews*	*Value Stream Mapping*	*Linkage to Care Chart Review*
Purpose	Record the purpose of visit to the clinic and if HTS offered during visit	Quantify the total time spent in clinic, total time waiting for services and when during the visit HTS is offered/completed.	Audit documentation to quantify ARV initiation and laboratory results post diagnosis.
Data Sources	Patient Survey	Direct Observation	Chart Review
Sampling	All patients that leave the clinic sampled for 2 days	All patients that attend the clinic for one day	HIV positive patients
Head Count	4595		947
Sampled n (%)	2989 (65%)	567	866 (91.4%)

988 HIGH PERCENTAGE OF UNDIAGNOSED HIV CASES IN A HYPER-ENDEMIC SOUTH AFRICAN POPULATION

Alain Vandormael[1], Tulio de Oliveira[1], Frank Tanser[1], Till Bärnighausen[2], Joshua T. Herbeck[3]

[1]University of KwaZulu-Natal, Durban, South Africa, [2]Heidelberg University, Heidelberg, Germany, [3]University of Washington, Seattle, WA, USA

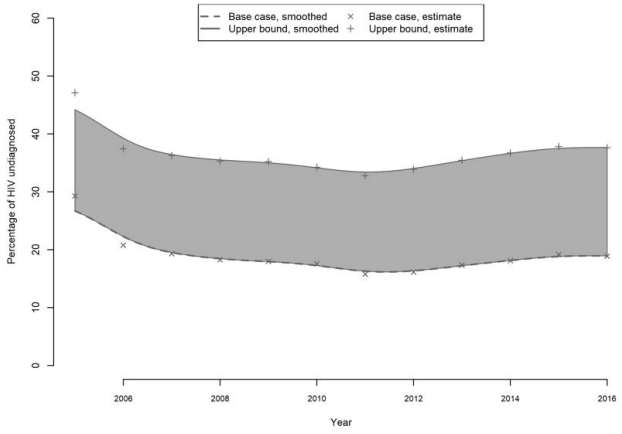
Background: Undiagnosed HIV infections could undermine efforts to reverse the global AIDS epidemic by 2030. In this study, we estimated the percentage of HIV-positive persons who remain undiagnosed within a hyper-endemic South African community.

Methods: The data comes from a population-based surveillance system located in the Umkhanyakude district of the northern KwaZulu-Natal province, South Africa. We annually tested 38,661 adults for HIV between 2005 and 2016. Using the HIV-positive test results of 12,039 (31%) participants, we then back-calculated the incidence of infection and derived the number of undiagnosed cases from this result.

Results: The percentage of undiagnosed HIV cases decreased from 29.3% in 2005 to 15.8% in 2011. During this period, however, approximately 50% of the participants refused to test for HIV, which lengthened the average time from infection to diagnosis. Consequently, the percentage of undiagnosed HIV cases reversed direction and steadily increased from 16.1% to 18.9% over the 2012 to 2016 period.

Conclusion: Results from this hyper-endemic South African setting show that the HIV testing rate is low, with long infection times, and an unsatisfactorily high percentage of undiagnosed cases. A high level of repeat HIV testing is needed to minimize the time from infection to diagnosis if the global AIDS epidemic is to be reversed within the next two decades.

Figure 1: Shows the percentage of undiagnosed HIV cases over the 2005 to 2016 observation period. The dashed line is the base case (BC) estimates and the solid line is the upper bound (UB). The BC assumption places an equal probability of infection on every time point between the latest HIV-negative and earliest HIV-positive test dates, and the UB assumes that the infection date occurs one day after the latest HIV-negative test date.



989 REDUCING TIME FOR HIV VIRAL LOAD RESULT DELIVERY TO ART FACILITIES IN MALAWI

Natasha Gous[1], Frank Chirwa[1], **Jeff Takle**[1], Alan Schooley[2]

[1]SystemOne, Boston, MA, USA, [2]University of California Los Angeles, Los Angeles, CA, USA

Background: HIV viral load (VL) testing is the preferred method for antiretroviral treatment (ART) monitoring in Malawi. Specimens are collected from ~650 facilities, tested at central laboratories and paper-based results are returned by courier to facilities. This results in long turnaround times (TAT) in result receipt (42-90days), delaying and often negating their use for clinical decision-making. Loss of results also occurs; CHAI estimates that only 50% of HIVVL results are returned to referring facilities in Malawi. A solar-powered result terminal was developed to improve the efficiency and TAT of result delivery from centralized laboratories to remote facilities. The terminal is being piloted in Malawi to assess impact.

Methods: Result terminal: Aspect ReporterTM(SystemOne) consists of a.) A small, solar-powered server which receives results over cellular network from HIVVL instruments located centrally; b.) An inexpensive tablet located in the facility displays results on a simple interface. Pilot: Two reference laboratories performing Abbott VL testing were connected to Aspect network. Aspect Reporters were implemented in 12 ART facilities. Analysis: Data from a subset of four ART facilities was collected to compare reliability (% loss of results) and time to result receipt (from test completion to result receipt at facility), pre- and post-installation of Aspect Reporter.

Results: Pre-Aspect: Time points for 79 specimens were collected. Mean time for delivery of paper results from the laboratory to the clinic was 13.5days (SD=10.5). Post-Aspect: Time points for 131 specimens were collected. Mean time for delivery of digital VL results from the laboratory to Aspect server was 0.5days (SD=0.3). For the pilot, an 'artificial', manual approval step was introduced on the server as a check. Mean time to delivery from the server to Aspect Reporter (n=117) was 6.2days (SD=5.9) due to approval. Thus, total mean time to digital result delivery from laboratory to clinic was 6.7days (SD=5.9); 50% reduction compared to paper delivery. Going forward, removal of the 'artificial' approval step will result in a 96% reduction in TAT (0.5days vs 13.5days). Reliability: 10.7% (n=14) results not approved for delivery.

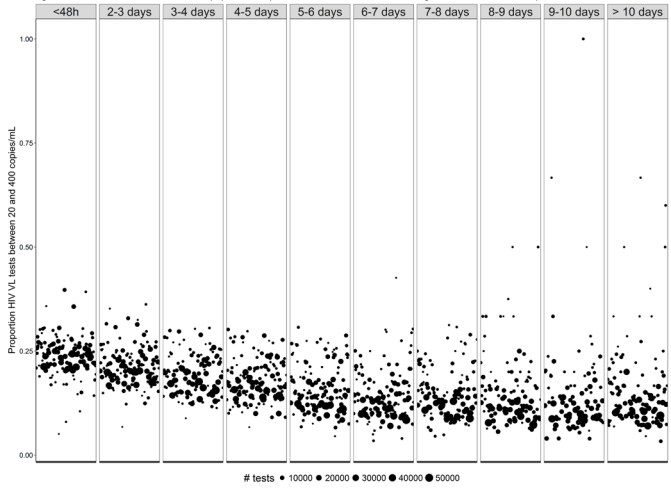
Conclusion: Aspect Reporter improves the time and reliability of result availability at facilities, improving the laboratory-clinical interface and allowing earlier patient management. Aspect Reporter has application for rapid reporting of other laboratory-based results to remote clinics.

990 IMPACT OF TESTING DELAY ON LOW-LEVEL VIRAEMIA IN SOUTH AFRICA: A PROGRAMME-WIDE VIEW

Nei-Yuan M. Hsiao[1], Elton Mukonda[1], Maia Lesosky[1], Jean Maritz[2], Wolfgang Preiser[2], Landon Myer[1]
[1]University of Cape Town, Cape Town, South Africa, [2]Stellenbosch University, Cape Town, South Africa

Background: Low-level viraemia (LLV) can be common in HIV-infected individuals receiving antiretroviral therapy (ART) and had been shown to be associated with risk of virological failure following a period of sustained virological suppression. In large ART programmes where viral load (VL) testing is centralised, delay in sample processing could affect the detection of these LLV due to sample degradation.
Methods: We examined the frequency of LLV in patients on ART in the public health care system of the Western Cape province, South Africa from 2009-2015 using routine laboratory VL data from the South African National Health Laboratory Service. We analysed the proportion of LLV test results by delay in sample processing time (<48h – 10days in 24h increments) over the sample period. The delay in processing is measured by turnaround time (TAT) which is calculated from the estimated time of collection till the time of test completion. LLV is defined as any detectable VL <400 copies/mL, we also calculated the proportion of VL test results falling between 400-1000 copies/mL. Results were stratified by calendar year and healthcare facility size.
Results: We analysed 1,067,153 VL episodes from 509 facilities and identified 209,312 samples with LLV (20%). While the median TAT had significantly reduced from 173 hours in 2009 to 71 hours in 2015, with the exception of 2009, the frequency of LLV detection had remained fairly constant over that period (14% in 2009, 19% in 2010, 22% in 2011, 22% in 2012, 22% in 2013, 22% in 2014 and 20% in 2015). Samples with increased TAT are associated with less frequent detection of LLV. The decrease in detection is observed in sample with TAT>48 hours. While 23.8% of samples tested within first 48 hours had LLV, the proportions of LLV were 21.4%, 20.1%, 19.6% and 17.8% for samples tested on day 3, 4, 5 and 6 respectively. Further delay in testing did not result in significant change in the frequency of LLV. The decrease in LLV detection rate remained despite taking size of facility and calendar years into consideration. These trends were not observed for VL results between 400-1000 copies/mL, with 3% detected in the first 48h compared to 4% on day 6.
Conclusion: The proportion of LLV decreases as TAT increase beyond the first 48 hours, pointing to potential early viral RNA decay due to compromised sample stability prior to plasma separation. As detection of LLV becomes more clinically relevant, the delay in testing should be minimised in large programmes.

Figure 1: Association between turnaround time and proportion of samples with low-level viraemia in medium and large health facilities in Western Cape, South Africa



991 RAPID VS. STANDARD TESTING FOR HIV AND HCV AT A DRUG DETOX: A RANDOMIZED TRIAL

Sabrina A. Assoumou[1], Samantha M. Paniagua[2], Benjamin Linas[1], Jianing Wang[1], Jeffrey H. Samet[2], Jonathan Hall[1], Curt G. Beckwith[3]
[1]Boston Medical Center, Boston, MA, USA, [2]Boston University, Boston, MA, USA, [3]Brown University, Providence, RI, USA

Background: HIV and Hepatitis C virus (HCV) share a common mode of transmission, injection drug use. Some jurisdictions have replaced point-of-care rapid testing (RT) with laboratory-based testing (LBT) to enable use of combined antibody-antigen assays that identify acute HIV cases. While identification of acute HIV cases allows for early intervention, there are potential benefits associated with RT, including immediate test result delivery. To examine differences in HIV and HCV testing approaches in a high-risk population, we conducted a prospective randomized trial of HIV and HCV RT versus LBT at the largest residential detoxification center in the Boston area.
Methods: Eligible participants (not aware of co-infection with HIV and HCV) completed a baseline questionnaire and were randomized to either HIV and HCV RT (Orasure) or LBT (HIV Combo Ag/Ab EIA, HCV EIA). For both groups, RT and specimen collection for LBT were performed by a trained counselor. RT was provided within 20 minutes; LBT results in 2-3 days. The primary outcome was the proportion of test results delivered. Logistic regression was used to determine factors associated with test result delivery.
Results: Among 341 individuals screened (from November 2016 to July 2017), 200 met inclusion criteria with the following characteristics: mean [SD] age, 39 [10] years; 46% White, 25% Black, 21% Hispanic, 7% other; and 58% (117/200) injected drugs, 31% (63/200) shared needles, 87% (149/171) had unprotected sex in the 6 months prior to admission. Of the 200 randomized participants, 99 received RT and 101 LBT; 17 were discharged prior to testing (4 RT, 13 LBT) and 7 assigned to LBT had hemolyzed samples that were not tested. Among all participants, 0.5% (1/200) had a reactive HIV test and 48% (96/200) reactive HCV tests; 96% (95/99) received test results in the RT arm and 51% (52/101) in the LBT arm. Test modality (aOR, 19.25, 95% CI, 7.05-52.50) and Black race (aOR, 0.34, 95% CI, 0.12- 0.98) were independently associated with result delivery after multivariable adjustment controlling for age, gender, race/ethnicity, high-risk behavior, unstable housing, past HIV or HCV testing, and treatment for mental health disorder.
Conclusion: To maximize HIV and HCV test result delivery to high-risk transient populations, use of RT should be considered over LBT in certain settings, such as residential detoxification centers. Additional studies are needed to identify reasons for lower test result delivery among Black individuals in this setting.

Table 1. Table 1.Odd ratios of successful result delivery by study arm and select characteristics

	n (%) with result delivery	Unadjusted Odds Ratio (95% confidence interval)	Adjusted Odds Ratio (95% confidence interval)
Testing arm: Rapid	95(95.9)	22.38 (7.647-65.50)***	19.25 (7.05-52.50)***
Testing arm: Venipuncture	52(51.5)	Reference	
Gender: Male[1]	88(71.0)	0.704 (0.362-1.369)	1.02 (0.44-2.48)
Age	---	0.991(0.962-1.022)	1.01 (0.97-1.06)
Unstable housing[2]	38(69.0)	0.738 (0.372-1.464)	0.57 (0.23-1.40)
High-risk behavior[3]	142(73.2)	0.546 (0.062-4.785)	0.34 (0.03-4.40)
History of testing[4]	136(74.3)	1.579 (0.553-4.505)	1.73 (0.49-6.08)
Prescription for mental health disorder in the last 6 months[5]	51(71.8)	0.950 (0.493-1.832)	0.85 (0.36-1.97)
Race			
Black	31(60.8)	0.431 (0.204-0.911)*	0.34 (0.12-0.98)*
Latino/Hispanic	31(73.8)	0.783 (0.335-1.827)	0.73 (0.27-2.06)
Other	13(86.7)	1.805 (0.376-8.669)	1.25 (0.23-6.74)
White	72(79.1)	Reference	

* for p value at 0.05,
** for p value at 0.01,
*** for p value at <0.0001
1.Female was the reference group
2.Living on the street or in an overnight shelter in the past 6 months
3.More than one sex partner in the past 6 months, condomless sex in the past 6 months, or lifetime history of injection drug use
4.Past history of HIV or HCV testing
5.Receiving a prescription for a psychological disorder (anxiety, depression, bipolar, PTSD or schizophrenia) in the last 6 months
6.Unless noted, the reference group is the group without the variable noted in the table.

992 HIV SELF-TESTING INCREASES TESTING IN YOUNG SOUTH AFRICAN WOMEN: RESULTS OF AN RCT

Audrey Pettifor[1], Kathleen Kahn[2], Linda Kimaru[1], Zola Mayakayaka[2], Amanda Selin[1], Noah A. Haber[1], Ryan Wagner[3], Xavier Gomez-Olive[2], Hailey Gilmore[4], Memory Mhembere[2], Daniel Westreich[1], Rhian Twine[2], Sheri A. Lippman[4]
[1]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]University of the Witwatersrand, Acornhoek, South Africa, [3]University of the Witwatersrand, Johannesburg, South Africa, [4]University of California San Francisco, San Francisco, CA, USA

Background: To meet the UNAIDS 90/90/90 goal it is imperative to increase HIV testing uptake. HIV Self-Testing (HIVST) may increase early HIV detection, particularly among young people. Secondary distribution of test kits to peers/partners may be a good way to reach young people who do not attend traditional health services.
Methods: From December 2016 – July 2017 we enrolled 284 South African young women age 18-24 years in a randomized control trial to examine HIV testing uptake among those randomized to either: 1) an invitation to a local

clinic for free HIV Counseling and Testing (HCT) or, 2) choice of free HCT or HIV Self-testing (HIVST) kits. Young women choosing HIVST in the choice arm were provided with 5 HIVST kits (OraQuick); young women randomized to or choosing HCT were given 5 invitations to test for free at local clinics. Four kits/invitations were intended for distribution to peers and partners plus one for themselves. Young women were invited to return 3 months after enrollment to assess testing uptake between the two arms and distribution to peers and partners. We examined differences in testing between arms using Wald crude risk differences and crude risk ratios.

Results: We randomized 144 young women to the HCT arm and 140 to the HIVST/choice arm. Of those randomized to choice, 134 (96%) chose HIVST and 6 chose HCT. By September 21, 2017, 247 women had returned for their 3-month visit (121 in the HIVST/choice arm, 126 in the HCT arm). At the 3-month visit, 97% of women in the HIVST/choice arm reported testing compared to 48% of women in the HCT arm, a risk difference of 48% (Relative Risk 2.00 95% CI 1.66-2.40). These women reported inviting 465 peers (80% female) and 35 partners to test-- 170 (34%) by HCT arm participants and 330 (66%) by choice arm participants.

Conclusion: We found that providing young women with a choice to self-test in addition to the option of clinic-based HCT led to 97% testing uptake within three months-virtually all through self-testing. In comparison, those offered HCT alone reported only half that amount of testing. In addition, we saw substantially more peer-referrals among women offered HIVST compared to the HCT arm. Many countries in sub-Saharan Africa are considering offering HIVST as another HIV testing option; we present strong evidence that this strategy will result in a substantial increase in HIV testing among young people compared with current practice.

993 FEMALE SEX WORKERS' INTERPRETATIONS OF HIV SELF-TEST RESULTS: A PERFORMANCE STUDY

Katrina F. Ortblad[1], Daniel K. Musoke[2], Thomson Ngabirano[3], Aidah Nakitende[2], Jessica E. Haberer[4], Margaret McConnell[1], Till Bärnighausen[5], Catherine E. Oldenburg[6]

[1]Harvard University, Boston, MA, USA, [2]International Research Consortium, Kampala, Uganda, [3]Uganda Health Marketing Group, Kampala, Uganda, [4]Massachusetts General Hospital, Boston, MA, USA, [5]Heidelberg University, Heidelberg, Germany, [6]University of California San Francisco, San Francisco, CA, USA

Background: HIV testing is essential for HIV treatment and prevention. Oral HIV self-testing increases HIV testing among female sex workers (FSWs) in Kampala, Uganda. However, for testers to learn their true HIV status through self-testing, they must correctly interpret HIV self-test results. Previous studies, not conducted among FSWs, may have overestimated HIV self-test performance because participants interpreted their own self-test results and these interpretations may have been biased by prior knowledge of HIV status. We evaluate the performance of FSWs' interpretation of HIV self-test result images.

Methods: Peer educators trained FSWs on how to use oral HIV self-tests and interpret the results; participants then had two opportunities to HIV self-test. One month after receiving the second test, we gave participants color images of oral HIVST results (strong HIV-negative, strong HIV-positive, inconclusive, and weak HIV-positive), identical to those in the manufacturer's instruction guide, and asked them to interpret these. We calculated the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of FSWs' interpretations. We estimated associations between participant characteristics and incorrect interpretation of HIV self-test results.

Results: From October-November 2016, 544 FSWs completed HIV self-test training. Incorrect interpretation of strong HIV-negative, strong HIV-positive, inconclusive, and weak HIV-positive self-test results was 15%, 18%, 23% and 61%, respectively. FSWs' HIV self-test interpretation had 82% sensitivity (95%CI: 79-86%), 85% specificity (95%CI: 82-88%); 92% NPV (95%CI: 89%-94%); and 68% PPV (95%CI: 64%-71%). Literacy and higher educational attainment were not associated with improved self-test result interpretation.

Conclusion: FSW commonly misinterpreted HIV self-test results, although they received realistic pre-self-test training. Understanding HIV self-test performance in isolation from prior HIV status knowledge is important because HIV self-tests may move HIV testing outside healthcare facilities, where they may be used for first time testing or to test others in this unregulated environment. As HIV self-testing becomes a routine component of national HIV responses in sub-Saharan Africa, strong HIV self-test training and support interventions are urgently needed to ensure correct interpretation of self-test results.

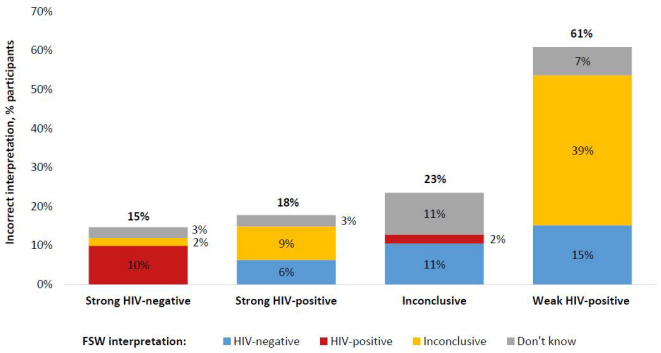


Figure 1. Incorrect result interpretation by self-test result.

The heights of the vertical bars indicate the overall proportion of misinterpreted tests; the color-coded components of the bars indicated the type of misinterpretation: HIV-negative (blue), HIV-positive (red); inconclusive (yellow); don't know (gray).

994 HIV SELF-TESTING AMONG MEN WHO HAVE SEX WITH MEN AND TRANSGENDER WOMEN IN MYANMAR

Andrea L. Wirtz[1], Soe Naing[2], Emily Clouse[1], Hsu Hnin Mon[1], Aung Zayar Paing[2], Stefan Baral[1], Chris Beyrer[1]

[1]Johns Hopkins University, Baltimore, MD, USA, [2]International HIV/AIDS Alliance Myanmar, Yangon, Myanmar

Background: Efforts to improve HIV diagnosis rely on innovative interventions, particularly for key populations. The HIV epidemic in Myanmar is concentrated among men who have sex with men (MSM) and transgender women (TW) and national efforts now focus on improving engagement in HIV testing and care. This implementation science study tested the acceptability and use of HIV self-testing (HIVST) to address care continuum losses by increasing HIV testing uptake to aid early diagnosis of infection.

Methods: We implemented a randomized trial in which HIV-uninfected MSM and TW were recruited via respondent-driven sampling in Yangon. Participants completed a baseline survey and were randomized to standard, voluntary counseling and testing (VCT) or to HIVST. To mitigate stigma, VCT-assigned participants were referred for testing at community-based organizations (CBO) serving MSM and TW. Biologic specimens were collected for confirmatory testing. Participants were asked to return to the study to report their HIV test result and the acceptability of their assigned testing method.

Results: A total of 577 MSM (84.7%) and TW (15.3%) participants were enrolled and randomized to VCT or HIVST between November 2015-July 2017. Self-reported HIV risk behavior was high: 29.8% had engaged in sex work (last 6 mo.); condom use at last sex was less than 30.0% for all partner types; and 32.8% had ever been tested for HIV. 342 (59.3%) returned for the second study visit to report test acceptability. VCT-assigned participants were marginally less likely to return, compared to HIVST participants (45.9% vs. 54.0%; p=0.055). HIVST participants were more likely to agree that, overall, their testing method was easy to implement and understand (98.4% vs. 95.4%; p=0.002). The majority (88.8%) of VCT-assigned participants to indicated they would test regularly if they could access HIVST. HIVST participants were more likely to report that HIVST would be the preferable testing modality for future HIV testing; HIVST was also favored for future testing by VCT participants (55.4%), followed by CBO clinics (36.3%) and government facilities (7.0%). HIVST identified 29 previously undiagnosed infections (9.9%) compared to 15 identified by VCT (5.3%; p<0.001).

Conclusion: HIVST is an acceptable, alternative testing modality compared to community-based VCT for MSM and TW in Myanmar. Likely, HIVST may have greater acceptability and effectiveness compared to testing in government facilities, where stigmatization of key populations is common.

995 EVALUATION OF TARGETED HIV SELF-TEST KIT DISTRIBUTION VIA A DIGITAL VENDING MACHINE

Alex Pollard[1], Gillian Dean[2], Suneeta Soni[2], Carrie Llewellyn[1], Carlos Peralta[3], Liliana Rodriguez[4], Jaime Vera-Rojas[2]

[1]Brighton and Sussex Medical School, Brighton, UK, [2]Brighton & Sussex University Hospitals NHS Trust, Brighton, UK, [3]University of Brighton, Brighton, UK, [4]Loughborough University, Loughborough, UK

Background: Novel strategies are needed to increase HIV testing in high-risk groups including men who have sex with men (MSM), and to meet goals to

reduce undiagnosed HIV. HIV self-testing is an attractive strategy enabling user autonomy in the timing, location and disclosure of testing as well as convenience. Self-testing also provides opportunities for providers to reach populations not engaged with conventional testing. We developed and evaluated a vending machine approach to target HIV self-testing to high-risk MSM in a UK community setting.

Methods: A cross-sectional survey in a sex-on-premises venue (sauna) assessed feasibility and informed development of a vending machine interface. Co-design workshops between designers and LGBT community volunteers explored attitudes towards self-testing and a vending machine interface to deliver HIV self-test kits in community settings (bars/clubs, pharmacies, university campuses and train stations). A bespoke vending machine distributing BioSure© self-test kits was installed in a sauna in this high-HIV-prevalence city (Brighton). A cross-sectional mixed methods evaluation was conducted with 30 users. Demographics were collected via the machine's user-friendly touch-pad screen. An online questionnaire and structured interviews gathered information on user-experience of the machine, and experience, acceptability and attitudes towards HIV self-tests accessed via a machine.

Results: The survey and co-design workshops found that 32% of 281 sauna users had never tested for HIV, despite high infection risks. Acceptability of self-testing before installation of the vending machine was 93%. A total of 95 testing kits were accessed between 8th July and 25th Sept 2017: mean age 35 (Range 18-65); 7.4% (n=7) had never tested for HIV before; 15.8% (n=15) had tested within the last 2-5 years. Uptake of tests was higher via the vending machine compared to HIV testing conducted by community outreach workers in the same venue and study period (95 vs 12). Qualitative interview and online questionnaires demonstrated high acceptability and support for this intervention, which was considered accessible and appropriately targeted.

Conclusion: Community co-design supported the development of an acceptable vending machine interface for the distribution of HIV self-testing kits. This delivered low-cost HIV self-tests to men with low levels of prior testing; and represents an acceptable targeted distribution method that could be applied in other settings.

996 COST ANALYSIS OF DIFFERENTIATED HIV SELF-TESTING KITS DISTRIBUTION IN ZAMBIA

Nurilign Ahmed[1], Lawrence Mwenge[2], Linda Sande[3], Collin Mangenah[4], Sarah Kanema[2], Mutinta Nalubamba[5], Sepiso Libamba[5], Euphemia Sibanda[4], Hendramoorthy Maheswaran[6], Cheryl Johnson[7], Karin Hatzold[8], Elizabeth L. Corbett[3], Helen Ayles[2], Fern Terris-Prestholt[1]

[1]London School of Hygiene & Tropical Medicine, London, UK, [2]Zambart, Lusaka, Zambia, [3]Malawi–Liverpool–Wellcome Trust Clinical Rsr Prog, Blantyre, Malawi, [4]Centre for Sexual Health and HIV/AIDS Research Zimbabwe, Harare, Zimbabwe, [5]Society for Family Health, Lusaka, Zambia, [6]University of Liverpool, Liverpool, UK, [7]WHO, Geneva, Switzerland, [8]Population Services International, Harare, Zimbabwe

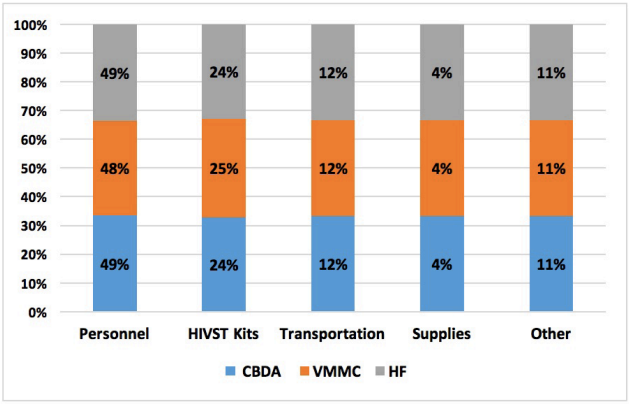
Background: HIV self-testing is a process whereby a person who wants to know his or her HIV status collects a specimen, performs the test and interprets the test result him/herself. The HIV Self-Testing Africa (STAR) project in Zambia utilised community-based distribution agents (CBDAs), voluntary medical male circumcision (VMMC) and health facility (HF) services to distribute HIVST kits. We present the cost of HIVST kits distribution strategies and examine the key cost drivers in Zambia.

Methods: We analysed project financial expenditure data between July 2016 and May 2017. All costs are presented in 2016 US$. Total and unit costs per kit distributed were estimated for CBDA, VMMC, and HF distribution.

Results: Over the lifespan of the project, 127,804 HIVST kits were distributed across 16 communities and distribution modes in Zambia, with CBDA distributing the vast majority of kits (81%), followed by HF (10%) and VMMC (9%). Personnel, HIVST prices and transport were the key cost drivers accounting for 49%, 24% and 12% of the total costs, respectively. The unit cost per HIVST kits distributed were $15.19 for CBDA, $14.71 for VMMC and $15.07 for the HF.

Conclusion: Our findings show that HIVST can be distributed within communities at a reasonable cost. Though higher than our previous estimates for facility-based testing (~$4.24 (Mwenge 2017), it reduces users' costs of testing, estimated in Malawi to be as high as $4 among men (Sande 2017) and therefore addresses, among others, financial barriers to testing. This lays the foundation for exploring economic efficiency in HIVST distribution modalities: it is expected that additional cost savings may be achieved through economies of scale by increasing the volume of the total population covered. Further research is needed to evaluate its cost-effectiveness and how distribution costs will change as programmes mature and scale up.

HIVST cost proportion (%) by cost lines and distribution model in Zambia (in 2016 US$)



997 COMPARING SELF-REPORTED VIRAL LOAD WITH HOME-COLLECTED HIV-RNA AMONG HIGH-RISK MSM

Richard A. Teran[1], Martin J. Downing[2], Mary Ann Chiasson[2], Hong Van Tieu[3], Laura Dize[4], Charlotte A. Gaydos[4], Sabina Hirshfield[2]

[1]Columbia University Medical Center, New York, NY, USA, [2]Public Health Solutions, New York, NY, USA, [3]New York Blood Center, New York, NY, USA, [4]Johns Hopkins University, Baltimore, MD, USA

Background: Among men who have sex with men (MSM), HIV transmission is attributed to both sexual risk behavior and unsuppressed HIV viral load (VL). In the US, an estimated 60% of HIV-positive MSM are virally unsuppressed. Studies show that self-perceived VL may influence sexual practices of HIV-positive MSM. Few US studies have used dried blood spot (DBS) collection outside of a clinical setting; however, improved DBS materials have streamlined biospecimen home collection from MSM recruited online. The current study compared self-reported VL with a lab-based HIV VL test from an at-home DBS kit.

Methods: From 09/2016-06/2017, US HIV-positive MSM (n=766) completing a 12-month online HIV prevention risk reduction intervention were invited to enroll in an at-home DBS collection study. Consenting participants were mailed a HemaSpot kit and instructed to provide a blood sample and return it by mail to a research laboratory. DBS samples were tested using an Open Mode protocol for DBS (1.0ml HIV-1 RNA DBS IUO US TT v11) on the m2000sp/m2000rt system.

Results: Of 554 consenting participants, 418 (75%) returned a kit for lab testing; of those, 337 (81%) had sufficient blood for HIV VL quantification. Of MSM returning a quantifiable kit, 71% were White, 12% Black, and 17% Hispanic. Median age was 38. Among 314 MSM self-reporting current antiretroviral therapy (ART), 49% had <90% adherence in the past month. Of the 337 quantifiable kits, 53% had a detectable VL: 99 kits (29%) had <832 copies/ml; 9 kits (3%) had 832-999 copies/ml; and 69 kits (20%) had >1,000 copies/ml [range: 1,023-1,202,265 copies/ml; median: 5,129 copies/ml]. Among men self-reporting an undetectable HIV VL (n=284), 48% returned a DBS kit with detectable VL; 13% of kits had >1,000 copies/ml. Median time between discordant self-reported undetectable VL and a lab-quantified VL was 43 days. Men living with HIV for >1 year were more likely to have a discordant self-reported and lab-quantified VL (52% vs. 31%; $p<0.01$).

Conclusion: Over half of home-collected DBS samples from HIV-positive MSM had a detectable VL despite most self-reporting ART. About half of men self-reporting an undetectable VL had a detectable lab-quantified VL, and were not treatment naïve, indicating a need for novel approaches to provide treatment services to high-risk HIV-positive MSM with a detectable VL who may be experiencing ART fatigue or not in care. Discordant self-reported and DBS-based VL in our study also highlights the need for validation of self-reported data.

998 HOW LOW CAN YOU GO? DIAGNOSIS OF ACUTE HIV INFECTION AT VERY LOW HIV RNA LEVELS

Donn Colby[1], Siriwat Akapirat[2], Supanit Pattanachaiwit[1], Rapee Trichaviroj[2], Suteeraporn Pinyakorn[3], Sasiwimol Ubolyam[1], Eugène Kroon[1], Carlo Sacdalan[1], Nitiya Chomchey[1], Nittaya Phanuphak[1], Merlin L. Robb[4], Praphan Phanunphak[1], Jintanat Ananworanich[3], Mark de Souza[1]

[1]Thai Red Cross AIDS Research Center, Bangkok, Thailand, [2]Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, [3]US Military HIV Research Program, Bethesda, MD, USA, [4]US Military HIV Research Program, Silver Spring, MD, USA

Background: Diagnosis of acute HIV infection (AHI) prior to development of HIV antibodies (Ab) in blood can be challenging. In the earliest stages of AHI, diagnosis may be made solely by the detection of HIV RNA in plasma. Guidelines caution that HIV RNA <5,000 copies/ml may be a false positive result. However, those recommendations are based on data from >15 years ago, when testing methodologies were less specific than with current technology.

Methods: The RV254/SEARCH010 cohort has recruited participants with AHI in Thailand since 2009. A total 230,036 screening tests were done and 462 AHI cases enrolled through April 2017. We longitudinally examined participants diagnosed with HIV infection based on initial low viral load (LVL-detectable plasma HIV RNA <5,000 copies/ml) with HIV Ab tests negative or inconclusive. HIV RNA (qualitative and quantitative) and HIV antibody [4th-generation (4thG) and 3rd-generation (3rdG) immunoassays (IA)] were performed at baseline, 12 and 24 weeks. Antiretroviral therapy (ART) was started on all at baseline. Data are presented as median (range) unless noted otherwise.

Results: There were 54 (12%) participants diagnosed with AHI based on LVL alone. Initial HIV RNA was 753 (29-4865) copies/ml; 57% were <1,000 copies/ml. Testing was repeated concurrently with starting ART after 3 (1-6) days with a median change of +1.3 (-0.4 to +3.4) $\log_{10}$ copies/ml. No false positive HIV RNA tests were identified; all tests were confirmed by repeat HIV RNA, of which 65% were >5,000 copies/ml. Only 3 participants had a fall in HIV RNA at the second test: all had started 3-drug post-exposure prophylaxis (PEP) on the day of the initial test. HIV RNA became undetectable at 4 (IQR 2-8) weeks on ART. Repeat HIV serology with 3rdGIA showed HIV Ab seroconversion in 90% (44/49) at 12 weeks and 88% (43/49) at 24 weeks. Surprisingly, 4thGIA was less sensitive: 63% (31/49) and 51% (25/49) positive at 12 and 24 weeks, respectively. Only 3 participants, 2 of whom received PEP, had both repeat HIV RNA <5,000 copies/ml and negative HIV Ab at 12 weeks.

Conclusion: Diagnosis of AHI based on HIV RNA <5,000 copies/ml alone had a positive predictive value of 100%: no false positive tests were identified. ART can safely be started in these individuals concurrently with confirmatory HIV RNA and Ab testing and sequentially thereafter. The diagnosis of HIV may be more challenging with the use of PEP, and potentially PrEP, which may blunt or delay the HIV Ab response.

999 VALIDATION OF THE AMSTERDAM RISK SCORE FOR RECENT HIV INFECTION AMONG MSM

Timothy Lin[1], Maartje Dijkstra[2], Godelieve J. de Bree[2], Maarten F. Schim van der Loeff[2], Martin Hoenigl[1]

[1]University of California San Diego, La Jolla, CA, USA, [2]Academic Medical Center, Amsterdam, Netherlands

Background: Diagnosis of acute HIV infection (AHI) is challenging and resource-intensive. Dijkstra and colleagues recently described a risk- and symptom-based score that was moderately predictive for seroconversion in a 6 to 12-month period preceding a follow-up visit in men who have sex with men (MSM) in Amsterdam ("Amsterdam Score"). They propose that the Amsterdam Score may reduce HIV nucleotide amplification testing (NAT) and increase diagnostic yield. The hypothesis of this study was that the Amsterdam Score will also be at least moderately predictive for AHI in San Diego (receiver operating characteristic [ROC] area under the curve [AUC] >=0.70), in a cohort with 3-times more HIV-positive test events, but a similar age distribution (33 [interquartile range 27-44] vs 34 [29-41] in Amsterdam).

Methods: MSM who tested positive for AHI (antibody-negative, HIV NAT-positive) from 2007 to 2017 or tested NAT-negative in 2017 with the Early Test community-based HIV screening program in San Diego were included for analysis. The Amsterdam Score was calculated for each participant using values described previously with minor adjustments (Table 1). Cases with missing variables were deleted listwise. The Amsterdam Score was assessed with ROC curves; an optimal cut-off score was determined with Youden's index.

Results: 712 MSM (79 AHI, 633 HIV NAT-negative) were included in the analysis. The Amsterdam Score yielded a ROC curve with AUC of 0.89 (95%CI 0.86 to 0.93). The optimal cut-off score was >=1.8, yielding a sensitivity of 78.5%, specificity of 82.8%, positive predictive value of 36.3%, negative predictive value of 96.9%, positive likelihood ratio of 4.56, and negative likelihood ratio of 0.26. 24.0% of participants would have met this cut-off for NAT testing.

Conclusion: The Amsterdam Score was highly predictive (AUC 0.89) of AHI in MSM in San Diego compared to moderately predictive (AUC 0.78) in the original validation cohort. The improved performance may be attributable to more stringent inclusion of only AHI or HIV NAT-negatives in the San Diego cohort. The higher optimal cut-off of >=1.8 (compared to >=1.5 in the Amsterdam cohort) may be explained by overall higher risk behavior in the Early test cohort. Combined risk- and symptom-based scores may demonstrate improved generalizability across different populations compared to existing risk-based scores, and may improve the yield of AHI-diagnosis strategies particularly in settings that do not, or cannot feasibly, routinely test for AHI.

Table 1: Amsterdam Score variables, score values, and proportions in the San Diego Cohort

Variable[a]	Score value[a]	Proportion (Y) in AHI (95%CI[b])	Proportion (Y) in HIV-negative (95%CI)
Symptoms (Y/N)[c]:			
Fever	1.6	59.5% (48.4 to 70.6%)	4.3% (2.7 to 5.8%)
Lymphadenopathy	1.5	24.1% (14.4 to 33.7%)	4.4% (2.8 to 6.0%)
Oral thrush[d]	1.7	-	-
Weight loss	0.9	22.8% (13.3 to 32.2%)	1.4% (0.5 to 2.4%)
Risk factors In the previous 6[e] months (Y/N):			
Gonorrhea	1.6	6.3% (0.8 to 11.8%)	3.0% (1.7 to 4.3%)
Condomless receptive anal intercourse	1.1	92.4% (86.4 to 98.4%)	46.9% (43.0 to 50.8%)
>5 sexual partners.	0.9	41.8% (30.7 to 52.9%)	21.9% (18.6 to 25.1%)

[a] Per Dijkstra et al. BMC Infectious Diseases (2017) 17:425 DOI 10.1186/s12879-017-2508-4.
[b] 95% confidence interval
[c] Assessed for 14 days prior to testing in the San Diego cohort
[d] Oral thrush was not assessed in the San Diego cohort.
[e] Risk factors were assessed for the previous 3 months in the San Diego cohort.

1000 DEVELOPMENT AND VALIDATION OF THE SAN DIEGO SYMPTOM SCORE FOR ACUTE HIV INFECTION

Timothy Lin, Tara Tenenbaum, Sara Gianella, Susan J. Little, Martin Hoenigl

University of California San Diego, La Jolla, CA, USA

Background: Diagnosing and treating acute HIV infection (AHI) decreases transmission, preserves immune function, but is resource-intensive. Risk-based scores have been developed to predict for AHI, but symptom-based scores have the potential to be generalizable among different risk strata. The objective of this study was to derive and validate a "San Diego Symptom Score" (SDSS) which we hypothesized would be at least moderately predictive for AHI (receiver operating characteristic [ROC] area under the curve [AUC]≥0.7).

Methods: Analysis included adults who self-presented to the Early Test community-based HIV screening program in San Diego and 1) tested positive for AHI (antibody-negative, HIV nucleotide amplification test [NAT]-positive) from 2007 to 2017 or 2) tested HIV NAT-negative in 2017. Participants were assessed for 11 symptoms in the 14 days prior to the testing event. The sample was retrospectively randomized 2:1 into a derivation and validation set. In the former, symptoms with p<0.2 for AHI in univariate logistic regression models were entered into a multivariate model. Symptoms with p<0.05 were then assigned a score value equivalent to its odds ratio. The score was assessed in the validation set using ROC curve AUC. A cut-off score was found using Youden's index.

Results: 1003 participants (738 men who have sex with men (MSM), 151 non-MSM men, 111 ciswomen, 2 transwomen, 1 declined to disclose gender) were included, of which 114 had AHI (109 MSM, 3 non-MSM men, 1 ciswoman and 1 transwoman). Compared to HIV-negative cases, AHI cases were of similar median age (32[interquartile range 25-42] vs 33[27-43], p = 0.11 by Mann-Whitney U) and reported more symptoms (4[2-6] vs 0[0-1], p<0.01). In HIV-negative cases, men and women reported similar a number of symptoms (0[0-1] vs 0[0-1], p=.850). This study sample was representative of the overall Early Test

cohort by sex, gender and age. In the derivation set myalgia, fever and weight loss were significant in the multivariate model (Table 1). In the validation set the SDSS yielded AUC of 0.85(95%CI 0.77-0.93). A cut-off score of ≥9 was 71% sensitive, 97% specific, with positive predictive value of 76%, negative predictive value of 96% and diagnostic odds ratio of 65.1(95%CI 26.4-160.8).
Conclusion: The SDSS accurately predicts for AHI in a cohort self-presenting for screening, and may inform allocation of diagnostic resources in settings that do not routinely test for AHI. Validation in other populations with different risk behaviors is needed.

Table 1:
Univariate logistic regression models and multivariate logistic regression model for AHI[a] vs. HIV-negative

	Univariate symptom models		Combined multivariate symptom model	
Symptoms (Y/N)	**OR[b] (95%CI[c])**	**P-value**	**OR (95%CI)**	**P-value**
Headache	3.4 (2.0-5.7)	<.001	0.8 (0.4-1.7)	.546
Pharyngitis	4.9 (2.9-8.2)	<.001	1.9(0.9-4.0)	.075
Rash	3.6 (1.9-7.1)	<.001	1.3(0.5-3.4)	.610
Myalgia	**16.8 (9.4-30.1)**	**<.001**	**7.9(3.3-18.7)**	**<.001**
Fatigue	8.6 (5.0-14.6)	<.001	0.9(0.3-2.2)	.764
Fever	**25.0 (13.7-45.7)**	**<.001**	**10.9(4.6-26.1)**	**<.001**
Night sweats	10.6 (5.9-19.0)	<.001	1.3(0.5-3.4)	.576
GI symptoms[d]	4.1 (2.3-7.0)	<.001	0.5(0.2-1.4)	.216
Arthralgia	8.5 (4.3-17.0)	<.001	0.8(0.3-2.4)	.681
Weight loss[e]	**14.9 (6.3-35.1)**	**<.001**	**4.1(1.1-15.1)**	**.035**
Lymphadenopathy	5.8 (2.9-11.7)	<.001	1.5(0.6-3.9)	.435

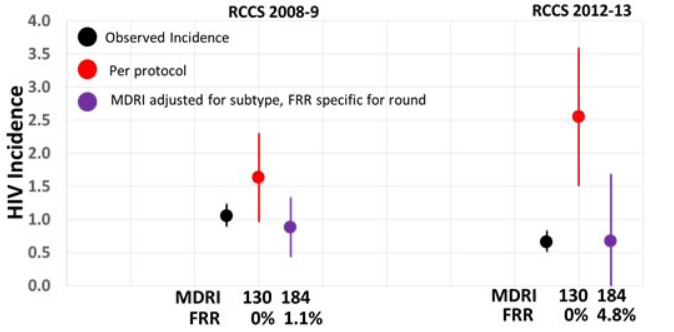
[a] Acute HIV infection (
[b] Odds ratio
[c] 95%CI confidence interval
[d] General gastrointestinal symptoms (e.g. nausea, vomiting, or diarrhea)
[e] Weight loss >2.5kg.

1001 CAN THE LAG-AVIDITY ASSAY MEASURE AN INCIDENCE DIFFERENCE IN EAST AFRICA?

Oliver Laeyendecker[1], Ronald H. Gray[2], Kate Grabowski[3], Steven J. Reynolds[1], Anthony Ndyanabo[2], Joseph Ssekasanvu[3], Reinaldo Fernandez[3], Maria Wawer[3], David Serwadda[4], Thomas C. Quinn[1]
[1]NIAID, Baltimore, MD, USA, [2]Rakai Health Sciences Program, Kalisizo, Uganda, [3]The Johns Hopkins University, Baltimore, MD, USA, [4]Makerere University, Kampala, Uganda

Background: A combination of the Limiting-Antigen Avidity Assay (LAg-Avidity) with viral load (VL) >1000 copies/mL is being used internationally for cross-sectional estimation of population-level HIV incidence. However, the capacity of this method to measure a point estimate and a change in incidence over time has not been validated in an East African setting where HIV-1 subtypes A and D circulate.
Methods: We analyzed longitudinal data for two time periods in the Rakai Community Cohort Study (RCCS) in Uganda. Between survey Rounds 12 and 13 (2006-2007 and 2008-2009) the observed incidence was 1.05/100 person years (95% CI 0.90, 1.23). Between Rounds 14 and 15 (2010-2011 and 2012-2013) the observed incidence was significantly lower, 0.66/100 person years (95% CI 0.52, 0.83), P<0.05. The performance of the current LAg-Avidity protocol, with mean duration of recent infection (MDRI) of 130 days and false recent rate (FRR) of 0% was compared to a subtype specific MMDRI and FRR calibrated by survey round.
Results: Based on gp41 sequence data, the subtype proportion in the RCCS was 45% A and 55% D, and the subtype adjusted MDRI was 184 days. In Round 13 there were 9,973 subjects, of whom 1244 were HIV-positive, with 422 were on ART. Of the 742/822 remaining subjects with samples available for testing, 49 were classified as recent and the FRR was 1.1% (6/544). In Round 15 there were 6749 subjects, of whom were 985 HIV-positive, with 423 were on ART. Of the 500/562 remaining subjects with samples available for testing, 52 were classified as recent and the FRR was 4.8% (16/332). Per protocol cross-sectional R13 incidence was 1.63 (95% CI 0.97, 2.30), and the R15 estimate was 2.55 (95% CI 1.51, 3.59), P<0.05. Both per protocol estimates exceeded the observed incidence. When using the MDRI adjusted for subtype and a round specific FRR the incidence estimates was 0.88% (95%CI 0.44, 1.33) for R13 and 0.67% (95% CI 0.00, 1.68) for R15, P=0.54, which were closer to the observed incidence.
Conclusion: In this subtype A/D epidemic, the per protocol methods of LAg-Avidity +VL over estimated observed incidence and failed to detect the decline in incidence between the two time periods. In contrast, when the method was adjusted by survey-specific FRR and an MDRI calibrated for the population's subtype distribution, the HIV incidence estimates were similar to observed incidence and detected declines in incidence.

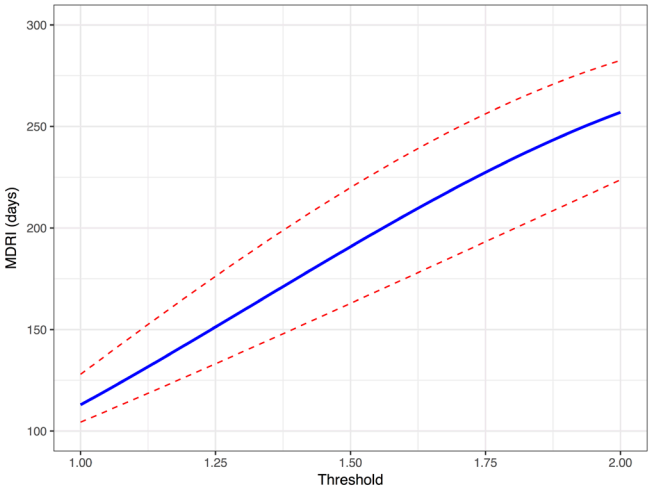
Comparison of Observed to Estimated HIV Incidence in the Rakai Community Cohort Study

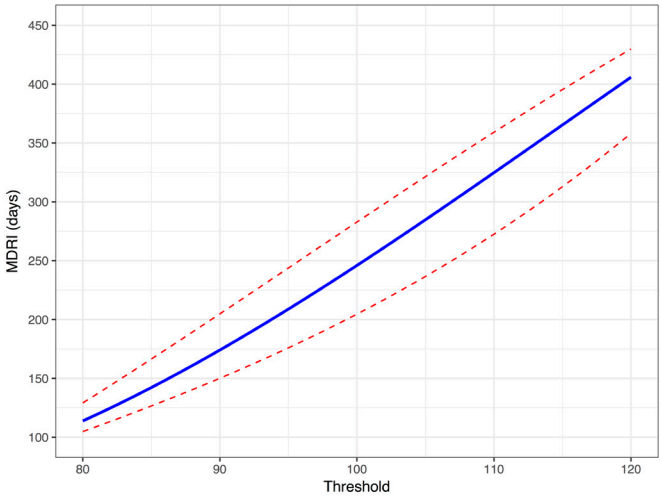


1002 PERFORMANCE VALIDATION OF THE SEDIA LAG ASSAY IN SOUTH AFRICAN BLOOD DONORS

Eduard Grebe[1], Marion Vermeulen[2], Tinus Brits[2], Ronel Swanevelder[2], Genevieve Jacobs[2], Michael P. Busch[3], Alex Welte[1]
[1]Stellenbosch University, Stellenbosch, South Africa, [2]South African National Blood Service, Johannesburg, South Africa, [3]Blood Systems Research Institute, San Francisco, CA, USA

Background: Tests for 'recent' HIV infection have found significant application in major population-level incidence (and trend) estimation projects. Design and validation of such tests depends crucially on robust estimation of a Mean Duration of Recent Infection (MDRI), which is usually based on data with repeated observations of seroconverting subjects from studies with different primary goals, rendering the production of such estimates particularly difficult and expensive.
Methods: The MDRI of a test is estimated by fitting a statistical model for the probability of testing recent as a function of time since infection. In the usual context of seroconverter cohorts, this is applied to multiple observations anchored to a 'point estimate' of infection time, based on interval censoring applied to diagnostic test data. Midpoints of seroconversion intervals are not appropriate to single observations at the time of first positive specimens from previously negative blood donors. We adapted the methodology to cater to single observations, even with very imprecise infection time estimates by averaging over unobserved (possible) infection times. Intervals were adjusted for the sensitivity of screening assays used. We estimated MDRI for the established Sedia LAg recency test, using data from the South African National Blood Service, at a range of discriminatory thresholds. We used data from 2,973 seroconverting repeat blood donors, overwhelmingly with subtype C infections and with a median inter-donation interval of 357 days. Reproducibility of the MDRI estimates was investigated using bootstrap resampling.
Results: The figure shows estimated MDRI values, as a function of normalised optical density (ODn) recency discrimination threshold. The MDRI at the standard threshold of 1.5 is 189 days (95% CI: 161-215) and at a threshold of 2.0 is 257 days (95% CI: 223-282).
Conclusion: The Sedia LAg assay's performance in South African blood donors is similar to its performance in a previously-described multi-origin subtype C panel. These results provide context-specific recency test characteristics to support estimating incidence in first-time blood donors. The results demonstrate, for the first time, that data from repeat donors can be used to calibrate tests for recent infection. Specimens from seroconverting repeat blood donors are a potentially rich source of data on early pathogenesis and early infection biomarkers, as long as appropriate averaging is performed over uncertain infection times.





1003 INNATE DYNAMIC RANGE OF ABBOT PRISM HIV O PLUS IS ADEQUATE FOR RECENCY STAGING

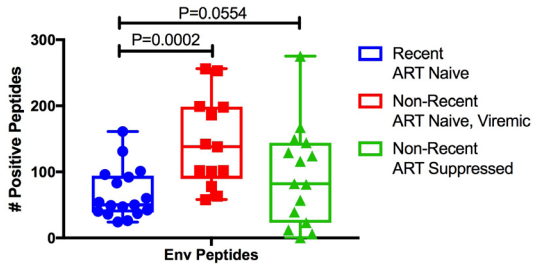
Eduard Grebe[1], Marion Vermeulen[2], Tinus Brits[2], Ronel Swanevelder[2], Genevieve Jacobs[2], Michael P. Busch[3], Alex Welte[1]
[1]Stellenbosch University, Stellenbosch, South Africa, [2]South African National Blood Service, Johannesburg, South Africa, [3]Blood Systems Research Institute, San Francisco, CA, USA

Background: Tests for 'recent' HIV infection have found significant application in major population-level incidence (and trend) estimation projects. Recency assays are often modifications of diagnostic assays designed to extend the dynamic range and facilitate the application of recency discrimination thresholds. This raises the prospect that diagnostic platforms with high innate dynamic range may allow adequate recency staging to support incidence estimation. We investigated the suitability of the Abbott PRISM HIV O Plus assay for recency staging using data from the South African National Blood Service, which uses the assay for routine screening, by estimating the Mean Duration of Recent Infection (MDRI) for a range of recency discrimination thresholds.
Methods: We estimated MDRI by fitting regression models for the probability of testing recent as a function of time since infection. In the context of blood donations, repeat observations from seroconverting donors are not routinely available, and time since infection is often very imprecisely known. We developed a method that does not depend on a 'point estimate' of infection time, but averages over unobserved (possible) infection times in repeat donors, and utilises a single PRISM signal-to-cutoff ratio (S/CO) from the positive donation. The analysis utilised specimens from 3,675 seroconverting repeat blood donors, with a median inter-donation interval of 341 days. Intervals were adjusted according to the sensitivity of screening assays. Reproducibility of the MDRI estimate was assessed by resampling the data in 10,000 bootstrapping iterations.
Results: The figure shows MDRI values against S/CO recency discrimination thresholds. At plausible thresholds, the MDRI ranges from approximately 100 days to over 300 days, with coefficients of variation ranging from 4% to 9%. At an S/CO threshold of 80 the MDRI is estimated at 117 days (95% CI: 107-130) and at a threshold of 100, at 252 days (206-282).
Conclusion: These MDRI estimates are comparable to that of the widely-used LAg assay when assessed using similar data from the same population. This is particularly promising given that the PRISM platform was not designed for staging. The results suggest that the platform's performance is sufficient to support estimating incidence in first-time blood donors using routinely-available screening data, without the need for additional recency testing.

1004 MEASUREMENT OF ANTIBODY EPITOPE SIGNATURES TO DETERMINE RECENCY OF HIV INFECTION

Kathryn E. Stephenson[1], Lisa M. Howe[1], Dan Barouch[1], Steven G. Deeks[2], Sheila M. Keating[3], Christopher D. Pilcher[2], Timothy J. Henrich[2]
[1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]Blood Systems Research Institute, San Francisco, CA, USA

Background: One of the challenges in HIV epidemiology is the generation of reliable estimates of HIV incidence in cross-sectional surveys. Most tests for recent HIV infection measure either the magnitude or avidity of HIV-specific antibodies: both parameters are sensitive but not specific. Assays that quantify the epitope diversity of HIV-specific antibodies are a potential strategy to determine recent HIV infection. The hypothesis is that the greater the duration of HIV infection, the greater the epitope binding diversity of HIV-specific antibodies. We therefore used a novel assay, the global HIV peptide microarray, to define antibody epitope signatures associated with different stages of HIV infection.
Methods: Plasma samples from 3 groups were obtained from the Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA): ART-naïve individuals with recent HIV infection (<12 mos, N=17), ART-naïve individuals with non-recent infection (>12 mos, N=17) and ART-suppressed individuals with non-recent infection (N=15). Samples were incubated with the peptide microarray, a multiplex platform to measure antibody binding to 6,654 peptides from across the HIV proteome and covering the majority of global sequences. Positive peptide responses were tallied by protein, with fewer positive responses denoting a narrower antibody epitope signature.
Results: ART-naïve individuals with recent HIV infection had significantly fewer positive HIV Env peptides than those with non-recent infection (median of 50 vs. 138, P=0.0002). The expansion of positive responses was observed at the V3 loop of Env, which is involved in coreceptor engagement. Positive Env responses were also significantly and strongly correlated with the duration of HIV infection (days from detectable infection) among ART-naïve participants (P<0.0001, R=0.67 by Spearman test). This positive association persisted when ART-suppressed participants were included in the analysis (P=0.0078, R=0.39).
Conclusion: Recent HIV infection was associated with a narrow epitope signature, while chronic HIV infection (even among persons with low HIV RNA) was associated with a broader and more diverse epitope signature. This data suggests that the global HIV peptide microarray can be used to measure epitope signatures associated with recent and non-recent HIV infection, independent of HIV RNA. Out data suggest that further optimization of the microarray in larger cohorts may allow for high throughput applications.



1005 DISTANCE TO CLINIC IS A BARRIER TO PrEP UPTAKE & RETENTION IN UGANDA SEARCH COMMUNITY

Christopher Mayer[1], Asiphas Owaraganise[2], Jane Kabami[2], Dalsone Kwarisiima[3], Catherine A. Koss[4], Edwin D. Charlebois[4], Moses R. Kamya[5], Maya L. Petersen[6], Diane V. Havlir[4], **Britta Jewell**[6]

[1]Albany Medical College, Albany, NY, USA, [2]Infectious Diseases Research Collaboration, Kampala, Uganda, [3]Makerere University Joint AIDS Program, Kampala, Uganda, [4]University of California San Francisco, San Francisco, CA, USA, [5]Makerere University, Kampala, Uganda, [6]University of California Berkeley, Berkeley, CA, USA

Background: Geographic and transportation barriers have previously been associated with poorer HIV-related health outcomes in sub-Saharan Africa, but data on such barriers for prevention are limited. The intervention arm in Phase II of the SEARCH Study (NCT01864603) is investigating a targeted, population-based approach to PrEP in rural communities in East Africa. We estimated the effect of distance to clinic and other transportation-related barriers on PrEP uptake and retention in Ruhoko, an intervention community in southwestern Uganda.

Methods: Adult (≥15) participants in Ruhoko were eligible for PrEP based on a risk score, having an HIV-discordant partner, or self-referral at either the community health campaign (CHC) or home visits. We collected data from PrEP-eligible households on GPS-measured distance to clinic, walking time to clinic, and road difficulty. Distance, time to clinic, and road difficulty were measured by walking participant transportation routes to clinic using GPS coordinates for each PrEP-eligible household. A sample of participants was also asked to identify participants' primary barriers to PrEP use with a semi-quantitative questionnaire. We used multivariable logistic regression to evaluate the association between transportation barriers and i) PrEP uptake among PrEP-eligible individuals and ii) 4-week retention among PrEP initiators, and reported descriptive statistics on named barriers.

Results: Of 701 participants eligible for PrEP, 272 (39%) started PrEP within 4 weeks of CHC/home visit; of these, 45 (17%) were retained at 4 weeks. Participants with a distance to clinic of ≥2 kilometers were less likely to start PrEP (aOR 0.35; 95% CI 0.15-0.81, p=0.014) and less likely to be retained on PrEP once initiated (aOR 0.26; 95% CI 0.09-0.76; p=0.013) [Table 1]. Time to clinic (aOR 0.35; 95% CI 0.13-0.96, p=0.42) and road difficulty (aOR 0.27; 95% CI 0.07-0.97, p=0.044) were also predictive of lower odds of retention. Of participants asked to name barriers to PrEP use (N=98), the most frequently cited were "needing to take PrEP every day" (N=18) and "low/no risk of getting HIV: (N=18). Transportation-related barriers, including "clinic is too far away" (N=6) and "travel away from home" (N=4) were also reported.

Conclusion: Distance to clinic is a significant predictor of PrEP uptake and retention in a community in rural Uganda. Interventions that address geographic and transportation barriers may improve PrEP uptake and retention in sub-Saharan Africa.

			UPTAKE				RETENTION			
	Parameter	Reference group	OR	*p*-value	aOR[1]	*p*-value	OR	*p*-value	aOR[1]	*p*-value
Distance to clinic	≥2 km	<2 km	0.35 (0.16-0.75)	0.007	0.35 (0.15-0.81)	0.014	0.30 (0.11-0.82)	0.019	0.26 (0.09-0.76)	0.013
Walking time to clinic	≥30 min	<30 min	0.53 (0.28-0.98)	0.044	0.62 (0.31-1.24)	0.180	0.41 (0.16-1.07)	0.068	0.35 (0.13-0.96)	0.042
Maximum road difficulty	>1	1	1.00 (0.67-1.50)	0.992	1.15 (0.74-1.80)	0.539	0.30 (0.09-1.00)	0.051	0.27 (0.07-0.97)	0.044

Table 1: Association between parameters and PrEP uptake (among PrEP-eligible, N=701) and 4-week retention (among PrEP initiators, N=272) in Ruhoko, Uganda. [1]aOR = adjusted odds ratio, adjusted for age, sex, and risk type (E = eligible by risk score; S = eligible by self-referral; D = eligible by having an HIV-discordant partner). Maximum road difficulty: 1 = low incline; navigable by boda-bodas; 2 = moderate incline; walking only; 3 = high incline; geographic barriers; walking only.

1006 GEOGRAPHIC ACCESS TO PrEP CLINICS AMONG US MSM: DOCUMENTING PrEP DESERTS

Kevin Weiss, Anna Bratcher, Patrick S. Sullivan, Aaron J. Siegler

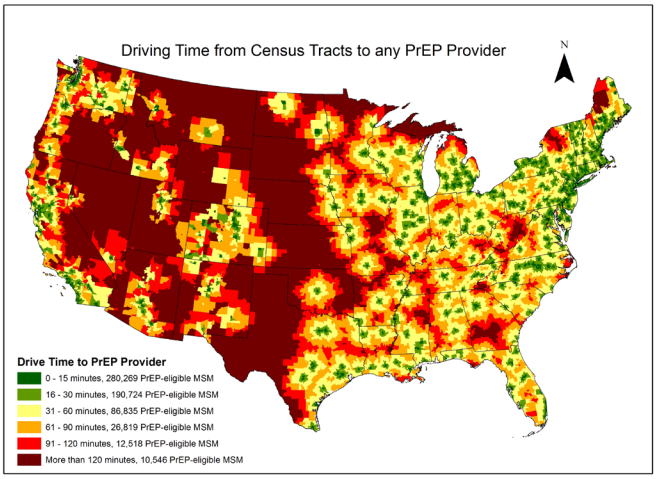
Emory University, Atlanta, GA, USA

Background: Pre-exposure prophylaxis (PrEP) is an efficacious HIV prevention strategy. Using a national database of publicly-listed clinics that prescribe PrEP in the contiguous United States, we explored 'deserts' with low access to PrEP as defined by driving time to the closest clinic.

Methods: MSM population estimates, county urbanicity, and PrEP provider data were sourced from public data and a national database of publicly listed PrEP providers. Using geographic information systems (GIS), we proportionally allocated county-level MSM estimates and a national PrEP-eligibility estimate to census tracts, areas with a median of 4000 persons. We mapped PrEP providers and calculated travel time, based on ideal traffic conditions, from census tract centroids to the nearest PrEP providers. We classified tracts as being part of a 'PrEP desert' based on 30-minute and 60-minute drive travel times to the nearest PrEP-providing clinic.

Results: Over one-fifth of MSM (620,150/2,904,089; 21%) lived in census tracts farther than a 30-minute drive away from the nearest PrEP-providing clinic, and 8% (228,391/2,904,089) lived farther than a 60-minute drive. Similar proportions of PrEP-eligible MSM (136,718/607,711; 23%) lived farther than a 30-minute or (49,883/607,711, 8%) 60-minute drive from the nearest PrEP-providing clinic. Using a 60-minute definition of PrEP desert, two-thirds (65.5%) of all deserts were in micropolitan or noncore areas, accounting for 49.2% (28,874) of all PrEP-eligible MSM in deserts. Using the same cutoff, seven of nine geographic census divisions had more than 15,000 MSM living in deserts and six of nine divisions had more than 5,000 PrEP-eligible MSM living in deserts.

Conclusion: Substantial geographic areas within the United States do not have nearby, publicly-listed clinics that prescribe PrEP. Large numbers of MSM have limited access to PrEP, living in 'deserts' that require substantial driving time to care. Our estimates of the proportion of MSM living in PrEP deserts are conservative, because driving time calculations use ideal traffic conditions. Moreover, many PrEP-eligible MSM may not have access to a car, which could substantially increase transit times. Given a requisite of four annual visits per year for PrEP care, substantial travel time to care could limit PrEP scale-up. HIV prevention programs must consider travel burden and transportation access as a key part of expansion to more effectively reach both urban and rural MSM in need.



Projection: USA Lambert Conformal Conic

1007 THE PrEP CASCADE AT NYC SEXUAL HEALTH CLINICS: NAVIGATION IS THE KEY TO UPTAKE

Preeti Pathela[1], Kelly Jamison[1], Susan Blank[1], Tarek Mikati[1], Trevor Hedberg[1], Sarit A. Golub[2], Lena Saleh[1], Christine M. Borges[1]

[1]New York City Department of Health and Mental Hygiene, Long Island City, NY, USA, [2]City University of New York, New York, NY, USA

Background: New York City's public Sexual Health Clinics reach many people at high risk for HIV acquisition. Staff provide on-site PrEP navigation, and follow up to maximize patient-linkage to ongoing PrEP care. Our aim was to

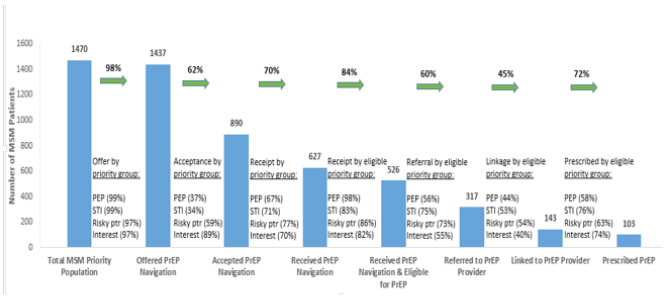
understand uptake of this intervention and related patient-level factors, which is critical to improving the PrEP cascade.

Methods: We analyzed medical record data for HIV-negative men who have sex with men (MSM) with clinic visits during April-June 2017. Hierarchical PrEP priority criteria were: 1) HIV post-exposure (PEP) use (past-year); 2) selected sexually transmitted infections (STI) (past-year); 3) higher-risk (HR) partners (HIV-positive sex/needle-sharing); 4) interest in PrEP. We constructed a PrEP cascade and used multivariable regression to identify factors (priority group, race/ethnicity, age, insurance status) associated with acceptance of PrEP navigation and referral, linkage to PrEP provider (<60 days), and PrEP prescription.

Results: Over a 3-month period, 1470 of 4761 MSM were PrEP priority patients: 13% PEP users, 32% with prior STI, 9% with HR partners, 46% with PrEP interest. Of those offered navigation, 62% (890/1437) accepted; prior STI and PEP patients had lowest acceptance (34-37%). 70% of acceptors (627/890) received navigation. Of MSM eligible for referral, 60% (317/526) accepted referral; 45% (143/317) linked to a PrEP provider, and 72% (103/143) were prescribed PrEP; overall 20% (103/526) of referred MSM received PrEP. Compared to MSM with PrEP interest, MSM with PEP history (OR 0.07, 95% CI 0.05-0.10), prior STI (OR 0.06, 95% CI 0.05-0.09), or HR partners (OR 0.18, 95% CI 0.11-0.28) were much less likely to accept navigation. Black (OR 1.63, 95% CI 1.15-2.30), Hispanic (OR 1.85, 95% CI 1.34-2.57) and MSM of other races (OR 1.64, 95% CI 1.08-2.49) were more likely than white MSM to accept navigation. Once navigated, MSM with STI or HR partners were twice as likely as those with PrEP interest to accept referrals; referral acceptance did not differ by other factors. Probability of linkage and prescription did not vary by patient factors.

Conclusion: Although MSM in key priority groups (e.g., prior STI) showed low navigation uptake, those who accepted navigation had higher referral rates than other groups, suggesting a need for up-front engagement. Clinics offering sexual health services are ideal PrEP implementation settings, reaching racial minority populations likely to accept PrEP, and helping 1 in 5 MSM benefit from these HIV prevention services.

Figure. PrEP Navigation Outcomes, New York City Sexual Health Clinics, April-June 2017



1008 OUT-OF-POCKET COSTS IMPEDE PrEP USE AMONG YOUNG MSM IN THE PRIVATE HEALTHCARE SYSTEM

Rupa R. Patel[1], Sunidhi Singh[1], Christian Farag[1], Kenneth H. Mayer[2], Philip A. Chan[3], Amber Salter[1], Leandro A. Mena[4], Zachary Feinstein[1], John Crane[1], Timothy McBride[1]

[1]Washington University St Louis, St Louis, MO, USA, [2]Harvard University, Cambridge, MA, USA, [3]Brown University, Providence, RI, USA, [4]University of Mississippi, Jackson, MS, USA

Background: The extent that out-of-pocket (OOP) costs (i.e., costs not covered by the insurance company or self-paid) impede PrEP use has not been quantified. We assessed individual OOP costs and its effect on PrEP utilization among young adult MSM.

Methods: We reviewed intake demographic, behavioral and billing data among MSM receiving PrEP care at the Washington University in St. Louis Infectious Diseases Clinic from June 2014 to July 2017. MSM 18-35 years who were prescribed PrEP for ≥3 months were included in the study. The primary outcome was PrEP utilization, defined as self-report of continuing PrEP at 3-month follow up. Billing data included office visit charges made to individuals (i.e. copayments, coinsurance) and insurance companies, costs that individuals were responsible for after insurance reimbursement, the amount individuals paid, and the debt an individual accrued (i.e., the difference between the total amount a person was responsible for and paid). Medians (IQR) are reported. Logistic regression was performed to assess the relationship between OOP charges, payments, and accrued debt on PrEP utilization. Wilcoxon tests were used to compare costs between race and insurance categories.

Results: Of 149 MSM, the median age was 26 years (24, 30), 54% were White, 30% were Black, 4% were Latino, 67% were college graduates, and annual income was $25300; 83% had private, 8% had public, and 9% had no insurance. The median total OOP charge for the initial PrEP office visit was $40 ($20, $79), payment was $20 ($0, $45), and accrued debt was $0 ($0, $25). When adjusting for race and insurance, young adult MSM with any debt (>$0) were less likely to continue PrEP compared to those with no debt (OR:3.65, 95% CI:1.14-11.72); adjusting for the same factors, MSM with debt ≥$25 were less likely to continue PrEP (OR:5.94, 95% CI:1.75-20.19). Among Black and non-Black MSM, OOP payments ($0 and $25; P<0.001, respectively) and accrued debt ($31 and $0; P<0.001) significantly differed. Among the uninsured and insured, OOP charges ($212 and $36; P<0.001, respectively) and accrued debt ($92 and $0; P=0.001) differed.

Conclusion: This study quantified amounts (>$0, ≥$25) at which individual out-of-pocket costs impede PrEP utilization among young adult MSM, regardless of insurance coverage, who are accessing care within the US private healthcare system. Black MSM were disproportionately affected. Public sector financing to cover individual medical costs is needed to reach the population-level benefit of PrEP.

1009 HIGH DISCONTINUATION OF PRE-EXPOSURE PROPHYLAXIS WITHIN SIX MONTHS OF INITIATION

Chelsea L. Shover[1], Marjan Javanbakht[1], Steven Shoptaw[1], Robert Bolan[2], Pamina Gorbach[1]

[1]University of California Los Angeles, Los Angeles, CA, USA, [2]Los Angeles LGBT Center, Los Angeles, CA, USA

Background: The study was conducted to characterize longitudinal use of HIV pre-exposure prophylaxis (PrEP) at a Federally Qualified Health Center in Los Angeles, CA. We aimed to examine duration of PrEP use, and sociodemographic characteristics associated with discontinuation. We hypothesized that most patients would use PrEP for at least six months, and most of those who discontinued would do so without returning for a first follow-up appointment.

Methods: Records were obtained from patients prescribed tenofovir/emtricitabine as PrEP at the Los Angeles LGBT Center prior to March 1, 2017. "Active" PrEP patients were defined as those who had a PrEP prescription within the past 120 days. Among those not active, last visit with PrEP prescription was a proxy for discontinuation of PrEP use. Patients were followed through the earliest of discontinuation or August 31, 2017. Potential demographic correlates of discontinuation were analyzed using logistic regression.

Results: During the study period, 1,764 individuals initiated PrEP. The majority were cisgender men (94%) or transgender women (4%); White (44%), Hispanic (30%), or Black (8%); over 30 (55%). Fifteen percent (n=271) did not return for a follow-up appointment within 120 days of initial visit. By three months, 32% (n=572) discontinued, and 45% (n=802) discontinued by six months. A remaining 55% (n=972) continued attending PrEP follow-up appointments for at least six months. Black race/ethnicity (AOR: 1.6, 95% CI 1.0 2.5) and bisexual orientation (AOR: 1.8, 95% CI 1.2, 2.6) were associated with greater odds of discontinuation at baseline compared to white race/ethnicity or gay sexual orientation, respectively. Discontinuation by six months was associated with age, but not gender, sexual orientation, or race/ethnicity. Compared to those over 50, those between 18-24 (AOR = 2.6, 95% CI 1.6, 4.2); 25-29 (AOR = 1.9, 95% CI 1.3, 2.9), or 30-39 (AOR = 1.5, 95% CI 1.0, 2.3) had higher odds of discontinuing by six months.

Conclusion: A substantial proportion of PrEP patients stopped attending follow-up visits within six months of initiation, with differential discontinuation by age, race/ethnicity, and sexual orientation. Further investigation could distinguish between PrEP discontinuation due to changed HIV risk versus barriers to continuation such as health insurance, competing priorities, or medication factors. Such analysis could improve PrEP implementation in community settings.

Figure 1. Longitudinal use of HIV Pre-exposure prophylaxis (PrEP): Discontinuation among patients prescribed PrEP (n=1,764) prior to March 1, 2017 at the Los Angeles LGBT Center

1010 PrEP IMPLEMENTATION AND PERSISTENCE IN A COUNTY HEALTH DEPARTMENT IN ATLANTA, GA

Charlotte-Paige M. Rolle[1], Udodirim Onwubiko[2], Jennifer Jo[1], Anandi N. Sheth[1], Colleen F. Kelley[1], **David P. Holland**[2]
[1]Emory University, Atlanta, GA, USA, [2]Fulton County Board of Health, Atlanta, GA, USA

Background: HIV Pre-Exposure Prophylaxis (PrEP) uptake is slower in the Southern US and may be limited by structural barriers such as lack of healthcare access. For marginalized populations, county health departments may be important PrEP access points; however, there are little data on successful PrEP programs at these venues outside of incentivized demonstration projects. We implemented an open-access, free PrEP clinic at a county health department in Atlanta, GA and describe early PrEP uptake and persistence estimates.

Methods: The Fulton County Board of Health (FCBOH) PrEP clinic launched in October 2015, and eligible clients who expressed interest initiated PrEP and attended follow-up visits per CDC guidelines. FCBOH covered all costs associated with provider visits and PrEP lab monitoring; clients used their health insurance and/or manufacturer assistance program to obtain the drug. Clients engaged in quarterly follow-up and seen within the last 6 months were defined as "persistent", whereas clients with a lapse in follow-up of ≥ 6 months were defined as "not persistent." Factors associated with PrEP persistence were assessed with unadjusted odds ratios.

Results: Between October 2015 and March 2017, 373 clients were screened for PrEP eligibility in accordance with CDC guidelines. Almost all were eligible [367/373 (98%)]; however, 151/367 (41%) did not return to start PrEP after screening. Over half [216/367 (59%)] of PrEP eligible clients attended an enrollment visit, and 201/216 (76%) received a prescription for PrEP. Of 201 clients who started PrEP, 88% were male, 65% were black, 72% were men who have sex with men, 78% reported inconsistent condom use, and 80% had a prior sexually transmitted infection. As of March 2017, only 78/201 (39%) clients remained persistent in PrEP care, and the only evaluated factor significantly associated with PrEP persistence was lack of health insurance (OR 2.68, 95% CI 1.38, 5.36; Table 1). Among persistent clients who have started PrEP, there have been no HIV seroconversions thus far.

Conclusion: Implementation of PrEP in the county health department setting is feasible and appears to be an effective strategy to reach key populations in need of HIV prevention services. However, we have identified significant challenges with PrEP uptake and persistence in our setting. Further research is needed to fully understand mediators of PrEP persistence and inform interventions to optimize health department-based PrEP services.

Table 1-Factors associated with PrEP persistence among PrEP clinic enrollees at the FCBOH in Atlanta GA 2015-2017

Characteristic	PrEP Persistent (n=78) n (%)	PrEP non-persistent (n=123) n (%)	Unadjusted OR (95% CI)
Sex			
Female	8 (10)	16 (13)	Ref
Male	70 (90)	107 (87)	1.31 (0.55, 3.22)
Age			
<30 y.o.	27 (35)	54 (44)	Ref
≥30 y.o.	51 (65)	69 (56)	1.48 (0.82, 2.66)
Race			
Black	55 (71)	76 (62)	Ref
White	15 (19)	29 (24)	0.72 (0.35, 1.46)
Hispanic	7 (9)	12 (10)	0.81 (0.30, 2.18)
Other*	1 (1)	6 (5)	0.23 (0.03, 1.99)
Education			
Pre-college/Vocational	15 (19)	31 (25)	Ref
College	40 (51)	54 (44)	1.53 (0.73, 3.21)
Post-College/Professional	6 (8)	7 (6)	1.77 (0.51, 6.20)
Income			
<10,000 annually	21 (27)	37 (30)	Ref
≥10,000 annually	39 (50)	55 (45)	1.25 (0.64, 2.45)
Insurance			
Yes	15 (19)	48 (39)	Ref
No	63 (81)	75 (61)	**2.68 (1.38, 5.36)**
Sexual Orientation			
Homosexual	58 (74)	87 (71)	1.20 (0.63, 2.28)
Bisexual/Other	20 (26)	36 (29)	Ref
Relationship status			
Committed relationship	42 (54)	61 (50)	0.97 (0.46, 2.04)
Single	16 (21)	24 (20)	Ref
Referral Source			
STI clinic	35 (45)	56 (46)	Ref
Friend	13 (17)	25 (20)	0.83 (0.38, 1.84)
CBO/ASO/External partners	14 (18)	17 (14	1.32 (0.58, 3.00)
Internet/social media	6 (8)	7 (6)	1.37 (0.43, 4.42)
Condom use[a]			
Always	14 (18)	22 (18)	Ref
Sometimes	46 (59)	64 (52)	1.13 (0.52, 2.44)
Never	4 (5)	11 (9)	0.57 (0.15, 2.15)
Prior reported STI Diagnosis			
Yes	53 (68)	79 (64)	1.23 (0.56, 2.70)
No	12 (13)	22 (18)	Ref
Number of partners			
≤5 partners	49 (63)	79 (64)	Ref
≥6 partners	16 (21)	21 (17)	1.23 (0.59, 2.58)

Note. Significant p-values (<0.05) have been bolded for ease of interpretation.
Abbreviations. PrEP, Pre-Exposure Prophylaxis; OR, Odds Ratio; HS, High School; STI, Sexually Transmitted Infection; CBO, Community-based organization; ASO, AIDS Service organization
*Other includes Asian, Hawaiian and Pacific-islander
[a]Condom use was self-reported

1011 HIV PREEXPOSURE PROPHYLAXIS AS A GATEWAY TO PRIMARY CARE

Julia L. Marcus[1], Kenneth Levine[2], Chris Grasso[2], Douglas Krakower[3], Victoria Powell[2], Kyle T. Bernstein[4], Stephen L. Boswell[2], Kenneth H. Mayer[2]
[1]Harvard University, Cambridge, MA, USA, [2]Fenway Health, Boston, MA, USA, [3]Beth Israel Deaconess Medical Center, Boston, MA, USA, [4]CDC, Atlanta, GA, USA

Background: The HIV-prevention benefits of preexposure prophylaxis (PrEP) have been well-established, but it is unknown whether PrEP is associated with increased utilization of non-HIV-related health care.

Methods: We conducted a cross-sectional study of potential PrEP candidates at Fenway Health, a large primary care clinic and PrEP provider in Boston, Massachusetts, during 2012-2016. For each year, we assessed use of PrEP and routine primary care among HIV-uninfected patients tested for rectal gonorrhea or chlamydia. We used multivariable Poisson models with generalized estimating equations to obtain prevalence ratios (PRs) comparing the proportion of PrEP users and non-PrEP users who received influenza vaccination, hemoglobin A1c or glucose testing, tobacco screening, and depression screening. Adjusted models included age, gender, race/ethnicity, and year, and diabetes and hypertension diagnoses were additionally included in the model assessing hemoglobin A1c or glucose testing.

Results: We identified 5815 HIV-uninfected individuals with at least one rectal gonorrhea or chlamydia test at Fenway Health during 2012-2016, with 2046 (35%) prescribed PrEP during the study period. Compared with non-PrEP users, PrEP users were more frequently cisgender men (97% vs. 85%, P<0.001) and older at the time of their first rectal test (mean age 34 vs. 33 years, P=0.043). PrEP users more often had hypertension (10% vs. 7.9%, P=0.006), but there was no difference between PrEP users and non-PrEP users in the frequency of diabetes (6.7% vs. 6.1%, P=0.32). After adjustment for demographic characteristics, a higher proportion of PrEP users received influenza vaccination (PR 1.58, 95% confidence interval [CI]: 1.48-1.69; P<0.001), tobacco screening (PR 1.13, 95% CI: 1.10-1.17; P<0.001), and depression screening (PR 1.19, 95% CI: 1.16-1.23; P<0.001) compared with individuals who were not prescribed PrEP. After additional adjustment for diabetes and hypertension diagnoses, PrEP users more frequently received hemoglobin A1c or glucose testing (PR 1.86, 95% CI: 1.77-1.94; P<0.001) compared with individuals who were not prescribed PrEP.

Conclusion: PrEP users more often received influenza vaccination, screening for tobacco use and depression, and tests related to diabetes screening and management. Longitudinal studies are warranted to determine if PrEP provides a gateway to primary care, thus extending its benefits to behavioral health, mental health, and prevention and management of other infectious and chronic diseases.

1012 TRENDS IN PrEP UPTAKE, ADHERENCE, AND DISCONTINUATION AMONG YMSM IN CHICAGO

Ethan Morgan, Daniel T. Ryan, Kevin Morgan, Richard D'Aquila, Michael E. Newcomb, Brian Mustanski
Northwestern University, Chicago, IL, USA

Background: Understanding utilization and discontinuation of pre-exposure prophylaxis (PrEP) among young men who have sex with men (YMSM) outside trials and demonstration projects is key in order to inform interventions utilizing PrEP to slow the spread of HIV through this highly impacted population.
Methods: Data came from RADAR (N = 1031), an ongoing longitudinal cohort of YMSM (aged 16-29) in Chicago. Trends in PrEP use, adherence, and discontinuation were assessed across five time points of data collection. Poisson regression was utilized to assess trends in PrEP uptake, stratifying by race and ethnicity. Unadjusted and adjusted logistic regression models were utilized to assess the relationship between baseline characteristics and past six-month PrEP use.
Results: Across the first three visits in 2015 to 2017, PrEP use in the past six months increased: 6.6% in visit one to 17.5% in visit three. These increases were significant only among white (IRR=1.45; 95% CI: 1.04-2.02) and Hispanic (IRR=1.59; 95% CI: 1.11-2.28) participants; no significant increase was observed among black participants. PrEP use was significantly associated with condomless sex (AOR=2.95; 95% CI: 1.38-6.28), having more sexual partners (AOR = 1.07; 95% CI: 1.03-1.12), and older age (AOR=1.18; 95% CI: 1.07-1.30). Those who used marijuana were also significantly less likely to use PrEP (AOR=0.94; 95% CI: 0.89-0.99). PrEP use was not significantly associated with rectal STIs (AOR=1.34; 95% CI: 0.65-2.75). No significant association was observed between PrEP use and education, alcohol use, or other substance use. We also observed that a majority of individuals reported being at least 90% adherent to their PrEP medication across visits one (77.1%), two (83.3%), and three (81.8%). Sixty-five (33.0%) participants discontinued PrEP use prior to the interview date. Primary reasons for PrEP discontinuation included trouble getting to doctor's appointments (21.5%) and issues related to insurance coverage or loss (20.0%).
Conclusion: We observed an increasing trend of six-month PrEP use among white YMSM in Chicago, and not among those of other race/ethnicity, from 2015 to 2017. Individuals who reported high risk HIV behaviors were also more likely to have used PrEP. Future research should be targeted at understanding longitudinal time- or age-related trends in PrEP uptake as well the drivers of decisions about other prevention strategies following discontinuation of PrEP.

1013 PATTERNS AND CORRELATES OF PARTICIPANT RETENTION IN THE US PrEP DEMO PROJECT

Susanne Doblecki-Lewis[1], Daniel Feaster[1], Albert Y. Liu[2], Stephanie E. Cohen[2], Richard A. Elion[3], Oliver Bacon[4], Gabriel Cardenas[1], Michael Kolber[1], Megan Coleman[5]
[1]University of Miami, Miami, FL, USA, [2]San Francisco Department of Public Health, San Francisco, CA, USA, [3]The George Washington University, Washington, DC, USA, [4]University of California San Francisco, San Francisco, CA, USA, [5]Whitman-Walker Health, Washington, DC, USA

Background: Safe and effective use of Pre-exposure prophylaxis (PrEP) depends on retention in prevention care after initial engagement. In the U.S. PrEP Demonstration Project, daily oral tenofovir/emtricitabine was offered to eligible men who have sex with men and transgender women for 48 weeks. We assessed patterns of retention among those electing to participate in the project and who received at least one month of medication.
Methods: Patterns of retention were assigned to one of three categories: early loss to follow-up (ELTF) within the first 12 weeks of the study, retention throughout the follow-up period, or intermittent retention with missed visits resulting in less than full medication coverage during the study period. For each retention group, baseline and enrollment survey responses, demographics, and clinical characteristics were tabulated. Predictors were divided into demographic and behavioral domains and a multivariable model for each was created by adding in all variables within the domain in which $p<0.05$ in the initial models. These two models were combined including those predictors from these two intermediate models with $p<.05$. Odds Ratios were calculated for each of the variables retained in the final multivariable model.
Results: Overall, 366/557 (65.7%) of enrolled participants in the Demo Project were retained for all study visits, 127/557 (22.8%) had intermittent retention, and 64/557 (11.5%) had early loss to follow-up (ELTF). Multivariable analysis of characteristics revealed that Miami site compared to San Francisco site was associated with ELTF rather than full retention (aOR 2.53; CI:1.12-5.71) and also with intermittent rather than full retention (aOR 2.92; CI:1.52-5.59). Decrease in age by 10 years was associated with both ELTF (aOR 1.58; CI:1.14-2.21) and intermittent retention (aOR 1.48; CI:1.17-1.87) compared with full retention. Factors associated with ELTF but not intermittent retention compared with full retention were black race (aOR 4.30; CI:1.26-14.73), higher HIV risk perception (aOR 4.21; CI 1.63-10.87), lack of regular employment (aOR 2.66; CI: 1.36-5.19), and lack of prior awareness of PrEP (aOR 2.36; CI:1.19-4.68). Baseline STI rates were similar across groups when adjusted for reason for visit.
Conclusion: Tailored interventions addressing different potential causes and risk factors for loss from PrEP care may improve retention in services and consistency of PrEP use.

1014 INCREASING PrEP UPTAKE, PERSISTENT DISPARITIES IN AT-RISK PATIENTS IN A BOSTON CENTER

Kenneth H. Mayer[1], Chris Grasso[1], Kenneth Levine[1], Douglas Krakower[2], Victoria Powell[2], Stephen L. Boswell[1], Julia L. Marcus[3]
[1]Fenway Health, Boston, MA, USA, [2]Beth Israel Deaconess Medical Center, Boston, MA, USA, [3]Harvard University, Cambridge, MA, USA

Background: Although HIV pre-exposure prophylaxis (PrEP) was approved for high-risk persons in 2012, uptake was initially, slow and some groups were underrepresented among PrEP users. Centers caring for large numbers of high-risk people can facilitate monitoring trends and disparities in PrEP use.
Methods: A cross-sectional study was conducted in a Boston community health center (CHC) with the most PrEP experience in New England. For each year during 2012-2016, data were analyzed from potential PrEP candidates – i.e., HIV-uninfected patients screened for rectal sexually transmitted infections (STIs). Chi-square tests were used to compare demographic characteristics between patients who were and were not prescribed PrEP each year, and to test for trends over time.
Results: In 2012, 2.3% of 681 patients screened for rectal STIs were prescribed PrEP, whereas by 2016, 49% of 3333 were ($P<0.001$). Among rectally screened patients, PrEP use increased over time for all age, gender, race/ethnicity, and insurance type subgroups, except for cisgender women ($P=0.32$). PrEP uptake was consistently lower among younger patients screened for rectal STIs, with only 34% aged <25 years prescribed PrEP in 2016 compared with 53% of those aged ≥25 years ($P<0.001$). PrEP users were mostly White in all years, but PrEP uptake was highest in Hispanic patients in 2014-2016; in 2016, PrEP use was 39% and 41% among Asian and Black patients screened for rectal STIs, compared with 51% and 55% among White and Hispanic patients, respectively ($P<0.001$). All PrEP users were cisgender males in 2012; by 2016, 2.9% were transgender and 0.1% were cisgender women. Among rectally screened patients in 2016, 53% of cisgender males used PrEP compared with 21% of transgender patients and 1.7% of cisgender women ($P<0.001$). In 2016, a higher proportion of PrEP users had private insurance (82% vs. 76%) and a lower proportion had Medicaid or other public insurance (6.9% vs. 12%) compared with non-PrEP users ($P<0.001$). Among rectally screened patients in 2016, PrEP use ranged from 40% among those with Medicaid or other public insurance to 55% among privately insured patients ($P<0.001$).
Conclusion: PrEP uptake increased steeply at a Boston CHC, but in 2016, nearly half of rectally screened patients were not using PrEP, and disparities in uptake persisted. Strategies are needed to mitigate barriers to PrEP use among racial/ethnic minorities, cisgender and transgender women, and younger and underinsured individuals.

1015 DISPARITIES IN PrEP UPTAKE AMONG PRIMARY CARE PATIENTS SCREENED FOR HIV/STIs IN SF

Hyman Scott[1], Anne Hirozawa[1], Miranda Nordell[1], Monica Gandhi[2], Catherine James[1], Hali Hammer[1], Susan Scheer[1], Susan P. Buchbinder[1]
[1]San Francisco Department of Public Health, San Francisco, CA, USA, [2]University of California San Francisco, San Francisco, CA, USA

Background: Although pre-exposure prophylaxis (PrEP) across San Francisco is expanding, significant age, gender, and racial/ethnic disparities in uptake persist. Via a data-driven approach, we created a PrEP registry and a high-risk non-PrEP registry to identify patients in primary care who may benefit from targeted outreach.

Methods: Starting in January 2016, patients receiving PrEP within the San Francisco Department of Public Health Primary Care (SFPC) clinics were included in a registry if they had received a PrEP prescription from a SFPC medical provider and were confirmed HIV-negative via laboratory and medical chart review. In the absence of structured medical record data on HIV-risk, we used available laboratory data to identify high-risk non-PrEP patients if they were HIV-negative; were not prescribed PrEP; and either were screened for a rectal sexually transmitted infection, were diagnosed with syphilis in the past 12 months, or received ≥3 HIV tests in a 24 month period. This analysis compares PrEP patients to non-PrEP patients as of 5/31/2017. Chi-square tests measure the bivariate association between PrEP initiation, demographics, and active panel status (assigned to a SFPC clinic and primary care provider, with at least one primary care visit in the last 24 months). A multivariate logistic regression model with an outcome of not initiating PrEP was created.

Results: Overall, 451 patients were confirmed to have started PrEP and 2,109 patients were identified as high-risk non-PrEP patients. Non-PrEP patients were more likely to be female (45% vs 16%, p<0.01), Black (32% vs 14%, p <0.01), and ≥50 years (24% vs 18%, p=0.02); and less likely to be active on a care panel (52% vs 86%, p<0.01). In a multivariate analysis controlling for active panel status, non-PrEP patients were more likely to be women [adjusted OR (aOR) 5.64; 95%CI:4.22-7.54)], Black (aOR 2.85; 95%CI:2.03-4.00), Latino (aOR 1.38; 95%CI:1.02-1.87), and ≥50 years (aOR 2.18; 95%CI:1.60-2.95) than PrEP patients. Active panel status was a strong negative predictor of being a non-PrEP patient (aOR 0.13; 95%CI:0.09-0.17).

Conclusion: Age, gender, and racial/ethnic disparities remain in PrEP uptake across DPH-funded primary care clinics in San Francisco, suggesting that access to care is not sufficient to address these disparities. Additional interventions, informed by this data-driven approach, are needed to help both primary care providers and patients identify risk and, respectively, prescribe and initiate PrEP.

1016 EARLY ADOPTERS OF PrEP AMONG MSM IN INDIA AND DETERMINANTS OF EMERGING DISPARITIES

Viraj V. Patel[1], Alpana Dange[2], Sarit A. Golub[3], Shruta Neytra[2], Yashesh Parekh[1], Christopher Pina[1], Julia H. Arnsten[1], Jack Harrison-Quintana[4], Kenneth H. Mayer[5]
[1]Albert Einstein College of Medicine, Bronx, NY, USA, [2]Humsafar Trust, Mumbai, India, [3]Hunter HIV/AIDS Research Team, New York, NY, USA, [4]Grindr for Equality, Washington, DC, USA, [5]Fenway Health, Boston, MA, USA

Background: The degree of PrEP interest among MSM in India is unknown. We sought to understand the prevalence of PrEP use and characterize unlikely users in a sample of sexually active MSM at high risk of HIV infection.

Methods: From Jan-Feb 2017, we recruited sexually active, HIV-negative or unaware MSM (≥ 18 years) across India via multiple social media and MSM mobile dating sites to complete an online survey in Hindi or English, and assessed likelihood of PrEP use. We used multivariable GEE logistic regression, accounting for clustering by state, to identify factors independently associated with unlikely PrEP users (compared to likely users) in MSM at high risk of HIV infection (any condomless anal sex (CAS) or ≥3 anal sex partners in the past 6 months, or stimulant drug use with sex or a STI diagnosis in the past year).

Results: The 2,494 MSM completing the survey came from all states and 416 cities, 16% from rural areas; 18% responded in Hindi. Their median age was 26, most (83%) completed college, and 16% were categorized as being in poverty; 52% identified as gay/homosexual, 44% as bisexual, and 4% as heterosexual; 39% had never disclosed their sexual identity to anyone, and most (74%) had never disclosed same-sex behaviors to a doctor. In the past six months, participants had a median of 7 sexual partners, 54% had any CAS, and in the past year, 9% had a STI. Overall, only 16% were aware of PrEP, 1.3% (n=32) had used PrEP, and 37% were unlikely to use PrEP. PrEP users mostly completed the survey in English (90%), were <35 years old (87%), had high income (>₹20,000/month), college degrees (75%), and lived in urban areas (75%). In multivariable analyses, shown by aOR(95% CI), unlikely users had higher HIV related stigma: 1.2 (1.1,1.3); low risk perception: 2.9 (1.2,6.7)(REF: high risk); easy access to HIV testing 1.4(1.1,1.7)(REF: not easy); more CAS: 1.3 (1, 1.7); ≤4 sex partners/6 months: 1.3 (1,1.7) (REF: >4 partners); no drug use with sex: 1.4 (1.1,2)(REF: any use); ₹40,000/month); rural residence: 1.6 (1.2,2.2) (REF: metropolis); and older age: 1.02 (1,1.03).

Conclusion: In this first study of PrEP adoption among MSM in India, PrEP use was low, but interest was high. Implementation efforts targeting unlikely users and focusing on access and affordability may help mitigate emerging socioeconomic and geographic disparities in PrEP uptake.

Table. Characteristics of MSM at High Risk of HIV in India Unlikely to Use PrEP

	Adjusted Odds Ratio	95% CI	p
Perceived HIV Stigma*	1.23	1.13 1.33	<0.001
Low Perceived Lifetime HIV Risk (ref: >10%)*	2.89	1.24 6.73	0.014
Easy to access to free HIV testing (ref: not easy)*	1.37	1.10 1.71	0.005
≤4 sex partners in past 6 months (ref: ≥5 partners)*	1.31	1.04 1.66	0.023
% of Partners engaged in condomless sex/6 months*	1.34	1.08 1.66	0.007
No drug use with sex (ref: Yes)*	1.44	1.06 1.97	0.022
Not Out about sexual-identity (ref: out to anyone)*	1.21	1.01 1.46	0.043
Sexual Orientation (ref: Gay/Homosexual)			
Bisexual*	1.32	1.03 1.69	0.028
Heterosexual/Straight	1.01	0.63 1.62	0.976
Education (ref: Professional/Honors)			
Middle School or less*	3.37	2.04 5.57	<0.001
High School Diploma	1.08	0.73 1.59	0.706
Post-HS Diploma	1.16	0.81 1.66	0.413
College Graduate	0.92	0.73 1.16	0.48
Household Income (Rs/Month) (ref: >40,000)			
≤10,000*	1.34	1.09 1.64	0.005
10,001-15,000	1.06	0.75 1.50	0.732
15,001-20,000	0.95	0.71 1.27	0.709
20,001-40,000*	1.23	1.02 1.48	0.032
City Size (ref: Metropolitan area)			
Rural*	1.60	1.19 2.16	0.002
Semi-Urban	1.04	0.75 1.44	0.834
Urban	1.13	0.92 1.39	0.245
Age*	1.02	1.01 1.03	0.007

1017 ACCEPTABILITY OF PrEP AMONG A LARGE COHORT OF YOUNG TRANSGENDER WOMEN IN 2 US CITIES

Arjee J. Restar[1], Lisa Kuhns[2], Sari Reisner[3], Robert Garofalo[4], Matthew J. Mimiaga[1]
[1]Brown University, Providence, RI, USA, [2]Northwestern University, Chicago, IL, USA, [3]Harvard University, Cambridge, MA, USA, [4]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Background: Truvada as Pre-exposure prophylaxis (PrEP) is an efficacious biomedical prevention modality for individuals at increased risk of becoming infected with HIV, including young transgender women (YTW). However, no published studies to our knowledge have examined PrEP acceptability and its associated factors among this group. The current study examined the prevalence of PrEP acceptability and related factors among HIV uninfected, YTW in two major urban cities in the US.

Methods: Between 2012 to 2015, 300 sexually active YTW (aged 16-29) from Boston and Chicago enrolled in Project LifeSkills, the first behavioral HIV prevention efficacy trial for transgender women in the US. YTW were asked to complete a baseline assessment of socio- demographics and healthcare utilization characteristics, as well as PrEP acceptability, interest, and awareness. The present analysis was restricted to HIV uninfected YTW (n = 230), who maybe likely candidates for PrEP. Factors associated with PrEP acceptability (continuous scores, sample mean=23.4, range=10.0-30.0) were examined using multiple linear regression procedures.

Results: Participants' mean age was 23 years; the sample was 42% black, 13% Latina, 33% white, and 12% other minority race/ethnicity. In a final model, PrEP interest (β = 3.7, 95% Confidence Interval [95%CI] = 2.2 – 5.2) and having

providers who meet YTW's health needs (β = 2.9, 95%CI = 1.3 – 4.4) were associated with an increase in PrEP acceptability scores, whereas younger age (aged 21-25 vs 26-29 years) (β = –2.0, 95%CI = -3.6 – -0.4) and reporting transactional sex in the last 4 months (β = –1.5, 95% CI = -3.0 – -0.1) were associated with lower PrEP acceptability scores (all p's<0.05). The majority (66.1%) of YTW in this sample were interested in PrEP use. The most commonly reported reasons for being uninterested in PrEP included 1) concerns related to medication side effects (20.5%) and 2) mistrust with medical providers (16.7%).
Conclusion: Overall, PrEP acceptability was high among this community-recruited sample of sexually active YTW. Interventions that seek to build trust between providers and YTW, as well as provide culturally responsive sources of educational materials on PrEP related side effects may bolster PrEP acceptability, particularly among youth or those with recent sex work. PrEP programs that seek to meet YTW's other health needs (e.g., hormone therapy) in addition to PrEP services may also increase PrEP acceptability.

1018 AUTOMATED IDENTIFICATION OF POTENTIAL PrEP CANDIDATES USING ELECTRONIC HEALTH DATA

Douglas Krakower[1], Susan Gruber[2], John T. Menchaca[2], Sharon Ulery[3], Ira B. Wilson[4], Kenneth H. Mayer[3], Michael Klompas[2]
[1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]Harvard University, Boston, MA, USA, [3]Fenway Health, Boston, MA, USA, [4]Brown University, Providence, RI, USA

Background: To maximize the population-level impact of pre-exposure prophylaxis (PrEP), healthcare organizations need tools to identify persons at risk for HIV infection. We hypothesized that electronic health record (EHR) data could be used to identify patients (pts) at increased risk for acquiring HIV who might be candidates for PrEP.
Methods: We developed and evaluated automated algorithms to predict incident HIV infection using EHR data from a community health center in Boston specializing in health care for sexual and gender minorities. EHR data were extracted for 168 variables potentially associated with incident HIV for all pts with ≥1 clinical encounter during 2011-2016. EHR variables included patient demographics (e.g. age, gender), laboratory tests and results (e.g. tests for HIV and sexually transmitted infections), diagnosis codes (e.g. HIV counseling), coinfections (e.g. hepatitis B or C), suggestive routine care (e.g. anal cytology) and prescriptions (e.g. buprenorphine). Candidate HIV prediction algorithms were developed using machine learning methods (LASSO, ridge regression, random forest) and generalized linear models and were used to estimate risk for incident HIV for all pts. Algorithms were trained using 2011-2015 data and validated using 2016 data; pts using PrEP were excluded from analyses. We assessed algorithm performance using area under the receiver operator curves (AUC), sensitivity, specificity, and positive predictive value (PPV).
Results: Of 33,404 pts in care during 2011-2016, 64% were male (of whom 46% identified as gay/bisexual) and 8% were transgender/gender non-conforming, and 68% were white, 8% were Black, and 6% were Latino; HIV prevalence was 9% and 5% of pts used PrEP. In total, 423 pts (1.3%) had incident HIV, including 71 of 18,275 pts in care during 2016. AUCs for candidate prediction algorithms ranged from 0.43 to 0.83; LASSO had the highest AUC. Using a cut-off of the top 20% of patient risk scores, LASSO had a sensitivity of 73%, specificity of 81% and PPV of 1.5% for predicting incident HIV in 2016. We varied this cut-off to explore trade-offs in sensitivity, PPV, and population size identified as screen-positive. (Table)
Conclusion: Automated algorithms that integrate EHR data have favorable properties as population-level screening tools to identify patients who merit clinical evaluations for PrEP. Despite low PPVs, these algorithms offer an efficient means of reducing missed opportunities to provide PrEP to those patients most likely to acquire HIV.

Table. Performance of HIV prediction algorithm at identifying patients with incident HIV infection (n=71) among all patients in care during 2016 (n=18,275) at selected cut-offs.

Selected Cut-off	Sensitivity	Specificity	Positive Predictive Value	No. Patients above Cut-off	Percentage of Total Population above Cut-off
Top 20% of risk scores	73%	81%	1.5%	3861	22.3%
Top 10% of risk scores	32%	95%	2.5%	912	5.3%
Top 5% of risk scores	32%	95%	2.6%	863	5.0%
Scores above observed inflection point in risk scores (top 1% of risk scores)	8%	99%	3.5%	113	0.7%

1019 MONITORING PrEP USE AMONG WASHINGTON STATE MSM: RESULTS OF AN INTERNET SURVEY

Darcy W. Rao[1], Jason Carr[2], Kelly Naismith[2], Julia Hood[3], James P. Hughes[1], **Matthew R. Golden**[1]
[1]University of Washington, Seattle, WA, USA, [2]Washington State Department of Health, Olympia, WA, USA, [3]Public Health–Seattle & King County, Seattle, WA, USA

Background: Pre-exposure prophylaxis (PrEP) is a key component of the National HIV/AIDS Strategy. Many state and local health departments now promote and support the use of PrEP, yet monitoring PrEP use at the population level remains challenging. We report results of a statewide Internet survey of men who have sex with men (MSM) designed to measure PrEP use and related behaviors.
Methods: We used banner and broadcast advertisements on social media, sexual networking, and LGBTQ-interest websites and apps to recruit MSM to complete an online survey. For this analysis, eligible participants were cisgender men ages 16+ who lived in Washington State, reported oral or anal sex with a man in the past 12 months, and had never tested positive for HIV. Men who had used PrEP provided their dates of first and, if applicable, last use. Past users were asked to indicate their reasons for discontinuing, and men who had never used PrEP indicated their reasons for not initiating. We conducted bivariate and multivariable logistic regression to identify factors associated with PrEP use, and we estimated time to PrEP discontinuation by fitting a Kaplan Meier curve to reported data on time on PrEP.
Results: From January 1 to February 28, 2017, a total of 1,080 men responded to the survey and were eligible for this analysis. The median age of participants was 30, 68% identified as non-Hispanic white, and 49% had a 4-year college degree or higher education. Based on WA State guidelines, 33% of participants are recommended to initiate PrEP, and 30% met indications for discussing PrEP with a provider. Overall, 79% of respondents had heard of PrEP, 19% reported current use, and 4% reported past use. Current PrEP use was independently associated with age, higher education, and PrEP candidacy. In Kaplan-Meier analysis, an estimated 19% of men discontinue PrEP within 12 months of initiation (95% CI 14%, 26%). The primary reason for discontinuation was no longer feeling at high risk for HIV (52%). Among men recommended for PrEP, 31% reported current use, and 56% of those who had never used PrEP were interested in starting it. The primary reason for not starting PrEP among MSM for whom state guidelines recommend use was low perceived risk (29%). The survey cost $19 per complete response.
Conclusion: Internet-based surveys of MSM are a feasible, low-cost means of monitoring PrEP use. Our findings suggest that PrEP use in WA State is relatively widespread, although the majority of MSM for whom PrEP is recommended are not taking it.

PrEP use by demographic and behavioral characteristics among cisgender men who have sex with men in Washington State (N=1,080[a])

	Total n	Never used PrEP (%)	Currently using PrEP (%)	Used PrEP in the Past (%)	p-value[b]
Overall	1,080	77.0%	18.5%	4.4%	
Age					<0.001
16 to 29	510	85.5%	11.8%	2.7%	
30 to 49	392	65.3%	29.6%	5.1%	
50 and older	178	78.7%	13.5%	7.9%	
Race/ethnicity					0.555
Hispanic	198	80.8%	14.1%	5.1%	
Non-Hispanic white	725	76.0%	19.4%	4.6%	
Non-Hispanic black	42	73.8%	21.4%	4.8%	
Non-Hispanic other	102	80.4%	17.6%	2.0%	
Education					<0.001
<4-year college degree	540	85.4%	10.2%	4.4%	
4-year college or higher	525	67.8%	27.6%	4.6%	
PrEP candidacy					<0.001
Recommend[c]	303	63.4%	30.7%	5.9%	
Discuss[d]	271	70.1%	25.5%	4.4%	
Not indicated	338	93.2%	4.1%	2.7%	

[a] Denominators may vary due to missing data; [b] Pearson χ^2 p-value; [c] WA State guidelines recommend PrEP for MSM with a history of syphilis or rectal gonorrhea, use of methamphetamine or poppers, or exchange sex in the prior 12 months, and those in ongoing sexual relationships with HIV+ partners who are not on antiretroviral therapy (ART), on ART <6 months, or who are not virologically suppressed; [d] Guidelines recommend that medical providers discuss PrEP with MSM without the above criteria who report condomless anal sex (CAS) with a partner who is not main/primary, CAS with an HIV+ or unknown status partner, diagnosis of urethral gonorrhea or rectal chlamydia, or injection drug use in the past 12 months, and those in ongoing sexual relationships with HIV+ partners who have been on ART ≥6 months and who are virologically suppressed

1020 COMPARING THE CHARACTERISTICS OF BRAZILIAN MSM USING APP FOR SEXUAL ENCOUNTERS

Thiago S. Torres[1], Raquel B. De Boni[1], Mauricio Vasconcelos[2], Paula M. Luz[1], Brenda Hoagland[1], Ronaldo I. Moreira[1], Alex Garner[3], Valdilea Veloso[1], Beatriz Grinsztejn[1]
[1]Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil, [2]Escola Nacional de Ciências Estatísticas, Rio de Janeiro, Brazil, [3]Hornet Networks, Los Angeles, CA, USA

Background: Geosocial networking (GSN) smartphone applications (apps) are becoming the main venue for sexual encounters among Brazilian men who have sex with men (MSM). As HIV infection risk has been increasing among MSM, the Brazilian government recently adopted pre-exposure prophylaxis (PrEP) which will be provided by the National Health System. Accordingly, an understanding of the profile of MSM who use apps for sexual encounters is needed to design combined prevention interventions tailored for this group.
Methods: Two cross-sectional online surveys using the same questionnaire were conducted in July 2016 and July 2017. Inclusion criteria were ≥ 18 years of age, cisgender, HIV uninfected and residence in any of the ten selected Brazilian capitals Chi-square tests were used to compare characteristics of MSM recruited in the two studies.
Results: A total of 2800 and 2497 MSM completed the survey in 2016 and 2017, respectively. Median age was 30 years (IQR25-36) in both years, but more MSM aged ≤24 years were included in 2017 (26.1% vs. 29.0; p=0.036). Compared to 2016, participants with the following characteristics were more represented in the 2017 survey: non-white (36.5 vs. 42.5; p<.001), bisexual (9.2% vs. 12.9%; p<.001), less educated (<12 years: 41.4% vs. 49.5%; p<.001) and lower monthly income (≤3 Brazilian Minimum Wage - USD 250: 34.1 vs. 45.4; p<.001). Scores on "The HIV Incidence Risk for MSM" scale (≥10 points: 66.5% vs. 68.2%, p=0.19) and STI diagnosis (12.4% vs. 14.0%; p=0.08) were similar. Perceived likelihood of getting HIV was higher in 2017 (21.1% vs. 25.3%, p=0.001), although more MSM reported never testing for HIV (14.3% vs. 20.3%, p<.001) and receiving money for sex (3.3% vs. 5.5%; p<.001). Having a male steady partner (18.0% vs. 19.3%; p=0.22), binge drinking (71.7% vs. 73.6%; p=0.13) and stimulants use (22.5% vs. 20.6%; p=0.08) were similar. Awareness of PrEP and nPEP was lower in 2017, while willingness to use oral daily PrEP and non-occupational post-exposure prophylaxis (nPEP) was higher. Willingness to use PrEP injection and HIV self-testing (HIVST) was higher in 2016 (Table 1).
Conclusion: Our results suggest that the use of GNS apps seems to have spread across younger and less educated MSM in 2017, which may explain the lower PrEP awareness in this year. As this population stratum is at the highest risk of HIV acquisition in Brazil, mobile health tools are a promising means to reach these individuals in order to increase awareness and demand of new prevention strategies.

Table 1. Awareness and willingness to use HIV prevention strategies (N=5297). Brazil, 2016 and 2017.

		2016 N=2800(%)	2017 N=2497(%)	Total N=5297(%)	p-value
Awareness	PrEP	**1702(60.8)**	1317(52.7)	3019(57.0)	**<.001**
	nPEP	**1700(60.7)**	1325(53.1)	3025(57.1)	**<.001**
	HIVST	732(26.1)	**820(32.8)**	1552(29.3)	**<.001**
Willingness	Oral daily PrEP	1472(52.6)	**1398(56.0)**	2870(54.2)	**0.012**
	Oral PrEP (on demand)	1042(37.2)	923(37.0)	1965(37.1)	0.851
	Injectable PrEP	**1365(48.7)**	1112(44.5)	2477(46.8)	**0.002**
	PrEP (during short periods)	2571(91.8)	2256(90.3)	4827(91.1)	0.060
	Condom	2057(73.5)	1849(74.1)	3906(73.7)	0.612
	nPEP	1800(64.3)	**1673(67.0)**	3473(65.6)	**0.036**
	HIVST	**1390(49.6)**	1062(42.5)	2452(46.3)	**<.001**

1021 HIV RISK PERCEPTION AMONG MEN WHO HAVE SEX WITH MEN: A RANDOMIZED CONTROLLED TRIAL

Jill Blumenthal[1], Donald E. Mulvihill[1], Sonia Jain[2], Sara Graber[1], Marvin Hanashiro[1], Eric Ellorin[1], Xiaoying Sun[2], Richard Haubrich[3], Sheldon Morris[1]
[1]University of California San Diego, San Diego, CA, USA, [2]University of California San Diego, La Jolla, CA, USA, [3]Gilead Sciences, Inc, Foster City, CA, USA

Background: Despite greater access to PrEP, one barrier to HIV prevention is inaccurate risk perception by MSM. Providing information about objective HIV risk could improve PrEP uptake.
Methods: PrEP Accessability Research and Evaluation 2 (PrEPARE2) was an RCT examining if providing a calculated HIV risk score affects PrEP uptake in at-risk HIV- MSM recruited from HIV testing sites. Participants received a baseline survey assessing demographics, risk behaviors and HIV risk perception. Self-perceived risk (SPR) score was the perceived likelihood of acquiring HIV based on 3 risk perception questions. The survey also generated an HIV risk score (CalcR), which estimated an individual's 1 year risk of acquiring HIV compared to the average risk for MSM based on reported condomless anal sex acts, STIs and needle sharing events. SPR and CalcR scores categorized risk as low, medium, high and very high. Participants randomized 1:1 to the intervention arm were provided the CalcR category; control subjects received standard risk reduction counseling. Participants were contacted at 8 weeks to determine if they had started PrEP (primary endpoint). Fisher's exact test was used to compare the difference in PrEP uptake between arms. Cohen's kappa coefficient evaluated the agreement between the 2 risk scores.
Results: Of 171 participants (n=85 control and n=86 CalcR intervention), median age was 32, 29% Latino, 60% White, 8% Black. Most had heard of PrEP (81%), and 57% thought they were good PrEP candidates. Participants had a median of 5 partners in the past 6 months (IQR: 3-10). SPR had poor agreement with the CalcR score (kappa=0.176) with more than one-third underestimating their HIV risk. At week 8, n=135 participants were reached for follow up, notably n=59 (70%) in control and n=76 (87%) in the intervention arm (p<0.001). Only 14 subjects reached for follow up initiated PrEP with no difference between randomized groups (CalcR 11%, control 10%, p=1.0). The most common reasons for not starting PrEP were low risk perception (36%), and not wanting to take pills (18%); 13% reported waiting for a PrEP visit.
Conclusion: In this cohort of at-risk MSM, providing an objective HIV risk score alone did not increase PrEP uptake, perhaps due to discordance between self-perceived and actual HIV risk. Further, many participants did not think their risk was high enough to use PrEP. Thus, HIV testing may be a crucial time to correct misperceptions about HIV risk and initiate same day PrEP to facilitate greater PrEP uptake.

Objective Compared to Subjective HIV Risk

		CalcR			Total
		Low	Moderate	High/V.High	
SPR	Low	42	**36**	**12**	90
	Moderate	10	38	**17**	65
	High/V. high	8	5	3	16
Total		60	79	32	171

1022LB DISTRIBUTION OF ACTIVE PrEP PRESCRIPTIONS AND THE PrEP-TO-NEED RATIO, US, Q2 2017

Aaron J. Siegler[1], Farah Mouhanna[1], Robertino Mera Giler[2], Scott McCallister[2], Howa Yeung[1], Jeb Jones[1], Jodie L. Guest[1], Michael Kramer[1], Cory Woodyatt[1], Elizabeth Pembleton[1], Patrick S. Sullivan[1]
[1]Emory University, Atlanta, GA, USA, [2]Gilead Sciences, Inc, Foster City, CA, USA

Background: Cumulative unique persons starting oral TDF/FTC for PrEP in the United States since 2012, including those actively on PrEP and those who have discontinued PrEP, is estimated to be 140,000. This study is the first to describe the magnitude and distribution of active PrEP prescriptions.
Methods: Data on active PrEP prescriptions, defined as ≥1 day of PrEP in Q2 2017 for unique persons, were generated from a national prescription database. An algorithm that includes a minimum 30 day prescription period was used to identify each TDF/FTC for PrEP prescription. Active PrEP prescriptions were calculated per population (PrEP prevalence) by region, gender, and age. HIV diagnoses from 2016, based on CDC surveillance data, were used as an epidemiological proxy for PrEP need. The ratio of PrEP prescriptions per new HIV diagnosis (PrEP-to-need ratio) was used to describe the distribution of prescriptions relative to need.
Results: A total of 61,298 unique individuals had active PrEP prescriptions: 58,603 male and 2,695 female; 6,422 aged ≤24; 24,144 aged 25-34; 15,197 aged 35-44; 10,786 aged 45-54; and 4,866 aged ≥ 55. Nationally, PrEP prevalence was 23.2/100,000 and the PrEP-to-need ratio was 1.5. Males had higher prevalence (45.5/100,000) than females (2.0/100,000), and more than four times the PrEP-to-need ratio (1.8 and 0.4). Persons aged ≤24 had low prevalence (12.3/100,000) and low PrEP-to-need ratio (0.8). The Northeast region had the highest prevalence (38.5/100,000), and the Midwest (18.7/100,000) and South (18.8/100,000) the lowest. The PrEP-to-need ratio was three times higher in the Northeast (2.9) than in the South (0.9). States with Medicaid expansion had higher prevalence (27.0/100,000) than states without expansion (17.1/100,000), and more than double the PrEP-to-need ratio (2.1 and 0.9).

Conclusion: Compared to cumulative starts, active PrEP prescriptions serve as a better indicator of persons potentially receiving protective effects of TDF/FTC for PrEP. Both active PrEP prescription prevalence and PrEP-to-need ratios had substantial variation. Females, persons under 25, residents of the Southern region, and residents of non-Medicaid expansion states all received fewer prescriptions per capita and lower levels of prescription in comparison to epidemic need. The PrEP-to-need ratio may be useful for future assessments of health disparities.

Table 1. Active PrEP prescription by region, age group, and gender in Q2 of 2017 in the United States

		Total	Age Group					Gender	
			≤24 years	25-34 years	35-44 years	45 -54 years	≥ 55 years	Males	Females
Midwest	N (%)	10,518 (17.2)	1,301 (20.3)	4,222 (17.5)	2,527 (16.6)	1,777 (16.5)	712 (14.6)	10,016 (17.1)	502 (18.6)
	PrEP prescription prevalence*	18.7	11.6	48.1	30.2	18.8	3.8	36.4	1.7
	PrEP-to-need ratio**	**2.1**	**1.0**	**2.5**	**2.8**	**2.4**	**1.6**	**2.4**	**0.5**
Northeast	N (%)	18,266 (29.8)	2,216 (34.5)	7,639 (31.6)	4,387 (28.9)	2,804 (26.0)	1,252 (25.7)	17,335 (29.6)	931 (34.5)
	PrEP prescription prevalence	38.5	24.6	103.1	62.0	34.0	8.0	75.7	3.8
	PrEP-to-need ratio	**2.9**	**2.0**	**3.6**	**3.6**	**2.6**	**1.7**	**3.6**	**0.6**
South	N (%)	18,503 (30.2)	1,706 (26.6)	7,072 (29.3)	4,651 (30.6)	3,518 (32.6)	1,591 (32.7)	17,687 (30.2)	816 (30.3)
	PrEP prescription prevalence	18.8	8.7	44.2	30.2	21.6	5.1	37.0	1.6
	PrEP-to-need ratio	**0.9**	**0.7**	**1.0**	**1.2**	**1.2**	**0.8**	**1.1**	**0.2**
West	N (%)	14,011 (22.9)	1,199 (18.7)	5,211 (21.6)	3,632 (23.9)	2,687 (24.9)	1,311 (26.9)	13,565 (23.1)	446 (16.5)
	PrEP prescription prevalence	22.8	9.6	48.8	37.0	27.0	7.0	44.5	1.4
	PrEP-to-need ratio	**1.8**	**0.8**	**1.9**	**2.2**	**2.1**	**2.0**	**2.0**	**0.4**

* Number of active PrEP prescriptions in Q2 2017 per 100,000 population.
** Ratio of active PrEP prescriptions in Q2 of 2017 per new HIV diagnosis in 2016.

1023 EFFECT OF ON DEMAND ORAL PrEP WITH TDF/FTC ON HSV-1/2 INCIDENCE AMONG MSM

Marie-Laure Chaix Baudier[1], Isabelle Charreau[2], Constance Delaugerre[1], Nadia Mahjoub[1], Martin Siguier[1], Catherine Capitant[2], Cécile Tremblay[3], François Raffi[4], Eric Cua[5], Gilles Pialoux[6], Laurent Cotte[7], Armelle Pasquet[8], Laurence Meyer[9], Jean-Michel Molina[1]

[1]Hôpital Saint-Louis, Paris, France, [2]INSERM, Villejuif, France, [3]Université de Montréal, Montreal, QC, Canada, [4]CHU de Nantes, Nantes, France, [5]CHU de Nice, Nice, France, [6]Tenon Hospital, Paris, France, [7]CHU de Lyon, Lyon, France, [8]Centre Hospitalier de Tourcoing, Tourcoing, France, [9]INSERM, Le Kremlin-Bicetre, France

Background: The use of topical tenofovir gel for HIV PrEP has been shown to reduce the incidence of HSV-2-infection by 51% in women in the Caprisa 004 Study. Oral tenofovir-based PrEP also reduced HSV-2 acquisition by 28% among heterosexual men and women in the Patrners PrEP study. No reduction of HSV-2 incidence was reported in the Iprex study among MSM with daily TDF/FTC but adherence was low. We wished to assess the impact of on demand TDF/FTC for PrEP on HSV-1/2 incidence in the ANRS IPERGAY PrEP trial among MSM.

Methods: Stored serum samples from participants enrolled in the blinded phase (TDF/FTC or placebo) of the ANRS Ipergay trial were tested at baseline and at their last visit for HSV-1 and HSV-2 antibodies using serological tests (BioPlex 2200 HSV-1 & HSV-2 IgG, Biorad). We also studied the shedding of HSV-2 in anal swab from HSV-2 seropositive patients. HSV1/HSV2 (HSV1 HSV2 VZV R-gene™ kit Argene) PCR was performed at baseline, M6 and M12.

Results: Of the 400 participants (199 in the TDF/FTC arm and 201 in the placebo arm), 39% were tested HSV-2 sero-positive and 70% HSV-1 sero-positive at baseline. Only 18% were sero-negative for both HSV-1 and HSV-2. Of the 218 HSV-2-seronegative participants with a median follow-up of 10.2 months (IQR: 6.1-23.5), 19 (9%) acquired HSV-2 infection. Overall HSV-2 incidence was 7.6% per 100 person-years; 8.1% (95% CI: 4.0%; 14.5%) in the TDF/FTC arm versus 7.0% (95% CI: 3.0%; 13.7%) in the placebo arm (p=0.75). For HSV-1, 14/108 (13%) seronegative participants acquired HSV-1 infection after a median follow up of 10.2 months. Overal incidence of HSV-1 infection was 11.7% per 100 person-years; 16.2% (95% CI: 7.4%; 30.8%) in the TDF/FTC arm versus 7.8% (95% CI: 2.5%;18.2%) in the placebo arm (p=0.19). Compared to participants receiving placebo, there was no difference in HSV-2 or HSV-1 sero-incidence among participants using > 15 pills/month of TDF/FTC. HSV-2 shedding was analyzed in 58 participants with available anal samples (28 in the placebo arm and 30 in the TDF/FTC arm), only 3 patients had HSV-2 positive PCR, 1 at baseline (4 900 copies/ml), 1 at M12 (115 500 copies/ml) and 1 at M6 (2 816 000 copies/ml) and M12 (595 000 copies/ml), the 2 latter being in the TDF/FTC arm.

Conclusion: The incidence of HSV-2 and HSV-1 was high in these high risk MSM using PrEP. On demand oral PrEP with TDF/FTC failed to reduce HSV-1/2 incidence in this population.

1024 INTEGRATING PrEP REFERRALS INTO STD PARTNER SERVICES INCREASES PrEP USE AMONG MSM

David A. Katz[1], Michael Barry[2], Julia C. Dombrowski[1], Teal Bell[3], Matthew R. Golden[1]

[1]University of Washington, Seattle, WA, USA, [2]Public Health–Seattle & King County, Seattle, WA, USA, [3]Washington State Department of Health, Olympia, WA, USA

Background: Men who have sex with men (MSM) with bacterial STDs are at elevated risk for HIV acquisition. STD partner services (PS) can be used to refer these men to pre-exposure prophylaxis (PrEP), but the effectiveness of these referrals is unknown.

Methods: In 2016, Disease Intervention Specialists (DIS) in King County, WA, attempted to provide PS to all early syphilis cases and MSM with gonorrhea and chlamydia as resources allowed. Public Health–Seattle & King County (PHSKC) defined MSM with any of the following as being at high risk for HIV: early syphilis, rectal gonorrhea, methamphetamine or poppers use, sex work, or an HIV-unsuppressed partner. DIS referred high risk MSM to the PHSKC STD clinic to initiate PrEP and all MSM to community PrEP providers. From April-September 2017, we interviewed a random sample of HIV-negative MSM who were offered PrEP referrals during their PS interview in 2016, stratified by risk and whether they accepted referrals. At follow-up, we assessed PrEP use and, for non-users, assessed current risk and offered new referrals. We compared outcomes across strata using chi-square or Fisher's exact tests.

Results: In 2016, medical providers reported 2633 cases of early syphilis, gonorrhea, or chlamydia in HIV-uninfected MSM in King County, of whom 1126 (43%) received PS. DIS assessed PrEP use in 1067 (95%) PS recipients, of whom 493 (46%) were on PrEP. Among 574 men not using PrEP, 377 (66%) were offered PrEP referrals (Table). Of 189 sampled (50% of eligible), 132 (70%) completed a follow-up interview, of whom 44 (33%) were using PrEP at follow-up and 4 (2%) had initiated PrEP but discontinued it. Of PrEP users, 70% were prescribed PrEP by community providers and 30% at the STD clinic. Men who accepted referrals at initial interview were significantly more likely to be using PrEP at follow-up (32/68=47%) than those who did not (12/64=19%) [p=.0006]. This effect was greater among high risk men (64% v. 19%; p=.0002) than lower risk men (29% v. 18%; p=.28). Of 88 not using PrEP at follow-up, 39 (44%) were interested in starting PrEP, 30 (77%) of whom accepted a referral to a PrEP provider or indicated they would seek PrEP from their own medical provider.

Conclusion: Almost half of HIV-negative MSM receiving STD PS in King County, WA, reported using PrEP. Integrating PrEP referrals into PS was associated with approximately one-third of non-users initiating PrEP, and following up with PS recipients to offer additional PrEP navigation services may further increase use.

Table. PrEP outcomes in a random sample of HIV-negative MSM receiving STD partner services (PS), stratified by HIV risk and PrEP referral acceptance at initial PS interview

Outcomes	Total	High risk, Referred	High risk, Not referred	Lower risk, Referred	Lower risk, Not referred	p-value
Initial PS interviews (% of total)	377	143 (38%)	97 (26%)	65 (17%)	72 (19%)	
In random sample (% of initial)	189 (50%)	50 (35%)	48 (49%)	46 (71%)	45 (63%)	<.0001
Completed follow-up interview (% of sample)	132 (70%)	34 (68%)	31 (65%)	34 (74%)	33 (73%)	0.89
PrEP use following initial referral						
Currently using PrEP (% of interviewed)	44 (33%)	22 (65%)	6 (19%)	10 (29%)	6 (18%)	<.0001
Receiving PrEP from PHSKC STD Clinic (% of current users)	13 (30%)	11 (50%)	1 (17%)	0 (0%)	1 (17%)	0.02
Acceptance of new PrEP referrals						
Not currently on PrEP (% of interviewed)	88 (67%)	12 (35%)	25 (81%)	24 (61%)	27 (82%)	<.0001
Interested in PrEP at follow-up (% of non-users)	39 (44%)	6 (50%)	9 (36%)	11 (46%)	13 (48%)	0.79
Identified as high risk at follow-up (% of interested)	27 (69%)	6 (100%)	8 (89%)	7 (64%)	6 (46%)	0.06
Accepted referral or will go to own provider (% of interested)	30 (77%)	5 (83%)	5 (56%)	10 (91%)	10 (77%)	0.29

1025 PARTNERS, NOT CONDOM USE, DRIVE STI RATES AMONG PrEP USERS IN COMMUNITY HEALTH CENTER

Sarit A. Golub[1], Stephanie Pena[2], Rachel A. Fikslin[3], Matthew Goldberg[3], **Asa Radix**[2]

[1]Hunter College, CUNY, New York, NY, USA, [2]Callen–Lorde Community Health Center, New York, NY, USA, [3]Hunter HIV/AIDS Research Team, New York, NY, USA

Background: The potential association between PrEP use and STI incidence is an important public health issue, and better understanding predictors of STI diagnosis among PrEP users is critical to developing companion behavioral support. This analysis presents data from SPARK, a PrEP demonstration/implementation project conducted at a community-based health center in New York City.

Methods: Participants were 300 MSM and transgender women (ages 18-63; 48% PoC) patients at the health center who chose to start PrEP. SPARK participants were followed for 12-months and tested quarterly for STIs (urethral/rectal gonorrhea/chlamydia and syphilis). Data were also collected on participants presenting to the health center between study visits for STI testing.

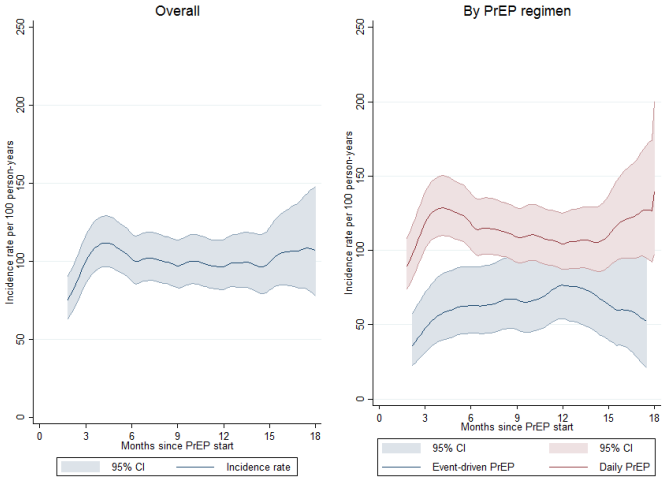
Analyses were restricted to the 261 participants (87%) who were retained at 12-months. We examined baseline demographic, behavioral, and psychosocial predictors of STI diagnosis over the 12-month follow-up, as well as change scores (e.g., changes in condom use and number of partners).
Results: 11% of participants had an STI diagnosis in the 6 months before starting PrEP. Over the course of 12-month follow-up, 44% of participants were diagnosed with an STI. Diagnoses per visit ranged from 16% (6M) to 10% (12M), and 23% of participants were diagnosed at interim (i.e., non-study) visits to the health center. STI diagnosis was associated with being under 25 ($p < .02$), but not with race/ethnicity, income, or education. In stepwise regression models including significant bivariate variables, four factors were retained as predictors of STI diagnosis: a) being under 25 (OR = 4.8); b) reporting more than 5 partners at baseline (OR= 3.5); c) STI diagnosis in 6-months prior to PrEP uptake (OR = 3.5); and d) increasing the number of partners from baseline to 12-months (OR=2.1). Average condom use decreased from baseline (60%) to 12-months (45%), but neither overall condom use nor change in condom use were associated with STI diagnosis.
Conclusion: The strength of baseline factors in predicting STI incidence suggests that risk compensation may be less significant than underlying behavior patterns in post-PrEP STI diagnosis. The known association between STI diagnosis and HIV seroconversion suggests that PrEP is effectively preventing new HIV infections. Particular attention and support is needed for younger PrEP users. Although many PrEP prevention messages stress condom use, number of partners appears to be a more important predictor of STI diagnosis among PrEP users.

1026 INCIDENT HIV, HEPATITIS C AND OTHER STI IN DAILY AND EVENT-DRIVEN PrEP USERS

Elske Hoornenborg, Liza N. Coyer, Roel C. Achterbergh, Amy Matser, Udi Davidovich, Maarten F. Schim van der Loeff, Henry J. de Vries, Maria Prins
Public Health Service Amsterdam, Amsterdam, Netherlands

Background: There are concerns that HIV pre-exposure prophylaxis (PrEP) use may lead to a rise in sexually transmitted infections (STI). We present interim results of HIV, hepatitis C virus (HCV) and bacterial STI incidence among men who have sex with men (MSM) and transgender persons (TGP) in the Amsterdam PrEP demonstration project (AMPrEP).
Methods: AMPrEP enrolment started in August 2015 at the STI clinic of the Public Health Service of Amsterdam, the Netherlands. Participants could choose between daily (dPrEP) and event-driven PrEP (edPrEP, i.e., 2 pills tenofovir/emtricitabine before sex and 2 times 1 pill after 24/48 hours). Switching between PrEP regimens was allowed at 3-monthly study visits. Participants were tested for HIV, HCV and STI at each study visit and additionally in case of symptoms or partner notification. Data until June 2017 were analysed. Incidence rates per 100 person years (py) were calculated overall and in each quarter since PrEP start. The association of time on PrEP with STI incidence was assessed in piecewise exponential survival models. STI incidence was compared between PrEP regimens by Poisson regression with random effects.
Results: Of 372 AMPrEP participants with follow-up data, 271 (73%) initially chose dPrEP and 101 (27%) edPrEP. Median follow-up time was 15 months (IQR 14-18). We recorded 108 switches (n=53 dPrEP to edPrEP; n=55 edPrEP to dPrEP) in 81 participants. HIV incidence was 0.42/100py (n=2, 95% CI 0.11-1.69) (dPrEP: 0.57; edPrEP: 0). HCV incidence was 1.29/100py (n=6, 95%CI 0.58-2.87) (dPrEP: 1.16; edPrEP: 1.68, p=0.666). Incidence of bacterial STI (chlamydia, gonorrhea, syphilis) was 97.8/100py (95%CI 89.3-107.1) and was significantly higher in dPrEP users than in edPrEP users (111.4 vs 57.9/100py, IRR 1.87, 95%CI 1.40-2.51). We found no significant change in STI incidence over time (p=0.697); incidence varied from 92.3/100py in month 0-3 to 90.4/100py in month 15-18 (figure). The incidence of anal STI was higher in dPrEP users than in edPrEP users (75.4 vs 30.6/100py, IRR 2.32, 95% CI 1.56-3.44).
Conclusion: Both HCV and STI incidence following PrEP start were high in this PrEP demonstration project for MSM and TGP. STI incidence was not increasing with time on PrEP. STI but not HCV incidence was higher in dPrEP than edPrEP users, possibly reflecting differences in sexual behaviour. HIV incidence was low in line with previous dPrEP and edPrEP studies. These data suggest that frequent screening for bacterial STI and HCV should be offered to PrEP users.

Figure. Incidence rate of any bacterial STI over time since PrEP start among daily and event-driven PrEP users participating in the Amsterdam PrEP demonstration project.



1027 SEXUALLY TRANSMITTED INFECTIONS AND ADHERENCE TO PrEP

Claire Bristow[1], David J. Moore[2], Michael Dube[3], Katya Calvo[4], Eric Ellorin[2], Jill Blumenthal[2], **Sheldon Morris**[2]
[1]University of California San Diego, La Jolla, CA, USA, [2]University of California San Diego, San Diego, CA, USA, [3]University of Southern California, Los Angeles, CA, USA, [4]Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, USA

Background: High levels of STI incidence have been reported in preexposure prophylaxis (PrEP) studies. We conducted an analysis from a PrEP adherence study to assess the incidence rates of STIs and determine if higher adherence was associated with higher incidence of STIs to suggest differences in risk taking by adherence.
Methods: Men who have sex with men (MSM) and transgender women, age 18+ years, at risk for HIV were recruited for participation in a PrEP adherence study at four urban Southern California medical centers. Chlamydia (CT) and gonorrhea (NG) nucleic acid amplification testing was performed at baseline and follow-up visits at week 4 and every 12 weeks throughout the 48-week study period. Adherence was measured by intracellular tenofovir diphosphate (TFV-DP) using dry blood spots collected at week 12 and 48. adherent was considered >719 fmol/punch, consistent with ≥4 doses per week and >1246 fmol/punch, consistent with 7 doses per week. Plasma FTC levels were also measured and adherent was considered >350 ng/mL, consistent with dosing within the past 24 hours.
Results: Three-hundred and ninety-four participants had 121 new CT/NG cases. The incidence rate of CT/NG was 43.5 per 100 person years of follow-up for first CT/NG infection in the study. Of the 75 incident NG cases and 98 incident CT cases, 16 (21.3%) and 33 (33.7%) had a positive NG and CT results at subsequent visits, respectively. Among those adherent to TFV-DP at week 12, the incidence rate of CT/NG was 44.9 per 100 person years (95% CI: 36.4, 53.4) compared to 35.2 per 100 person years (95% CI: 16.8, 53.6) among those not adherent at week 12 (IRR: 1.3 (95% CI: 0.7, 2.2)). Among those adherent to FTC at week 12, the incidence rate of CT/NG was 51.4 per 100 person years (95% CI: 37.4, 65.3) compared to 39.0 per 100 person years (95% CI: 29.8, 48.2) among those not adherent to FTC at week 12 (IRR: 1.3 (95% CI: 0.9, 1.9)). No STI rates were statistically different between groups. Similar results were found for adherence by cutoff of >1246 fmol/punch and for week 48 TFV-DP levels.
Conclusion: The incidence of CT and NG infections in this PrEP demonstration project was comparable to other PrEP studies. Although point estimates were higher for STI rates in those who were more adherent, as defined by 7 doses a week, 4 or more doses a week or dosing in last 24 hours, this finding was not statistically significant and therefore does not support the association between higher sexual risk taking with improved adherence.

Infection type	Adherence status	Number of incident cases	Number at risk	Number of person years spent at risk	Incidence density per 100 person years (95% CI)	Incidence rate ratio
STI Incidence by Anatomic Site						
NG Urine		8	375	485.1	1.6 (0.5, 2.8)	
NG Rectal		40	356	429.2	9.3 (6.4, 12.2)	
NG Throat		53	351	414.7	12.8 (9.3, 16.2)	
CT Urine		32	368	457.7	7.0 (4.6, 9.4)	
CT Rectal		86	339	365.3	23.5 (18.6, 28.5)	
CT Throat		6	178	238.3	2.5 (0.5, 4.5)	
Any NG		75	339	376.0	19.9 (15.4, 24.5)	
Any CT		98	329	340.0	28.8 (23.1, 34.5)	
CT and/or NG		121	301	278.0	43.5(35.8,51.3)	
Week 12 DBS TFV-DP (fmol/punch)						
Any CT	not adherent (≤1246)	52	183	182.3	28.5 (20.8,36.3)	
	adherent (>1246)	46	146	157.7	29.2 (20.7,37.6)	
Any NG	not adherent (≤1246)	35	196	215.2	16.3 (10.9,21.7)	reference
	adherent (>1246)	40	143	160.8	24.9 (17.2,32.6)	1.53 (0.98, 2.41)
CT and/or NG	not adherent (≤1246)	65	172	155.1	41.9 (31.7,52.1)	reference
	adherent (>1246)	56	129	122.9	45.6 (33.6,57.5)	1.09 (0.76, 1.55)
Any CT	not adherent (≤719)	10	55	47.8	20.9 (8.0,33.9)	reference
	adherent (>719)	88	274	292.2	30.1 (23.8,36.4)	1.44 (0.75, 2.77)
Any NG	not adherent (≤719)	10	60	51.9	19.3 (7.3,31.2)	
	adherent (>719)	65	279	324.1	20.1 (15.2,24.9)	
CT and/or NG	not adherent (≤719)	14	51	398	35.02 (16.8,53.6)	reference
	adherent (>719)	107	250	238.2	44.9 (36.4,53.4)	1.28 (0.73, 2.23)
Week 12 Plasma FTC-TP (ng/mL)						
Any CT	not adherent (≤350 ng/mL)	57	206	212.4	26.8 (19.9,33.8	
	adherent (>350 ng/mL)	41	123	127.6	32.1 (22.3,42.0)	
Any NG	not adherent (≤350 ng/mL)	42	208	226.8	18.5 (12.9,24.1)	
	adherent (>350 ng/mL)	33	131	149.3	22.1 (14.6,29.7)	
CT and/or NG	not adherent (≤350 ng/mL)	69	188	176.8	39.0 (29.8,48.2)	reference
	adherent (>350 ng/mL)	52	113	101.2	51.4 (37.4,65.3)	1.32 (0.92, 1.89)

1028 FACTORS IMPACTING APPROPRIATE HIV/STI SCREENING AND PrEP PERSISTENCE IN PRIMARY CARE

Matthew A. Spinelli[1], Hyman Scott[2], Eric VIttinghoff[1], Albert Y. Liu[2], Alicia Morehead-Gee[1], Rafael Gonzalez[2], Monica Gandhi[1], Susan P. Buchbinder[2]
[1]University of California San Francisco, San Francisco, CA, USA, [2]San Francisco Department of Public Health, San Francisco, CA, USA

Background: Given increasing PrEP uptake, to optimize PrEP safety and impact, persons at HIV-risk must have appropriate HIV/STI testing and persist on PrEP. We evaluated patient and provider characteristics associated with HIV/STI testing and PrEP persistence in the San Francisco Public Health Primary Care Clinics (SFPCC).

Methods: Demographic, lab, and prescription data were abstracted from charts of SFPCC PrEP users from 3/1/13-7/31/17. Multivariable logistic regression models assessed factors associated with lack of appropriate HIV/STI testing at PrEP initiation defined as HIV testing 30 days prior, and rectal, pharyngeal, urine, or vaginal gonococcus (GC) or C. trachomatis (CT) testing 90 days prior to or 7 days after initial prescription, respectively. We examined factors associated with PrEP persistence (number of days with an active prescription) using a Cox proportional-hazards model, defining discontinuation as 90 days without an active prescription.

Results: Overall, 401 PrEP patients had pharmacy and lab data available. Mean age was 37 years; 85% were male; 8% Asian, 13% Black, 26% Latino, and 36% White. PrEP prescriptions increased each year, from 108 patients in 2013/4 to 913 in 2016/7. PrEP panel size was 1, 2-5, or >5 for 19%, 32% and 49% of providers, respectively. Only 76% of patients received an HIV antibody test ≤30 days prior to PrEP initiation: 61% in 2013/14 and 83% in 2016/17. Lack of a baseline HIV test was associated with older age (p=0.01) and earlier prescription year (p=0.001 for trend). Among patients on PrEP for ≥6 months, 70% had follow-up HIV testing at least every 6 months. Only 71% received any baseline testing for GC or CT; lack of testing was also associated with older age (p<0.001) and earlier year (p<0.001 for trend). Median PrEP persistence was 11.3 months. In multivariable analysis, shorter persistence was associated with young age, Black race, earlier PrEP prescription index number, larger provider PrEP panel size, and current prescription of ≤30 pills (Table).

Conclusion: SFPCC PrEP users are a diverse and growing population cared for by both high and low volume providers. Short duration prescriptions were associated with worse persistence, and may be a barrier for PrEP users. Appropriate HIV/STI screening is suboptimal but improving with time, possibly related to SFPCC PrEP education initiatives. Strategies to address provider and patient barriers to appropriate HIV/STI screening and PrEP persistence are needed.

Table: Factors Associated with PrEP Discontinuation in a Cox-Proportional Hazards Model

		Adjusted Hazard Ratio (95% CI)	p-value
Age per 10 years		**0.88 (0.79-0.98)**	**0.02**
Female Sex		1.08 (0.82-1.41)	0.6
Race/ethnicity vs. White:	**Black**	**1.52 (1.02-2.21)**	**0.03**
	Latino	1.07 (0.82-1.41)	0.6
	Asian	0.83 (0.56-1.23)	0.3
	Other	1.16 (0.86-1.57)	0.3
Number of PrEP patients per provider vs. 1 patient per provider:	2-5	1.09 (0.79-1.51)	0.6
	>5	**1.46 (1.06-2.00)**	**0.02**
Year of PrEP Initiation vs. 2013/14:	2015	1.25 (0.86-1.81)	0.2
	2016	1.32 (0.88-1.98)	0.2
	2017	0.61 (0.34-1.09)	0.1
PrEP prescription index number		**0.79 (0.70-0.90)**	**<0.001**
Current PrEP prescription <= 30 days		**2.35 (1.39-3.96)**	**0.001**

1029 CHEMSEX DRUGS USE BY HAIR ANALYSIS AMONG MSM IN THE ANRS IPERGAY TRIAL.

Julie Chas[1], Gilles Peytavin[2], Diane Carette[3], Nicolas Fabresse[4], Isabelle Charreau[3], Catherine Capitant[3], Perrine Roux[5], Eric Cua[6], Laurent Cotte[7], Armelle Pasquet[8], François Raffi[9], Laurence Meyer[3], Gilles Pialoux[1], Jean-Michel Molina[4], **Jean-Claude Alvarez**[4]
[1]Tenon Hospital, Paris, France, [2]Bichat–Claude Bernard Hospital, Paris, France, [3]Paul Brousse Hospital, Villejuif, France, [4]Paris Center Hospital Group, Paris, France, [5]INSERM, Marseille, France, [6]Nice University Hospital, Nice, France, [7]CHU de Lyon, Lyon, France, [8]CHU de Lille, Lille, France, [9]CHU de Nantes, Nantes, France

Background: In the ANRS IPERGAY trial conducted among high risk MSM, 86% relative reduction of HIV-incidence was reported with on demand PrEP use with TDF/FTC. Use of Chemsex drugs is increasingly reported among MSM and is associated with higher risk behavior.

Methods: During the ANRS IPERGAY trial, participants (pts) were asked every four month to provide hair samples to detect drugs (except the GHB/GBL for technical reasons). When possible a segmental analysis was carried out, 1 cm corresponding to 1 month of drug use. A total of 86 molecules including conventional substances (cocaine, amphetamines, opiates) and 31 New Psychoactive Substances (NPS) were screened and quantified using Triple Quad TSQ Vantage (ThermoFisher®) in MRM mode.

Results: Sixty nine volunteers were enrolled, among the 429 pts of the Ipergay study population: median [IQR] age 35 years [28;41], number of sexual partners/2 months 9 [5;15], number of sexual intercourse/4 weeks 10 [5;16], similar to the overall IPERGAY population. A total of 219 hair segments (1.5 to 2.5cm length) were analyzed, corresponding each to 1.5 to 2.5 months of consumption. Drugs of abuse were detected in 87% (60/69) pts: 47 pts (68%) were tested positive to Cocaine, 41 (59%) MDMA, 26 (38%) Ketamine, 26 (38%) to one or more NPS, 9 (13%) Codeine, 6 (9%) Methamphetamine, 4 (6%) Amphetamine. The most frequently detected NPS were two cathinones, 14 Mephedrone and 11 4-MEC, followed by 5 ethylphenidate, 4 methylone, 4 methoxetamine, 3 methiopropamine, 3 PMMA, 3 MDPV, 1 metamfepramone, 1 5F-PB22, 1 methylphenidate, 1 diphenidine, 1 phendimetrazine, 1 phentermine, 1 N-methyl-2-AI and 1 dimethylone. No piperazine like TFMPP, α-PVP or m-CPP was found. No case of NPS use alone was found. MSM pts consumed NPS associated to cocaine, MDMA or ketamine in 25/26 (96%), 23/26 (88%), and 18/26 (69%) of cases respectively, showing poly-consumptions. Segmental hair analysis performed in 69% of cases showed wide range exposures, ranging from unique intake (concentration range 5-20 pg/mg) to chronic abuse (> 90 ng/mg for amphetamines) studied. Drugs detection in our study seems more important than the self-reported consumption of recreational drugs in the ANRS IPERGAY trial (44%).

Conclusion: Prevalence of NPS and especially synthetic cathinones use in the MSM PreP population is high but lower than conventional drugs like cocaine and amphetamine, especially MDMA. Hair analysis is the only way to accurately reflect drugs consumption and can improve prevention policies.

1030 ASSESSING PrEP NEEDS AMONG HETEROSEXUALS AND PEOPLE WHO INJECT DRUGS, WASHINGTON, DC

Irene Kuo[1], Anya Agopian[1], Jenevieve Opoku[2], Anthony Rawls[1], Rudy Patrick[3], Manya Magnus[1], Michael Kharfen[2], Alan Greenberg[1]
[1]The George Washington University, Washington, DC, USA, [2]District of Columbia Department of Health, Washington, DC, USA, [3]University of California San Diego, La Jolla, CA, USA

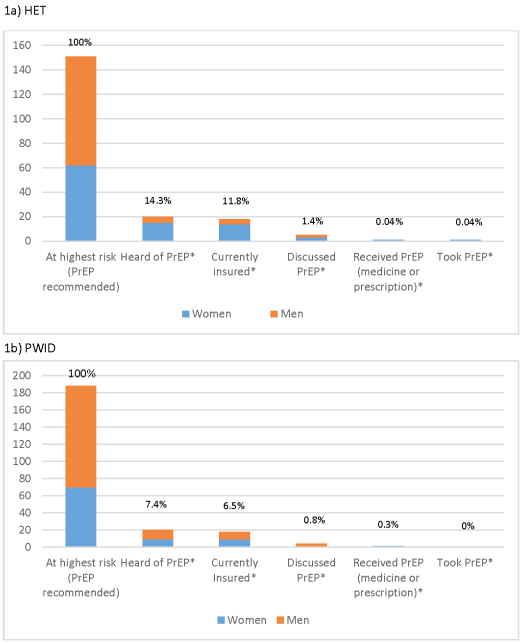
Background: PrEP is an effective biomedical intervention to prevent HIV transmission; however, uptake among heterosexuals at risk (HET) and people who inject drugs (PWID) recommended for PrEP has not been well-assessed. We used a PrEP continuum to assess the gap in knowledge, access and use of PrEP among HET and PWID in Washington, DC.

Methods: We used data from the National HIV Behavioral Surveillance System (NHBS), a community-based cross-sectional survey, collected in 2016 (HET N=503) and 2015 (PWID N=516). Participants were recruited using respondent-driven sampling; weighted percentages are presented. NHBS eligibility for HET included men/women who had sex with an opposite sex partner in the past year; PWID included men/women who reported past year injection drug use. We used CDC criteria to estimate the proportion of HIV-negative/unknown status participants recommended for PrEP use. The PrEP continuum included: ever heard of PrEP, having insurance, ever discussed PrEP with a provider, ever received PrEP or prescription, and ever took PrEP. The number of persons recommended for PrEP was used as the denominator for each continuum step, and the proportion calculated for each step was contingent upon cumulatively meeting all previous steps. Data in the PrEP continuum for both HET and PWID were also examined by gender.

Results: Among HET and PWID in NHBS, 20.8% and 35.2% respectively met the CDC criteria for PrEP; of those, 50.3% of HET and 32.0% of PWID were women. Among HET recommended for PrEP (Figure 1a), only 14.3% had ever heard of PrEP; 11.8% were insured, 1.4% had discussed PrEP with a provider; and <1% ever received PrEP and took PrEP. A higher proportion of HET women versus men had heard of PrEP and were currently insured (p=0.05). Among PWID recommended for PrEP (Figure 1b), 7.4% had ever heard of PrEP; 6.5% were insured; 0.8% had discussed PrEP with a provider; <1% had received PrEP; and none had taken PrEP. Similar proportions of male and female PWID were engaged in the PrEP continuum stages.

Conclusion: A substantial proportion of HET and PWID met the criteria for PrEP utilization, yet a large gap exists at each stage of the PrEP continuum for both groups. Overall PrEP knowledge and utilization was very low in both groups. While a larger proportion of HET women versus men were aware of PrEP and insured, there was no difference in PrEP uptake by gender in either population. New PrEP implementation programs should focus on increasing knowledge and uptake of PrEP in these populations.

Figure 1: The PrEP Continuum for a) Heterosexuals at High Risk for HIV (HET, 2016) and b) People Who Inject Drugs (PWID, 2015) in Washington, DC.



* The proportions of HET and PWID in each step of the continuum is contingent upon cumulatively meeting all previous steps of the continuum. For each step, gender breakdown of all HET/PWID who met that step is presented.

1031 STIMULANT USE AND CONDOMLESS SEX WITH MULTIPLE PARTNERS: EFFECT ON PrEP ADHERENCE

David Goodman-Meza[1], Matthew R. Beymer[1], Ryan M. Kofron[1], K. Rivet Amico[2], Christina Psaros[3], Lane R. Bushman[4], Peter L. Anderson[4], Robert Bolan[5], Wilbert C. Jordan[6], James F. Rooney[7], Amy R. Wohl[8], Raphael J. Landovitz[1]
[1]University of California Los Angeles, Los Angeles, CA, USA, [2]University of Michigan, Ann Arbor, MI, USA, [3]Massachusetts General Hospital, Boston, MA, USA, [4]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [5]Los Angeles LGBT Center, Los Angeles, CA, USA, [6]Charles R. Drew University of Medicine and Science, Los Angeles, CA, USA, [7]Gilead Sciences, Inc, Foster City, CA, USA, [8]Los Angeles County Department of Public Health, Los Angeles, CA, USA

Background: PrEP with TDF/FTC is highly effective for preventing HIV in diverse populations. Among MSM, stimulant use and condomless anal sex with multiple partners (CAS-MP) are known risk factors for HIV acquisition. CAS-MP has been associated with increased PrEP adherence, but less is known about the association with stimulant use. We hypothesized that stimulant use would modify the effect of CAS-MP, decreasing PrEP adherence.

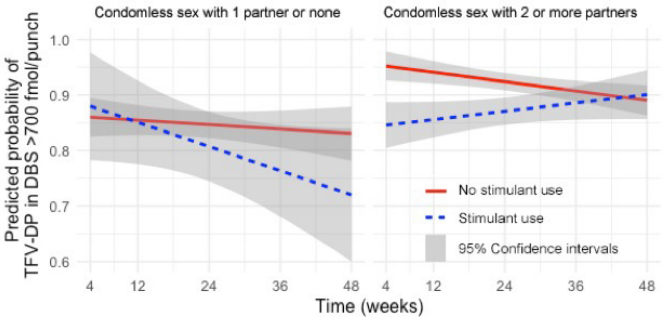
Methods: We performed a secondary analysis of PATH-PrEP, a two-site open label study evaluating PrEP for MSM in Los Angeles, California. TDF/FTC was offered to 296 MSM for 48 weeks between April 2014 and July 2016. Adherence levels to TDF/FTC were assessed via TFV-DP levels in dried blood spots (DBS) and TFV in plasma samples at 4, 8, 12, 24, 36 and 48 weeks. All participants received standardized adherence counseling, which was escalated if TFV plasma levels were below the limit of quantitation (<10 ng/mL). Risk behavior was assessed through a computerized survey instrument at all visits. We modeled an interaction between stimulant use (methamphetamine, ecstasy, or cocaine) and CAS-MP (2 or more partners) over time on protective TFV-DP levels in DBS (>700 fmol/punch). We included individuals with at least one follow-up visit (n=283). We used a generalized linear mixed model, controlling for age, ethnicity, enrollment site, education, income, and sex work. Predicted probabilities were estimated to plot the interaction and 95% CIs (figure).

Results: Median age was 33 (IQR 28-42), 51% were White, 28% Latino and 10% Black. At baseline, 61% reported CAS-MP and 34% reported stimulant use in the prior 30 days. Over all observed time points, 80% of samples had protective levels. At week 4, those reporting CAS-MP without stimulant use had higher odds of protective levels (AOR 2.4, 95% CI 1.3-4.6) than non-stimulant and non-CAS-MP (reference). Those with CAS-MP and stimulant use had decreased odds of protective levels (AOR 0.2, 95% CI 0.1-0.7). Over time, those

reporting CAS-MP without stimulant use did not have a significant change in odds of protective levels (AOR 1.00, 95% CI 0.96-1.03), while those who reported CAS-MP and stimulant use had increased odds of protective levels (AOR 1.07 per week, 95% CI 1.01-1.13).

Conclusion: Stimulant use moderated the effect of CAS-MP on adherence over time, increasing the odds of protective levels of PrEP, contrary to our initial hypothesis. Stimulant use should not be a deterrent to prescribe PrEP to high-risk individuals engaging in CAS-MP.

Figure. Interaction of Stimulant Use and Condomless Anal Sex with Multiple Partners on PrEP Adherence



1032 USE OF HIV PEP BY US COMMERCIALLY INSURED PERSONS INCREASED WITH AVAILABILITY OF PrEP

Ya-Lin A. Huang[1], Kenneth L. Dominguez[1], Anne Patala[2], Karen W. Hoover[1]
[1]CDC, Atlanta, GA, USA, [2]ICF International, Atlanta, GA, USA

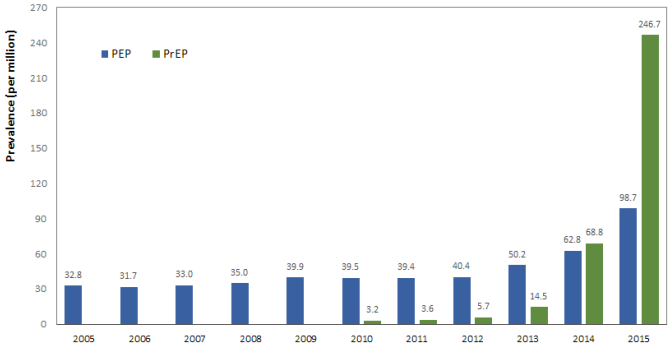
Background: Antiretroviral (ARV) drugs can be used for HIV postexposure prophylaxis (PEP) within 72 hours after exposure to the virus to prevent the risk of acquiring an infection. In 2005, CDC issued guidelines for PEP use and updated its recommendations in 2016. However, awareness of and access to PEP has been low, and population-level estimates of PEP use are lacking. In this study, we compared PEP and preexposure prophylaxis (PrEP) uptake among persons with commercial health insurance in the United States.

Methods: Using 2005-2015 MarketScan health services data, we developed an algorithm to identify persons prescribed PEP each year. First, we included persons who filled any ARV prescription in a given year and defined the earliest ARV prescription as the index date. Next, we excluded persons with HIV infection identified by an HIV diagnostic code or an ARV prescription before the index date. We further excluded persons with hepatitis B virus (HBV) infection if they had an HBV diagnosis and ARV prescriptions used to treat HBV. Lastly, we excluded possible PrEP users if their medications was prescribed for >30 days. Using similar methods, we estimated PrEP uptake for persons with a Truvada prescription on the index date who used it for >30 days. We characterized PEP users and estimated the prevalence of PEP and PrEP use by year.

Results: The number of persons prescribed PEP increased from 576 in 2005 to 2,797 in 2015; the prevalence of the PEP use increased from 32.8 per million in 2005 to 98.7 per million in 2015 (Ptrend <.001). The mean age of PEP users ranged from 34.1-36.4 years. The proportion of the male users among all users increased from 60% before 2014 to 70% after 2014. PEP use increased in metropolitan statistical areas from 90% in 2005 to 97% in 2015. When stratified by sex, the prevalence of male PEP users nearly quadrupled from 2005 (40.9 per million) to 2015 (149.2 per million) (Ptrend <.001); while the prevalence of the female users nearly doubled (from 25.3 per million in 2005 to 51.5 per million in 2015) (Ptrend <.001). Increases in PEP use mirrored increases in PrEP use (Figure).

Conclusion: We found an increasing trend in the prevalence of both PEP and PrEP use during 2005-2015. The increase in PEP use might be associated with increased awareness of PEP as a result of PrEP social media and educational campaigns that included information on PEP. Our methodology provides a feasible approach to estimate PEP use at the population level among users of private health insurance.

Figure. Prevalence proportion (per million) of persons prescribed PEP and PrEP among those with commercial insurance in the United States, 2005-2015



1033 HIV INCIDENCE AMONG MSM GIVEN PEP STARTER PACKS IN NYC SEXUAL HEALTH CLINICS, 2014-16

Christine M. Borges[1], Addie Crawley[1], Michael A. Castro[1], Susan Blank[2], Sarah L. Braunstein[1], Preeti Pathela[1]
[1]New York City Department of Health and Mental Hygiene, Long Island City, NY, USA, [2]CDC, Atlanta, GA, USA

Background: Patients receiving starter packs of PEP may not complete the full course and non-completers may have a disproportionately high risk of acquiring HIV. This analysis examined factors associated with medication-completion and HIV incidence in patients receiving HIV PEP starter packs.

Methods: We analyzed data on HIV-negative men who have sex with men (MSM) who received PEP starter packs at NYC sexual health clinics from April 2014-December 2015. PEP criteria were: anal/vaginal sex with an HIV-positive partner, condomless receptive anal sex (RAI) with a person of unknown HIV status, shared injected drugs with an HIV-positive person, or sexual assault <36 hours prior to clinic visit. Patients received 3 days of PEP on-site and were referred out for the remaining medication. We gathered follow-up information from both patients and providers to ascertain completion. All demographic, risk and completion information was recorded in the electronic medical record. We used multivariable regression to identify patient demographic and risk-related correlates of completion. We measured HIV incidence among patients with PEP completion information via a match with NYC HIV surveillance data through December 2016.

Results: 421 MSM received PEP starter packs; the majority were Black or Hispanic (56%) and <30 years (58%). Most reported either sex with an HIV-positive partner (47%) or condomless RAI with a partner of unknown status (47%.) Of patients for whom we had completion information (80%); 77% (257/335) reported completing the PEP course. Completion was not significantly associated with age, race, PEP criteria category, or STI diagnosis on day of clinic visit. There were 13 new HIV diagnoses for an overall HIV incidence of 2.1 per 100 person-years (PY), with higher incidence among non-Hispanic black MSM (3.5/100 PY; 95% CI: 1.3-7.8) and MSM under 30 (2.5/100 PY, 95% CI: 1.2-4.6). HIV incidence was lower among completers (1.7/100 PY, 95% CI: 0.8-3.2) than among non-completers (3.4/100 PY, 95% CI: 1.3-7.6), however, this was not a statistically significant difference.

Conclusion: Most patients who received starter packs completed full course PEP. HIV incidence was lower but not significantly different for completers versus non-completers. PEP starter packs are a viable option for those with a high risk of HIV acquisition who may also face barriers to accessing medication elsewhere. Because of continued HIV risk behavior, linkage to PrEP or other prevention is a key intervention following PEP.

1034 COVERAGE OF SEX EVENTS WITH ON DEMAND PrEP: A MEMS SUB-STUDY OF THE IPERGAY TRIAL

Rebecca Bauer[1], Emmanuelle Netzer[1], Claire Pintado[2], Catherine Capitant[1], Eric Cua[3], Nicolas Etien[4], Gilles Pialoux[2], Christian Chidiac[5], Cedric Etienne[3], François Raffi[6], Armelle Pasquet[7], Veronique Dore[4], Laurence Meyer[8], Jean-Michel Molina[2]
[1]INSERM, Villejuif, France, [2]AP–HP, Paris, France, [3]Nice University Hospital, Nice, France, [4]INSERM, Paris, France, [5]CHU de Lyon, Lyon, France, [6]CHU de Nantes, Nantes, France, [7]CHU de Lille, Lille, France, [8]INSERM, Le Kremlin-Bicetre, France

Background: Whether intermittent PrEP provides similar coverage of sex events compared to daily PrEP is still unclear. We wished to assess in the setting of the ANRS IPERGAY trial among men who have sex with men (MSM), the coverage of sex events with «on demand» event-based PrEP.
Methods: A 2-month sub-study was proposed to participants (pts) enrolled in the open-label phase of the trial. On demand TDF/FTC dosing regimen included two pills within 2-24h before sex, one pill 24h later and a last pill 48h after the first drug intake. Pts received an electronic MEMS device to record each bottle opening. Questionnaires collected information on daily PrEP intake and sexual behavior by text messages and computer assisted self-interviews. Adherence was also measured by pill count. PrEP full coverage was defined by ≥ 1 pill taken within 24 hours before sex and 1 pill taken within 48 hours following sex, and partial coverage as either one. Two groups of pts were defined according to the number of bottle openings: those who used intermittent PrEP (< 5 openings per week) and those using daily PrEP (≥ 5 openings per week).
Results: From March 1st, 2016 to May 3rd, 2016, the study was proposed to 228 pts and 54 pts were enrolled, all MSM with a median age of 41 years. Pts reported 361 sex events with a median of 4 sex events/pt/month (IQR: 2-8), 81 oral sex only (23%), 279 anal sex (77%) and one unknown. Among the 154 receptive anal sex events, 80% (124) were condomless. There was a strong correlation (r=0.92) between bottle openings and pill count. Forty-two pts (78%) used intermittent PrEP and 12 (22%) used daily PrEP, median number of bottle openings/month of 11.5 (IQR: 4-16) and 24.9 (IQR: 24-27) respectively (p<0.0001). Coverage of sex events is reported in the Table.
Conclusion: Reported PrEP coverage of sex events was high both with daily and intermittent PrEP. In the MSM using intermittent PrEP, coverage increased with at-risk practices and was highest for condomless receptive anal sex.

% Coverage (n/Nb sex events) / Sex Events	Daily PrEP % (n/N)		Intermittent PrEP % (n/N)	
	Full coverage	Partial coverage	Full coverage	Partial coverage
All sex events	92 (149/162)	8 (13/162)	68 (135/199)	22 (44/199)
Oral sex only	88 (30/34)	12 (4/34)	60 (28/47)	34 (16/47)
Anal sex	93 (119/128)	7 (9/128)	71 (107/151)	18 (28/151)
Condomless anal sex	92 (95/103)	8 (8/103)	79 (80/101)	14 (14/101)
Condomless receptive anal sex	95 (56/59)	5 (3/59)	82 (53/65)	9 (6/65)

1035 FEASIBILITY OF SHORT-TERM PrEP UPTAKE FOR MSM WITH EPISODIC HIGH-RISK FOR HIV

James E. Egan[1], Ken Ho[1], Ronald Dean Stall[1], Morgan T. Drucker[2], Ryan Tappin[2], Craig W. Hendrix[3], Mark A. Marzinke[3], William Clarke[3], Kenneth H. Mayer[2]
[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]Fenway Health, Boston, MA, USA, [3]The Johns Hopkins University, Baltimore, MD, USA

Background: Although TDF/FTC Pre-Exposure Prophylaxis (PrEP) was approved for daily use to prevent HIV transmission in at risk men who have sex with men (MSM), some may have discrete periods of high risk (e.g. on vacation), and this use has not been previously evaluated. The current study evaluated the feasibility of short term, fixed interval PrEP.
Methods: Participants agreed to participate in an open label study of TDF/FTC plus a focused behavioral intervention. At least 2-weeks prior to vacation participants received a single session cognitive behavioral therapy--based intervention and were given a 30-day supply of TDF/FTC and instructed to adhere to daily dosing starting 7-days prior to vacation through 7-days post vacation. Adherence was assessed via self-report and plasma TFV concentration levels within 3-days post-vacation. Safety labs and behavioral assessments were collected at baseline, post-trip, and at 3-months.
Results: 54 participants were enrolled in Boston and Pittsburgh, of which 48 completed the post-vacation visit. Participants were mostly white (72.2%), had a mean age of 30.0 (range 24-64), 83.3% identified as gay, and 68.5% were employed full-time. Only 3 individuals (6.3%) had drug levels below protective levels (≤4 daily doses during the week). There was high concordance between biological markers and self-reported adherence with 95.8% reporting their ability to take daily PrEP as excellent or very good; 6 participants reported missing 2 or fewer doses and only 1 participant missing six of seven doses. Of the 3 people with less than protective levels of drug, none reported drug use. 55.5% of participants reported being likely or very likely to remain on PrEP after the study. 1 participant became HIV-infected more than 2 months after vacation because of lapse in insurance to cover ongoing PrEP; no other did after 3 months of follow-up. 77% of the sample reported condomless sex during 1 to 14 of their vacation days. All who reported condomless sex were adherent to PrEP except for 1 participant who reported partial PrEP use and condomless sex on 8 days.
Conclusion: These findings suggest that most MSM can be adherent to short-term fixed-interval episodic PrEP (Epi-PrEP) during short high risk vacation periods. Time-limited dosing strategies may be a realistic, feasible, acceptable and useful option for some high-risk MSM whose behaviors are episodic, but non-random. For others, initiating PrEP on vacation may provide a helpful way to initiate long term PrEP.

1036 PrEP USE HISTORY OF PERSONS NEWLY DIAGNOSED WITH HIV: NEW YORK CITY, 2015-2017

Kavita Misra, Jamie Huang, Chi-Chi Udeagu
New York City Department of Health and Mental Hygiene, Long Island City, NY, USA

Background: The partner services (PS) program of the New York City (NYC) health department routinely interviews persons newly diagnosed for HIV in NYC. Since 2015, the interview has included questions on pre-exposure prophylaxis (PrEP) use prior to HIV diagnosis.
Methods: We performed a cross-sectional analysis of data from PS investigations and the NYC HIV/AIDS surveillance registry of persons newly HIV diagnosed from November 2015 to September 2017. We compare sociodemographic characteristics and sexual risk behaviors of persons who reported any PrEP use prior to diagnosis with those who did not. We describe self-reported period and duration of PrEP use, weekly pill dosing, and reasons for discontinuing PrEP.
Results: Over 22 months, 3739 (96%) of 3908 persons newly diagnosed with HIV in NYC were investigated for PS. Of these, 95 persons (3%) reported any PrEP use prior to HIV diagnosis. A significantly greater proportion of ever-PrEP users than non-users were male (90% vs 76%), transgender women (6% vs 3%), white (40% vs 14%) and men who had sex with men (MSM) (87% vs 66%). Females, blacks and heterosexuals constituted 3%, 22% and 4% of ever-PrEP users respectively, versus 21%, 46% and 29% of non-users. Reasons for discontinuing PrEP included HIV diagnosis (19%), payment/insurance issues (16%), provider-discontinued refills or documented poor adherence (16%) and side-effects (12%). Among the 81% of ever-PrEP users whose PrEP stop date preceded their HIV diagnosis date, the median period between PrEP cessation and first HIV positive test was 5 months. The median duration of PrEP use was 3 months and the average number of pills taken per week was 7. About 23% of ever-PrEP users were diagnosed in the acute phase of HIV infection and 38% were screened in the past year for sexually transmitted infections (STI). Six ever-PrEP users reported having used post-exposure prophylaxis (PEP). Condomless anal sex in the past year was reported by 77%, sex with a known HIV-positive partner by 41% and sex while drunk or high on drugs by 32%.
Conclusion: PrEP use prior to diagnosis was rare among newly HIV diagnosed persons investigated for PS in NYC. Disproportionately low percentages of black, heterosexual and female ever-PrEP users suggest disparities in PrEP awareness, availability and uptake. High risk sexual behaviors and STI diagnoses were commonly reported among the ever-PrEP users, indicating the need for stronger messaging on condom use in conjunction with PrEP, as well as substance use counseling.

1037 DECREASES IN HIV INCIDENCE IN A MONTREAL CLINIC COINCIDE WITH EXPANDING PrEP USE

Marieve Beauchemin, Zoe Greenwald, Jason Szabo, Louise Charest, Judith Fafard, Danièle Longpré, Stéphane Lavoie, **Réjean Thomas**
Clinique Médicale l'Actuel, Montreal, QC, Canada

Background: With the objective to eliminate HIV transmission for 2030 now signed into political action by Montreal's Fast-Track City Initiative, combined prevention measures are the key to eliminating HIV transmission. There is little evidence to link decreases in HIV incidence with increased rates of individuals initiating PrEP or changes in other combined prevention strategies.
Methods: To examine the effects of combined prevention on rates of HIV transmission, we measure annual trends in HIV incidence, PrEP consults, PEP episodes, number of individuals screened annually, mean number of HIV tests per individual annually, and at the proportion of seropositive patients having an undetectable viral load from 2011–2016 at Actuel, a large sexual health clinic serving a majority MSM population in Montreal. HIV incidence was calculated based on the number of HIV diagnoses per 100 individuals screened per year.

Results: From 2011 to 2016, HIV incidence dropped by 56%, from 2.31 to 1.03 new HIV diagnoses per 100 individuals screened annually (Table 1). Meanwhile, the number of consultations for PrEP increased exponentially and gradual increases were observed in number of PEP treatments and proportion of seropositive patients having an undetectable viral load, which reached 95% by 2016. Both the number of individuals screened annually and the number of tests per person increased from 2011 to 2016, by 47% and 31%, respectively.
Conclusion: This data shows a major drop in HIV incidence within the past five years. This decline, in parallel with the exponential increase in PrEP initiations, confirms the importance of ensuring PrEP is available to everyone who should need it. It is important to underline, however, this decline was already in progress and is likely attributable, at least in part, to progress towards treatment as prevention and other preventive efforts. Also, these results only represent the experience of one major clinic in Montreal. Continued efforts to monitor the potential influence of PrEP and other combined prevention methods on new HIV cases at a population level are essential.

Table 1. Trends in HIV diagnosis and combined prevention measures at Clinique l'Actuel 2011-2016

Year	HIV diagnoses (N=703)	People tested (N=21 950)	New HIV infections per 100 people tested	Average # tests per person per year	Annual percent change in HIV rates	PrEP consults (N=1318)	PEP consults (N=3214)	% of HIV patients with undetectable viral load
2011	126	5453	2.31	1.21		3	380	92
2012	120	5942	2.02	1.32	-12.60%	5	444	91
2013	145	5925	2.45	1.33	21.18%	27	472	93
2014	118	6369	1.85	1.36	-24.29%	94	514	94
2015	112	6988	1.60	1.52	-13.49%	460	665	94
2016	82	7991	1.03	1.59	-35.98%	729	739	95

1038 HIGH SEROCONVERSION RATES FOLLOWING PrEP DISCONTINUANCE IN A MONTREAL CLINIC

Zoe Greenwald, Marieve Beauchemin, Khadija Benomar, Gabrielle Landry, Michel Boissonnault, Louise Charest, Danièle Longpré, Stéphane Lavoie, **Réjean Thomas**
Clinique Médicale l'Actuel, Montreal, QC, Canada

Background: Variations in individual PrEP use have been described by the seasons of risk theory; whereby patients may start and stop PrEP episodically. However, measures of rates of episodic PrEP use, reasons for PrEP discontinuation and rates of seroconversion following PrEP stops are scarce.
Methods: We aim to measure rates of temporary and permanent PrEP discontinuations describe stop reasons and measure seroconversion rates subsequent to stops using the Actuel PrEP cohort (Montreal). We included PrEP users who had initiated PrEP and returned for ≥1 follow-up visit prior to September 2017 (N=1258). We describe PrEP discontinuation as: (1) temporary or (2) permanent discontinuations reported at a follow-up visit, or (3) patients lost to follow-up for ≥6 months. We describe the reported stop reasons and HIV incidence rates subsequent to discontinuance. Person-time at risk was calculated from stop date to date of seroconversion or else censored at last negative routine HIV test among patients who were maintained in care.
Results: Our cohort measured 450 consistent PrEP users (36%), 114 PrEP users (9%) who temporarily stopped and re-initiated PrEP at least once, 214 individuals who permanently discontinued PrEP (17%) and 480 individuals who have been lost to follow-up (38%). HIV incidence following discontinuation was 3.9 cases per 100 PY. Among individuals who discontinued PrEP, the most commonly reported stop reasons were side effects (14%), cost of PrEP or loss of private insurance (9%), individual preference (7%), and changes in sex life, such as entry into a stable relationship with seronegative partner (13%), entry into relationship with seropositive undetectable partner (4%), breakup with seropositive partner (4%) or sexual abstinence (10%).
Conclusion: This study adds evidence to the theory that, for some, PrEP use is a transient rather than constant HIV prevention method. However, the high rates of seroconversion following PrEP discontinuance indicate the need for clinical support which takes into consideration contextual lifestyle factors that may lead individuals to stop PrEP, while remaining at high risk for HIV infection. In turn, appropriate risk counseling for those who stop PrEP and the development of resources to reduce loss to follow-up among PrEP users should be implemented. In line with Montreal's Fast-Track City Initiative, the support of PrEP and other combined prevention measures remain key to ending the epidemic by 2030.

1039 USING HIV INCIDENCE ESTIMATES TO INFORM GUIDELINES FOR THE PrEP IMPACT TRIAL

Martina Furegato, Paula Blomquist, Sarika Desai, Hamish Mohammed, Holly Mitchell, Monica Desai, Owen N. Gill, **John Saunders**
Public Health England, London, UK

Background: Individuals who are clinically assessed to be at similar risk of HIV acquisition (>2 per 100 person-years) as HIV-negative individuals with a serodiscordant partner who is not known to be virally suppressed (<200 copies per ml) are considered to be eligible for HIV Pre-Exposure Prophylaxis (PrEP) in England. In order to support clinicians in making this assessment, we used HIV incidence estimates from surveillance data to define risk groups who may benefit from PrEP in England.
Methods: We reviewed longitudinal data from GUMCAD, the national sexually transmitted infections (STI) surveillance system in England, on attendees at sexual health clinics. The incidence of HIV per 100 person-years (95% confidence intervals) for attendees with a history of HIV testing, post-exposure prophylaxis for HIV (PEPSE), bacterial STIs or use of drugs in a sexual context before or during last sexual intercourse was determined using the Kaplan-Meier method. Separate analyses were performed for MSM and heterosexuals.
Results: Among MSM, the incidence of HIV was greatest in those who were diagnosed with infectious syphilis (4.5) in the past year followed by those prescribed at least one course of PEPSE (3.9) in the past year and by those diagnosed with a bacterial STI (3.6) in the past year and by those who used drugs in a sexual context (3.6) before or during the last sexual intercourse (Table 1). Among heterosexuals, the HIV incidence was below 1 per 100 person-years in all the sub-groups included (Table 1).
Conclusion: More heterosexuals than MSM are diagnosed with HIV outside the sexual health clinics, so in this study the incidence in the heterosexual group is underestimated. However, given the high degree of variability in HIV risk among MSM and heterosexuals, these findings provide evidence to guide clinical risk assessment an essential step to accessing PrEP. This may help clinicians target patients more efficiently, thus maximising the impact of PrEP.

Table 1: Number of seroconversions, person-years and HIV incidence (per 100 person-years) in men who have sex with men and heterosexual sexual health clinic attendees, England, 2015

	Number of seroconversions		Person-years		Annual HIV Incidence (95% CI)	
	MSM	Heterosexual men and women	MSM	Heterosexual men and women	MSM	Heterosexual men and women
HIV test 43-365 days prior to current attendance	166	5	10,507	127,589	1.6 (1.4 to 1.8)	0.004 (0.002 to 0.009)
Prescribed at least one course of PEPSE in the previous 12 months	247*	1	23,526*	322	3.9 (3.4 to 4.4)*	0.3 (0.04 to 2.2)
Diagnosed with a bacterial STI in the previous 12 months or at current attendance						
Any bacterial STI**	191	5	6,772	14,753	2.8 (2.4 to 3.3)	0.03 (0.01 to 0.08)
Rectal bacterial STI***	56	ǂ	1,567	ǂ	3.6 (2.7 to 4.6)	ǂ
Infectious syphilis	28	ǂ	626	ǂ	4.5 (3.1 to 6.5)	ǂ
Use of drugs in a sexual context before or during last sexual intercourse	2	1	55	310	3.6 (0.9 to 14.5)	0.3 (0.05 to 2.3)

* Estimates derived using data from 2011 to 2014
** Chlamydia, gonorrhoea, syphilis, NSGI, LGV, donovanosis or chancroid (excluding pharyngeal only diagnoses)
*** Chlamydia, gonorrhoea, NSGI or LGV
ǂ Not calculated due to small numbers

1040 PrEP INTEREST AND HIV-1 INCIDENCE AMONG MSM AND TRANSGENDER WOMEN IN COASTAL KENYA

Makobu Kimani[1], Elisabeth M. van der Elst[1], Oscar Chirro[2], Clifford Oduor[1], Elizabeth Wahome[1], Winston Kazungu[1], Mahmoud Shally[2], Don Operario[3], Susan M. Graham[4], Eduard Sanders[2]
[1]Kenya Medical Research Institute, Kilifi, Kenya, [2]KEMRI Wellcome Trust Rsr Prog, Kilifi, Kenya, [3]Brown University, Providence, RI, USA, [4]University of Washington, Seattle, WA, USA

Background: Pre-exposure Prophylaxis (PrEP) has recently been added as one of the combination HIV prevention methods by the Kenyan Health Ministry. Data on willingness to take PrEP and the association between PrEP interest and HIV-1 incidence among gay, bisexual, and other men who have sex with men (GBMSM) and transgender women (TGW) are lacking. We aimed to assess PrEP interest and HIV-1 incidence in GBMSM and TGW.
Methods: With assistance from 10 peer educators from a GBMSM community-based organization, we recruited HIV-1 negative GBMSM who had participated

in an oral self-testing study and linked them to preventive care. We collected sociodemographic, sexual orientation, gender identity, and risk behavior data, and retested all men for HIV-1 using rapid tests. We assessed PrEP interest and calculated HIV-1 incidence since the 2016 study. We also conducted 3 focus group discussions (FGD) to characterize potential PrEP users' perspectives on perceived challenges and outcomes of PrEP use and adherence.
Results: During May-July 2017, 168 (74.4%) GBMSM were tested for HIV-1, including 112 men who have sex with men and women (MSMW) and 42 men who have sex with men exclusively (MSME) and 14 TGW. Overall, the median age was 26 years (interquartile range: 23-30). A total of 130 (59.1%) participants reported either primary schooling or no education, and 51 (30.4%) reported transactional sex in the past 6 months. Nine new HIV-1 infections were detected: 2 in MSMW, 4 in MSME, and 3 in TGW for an estimated HIV-1 incidence of 4.5 (95% confidence interval: 1.1-18.2), 3.4 (95% CI: 1.2-9.2), and 20.6 (95% CI: 6.6-63.8) per 100 person years, respectively. All but two participants were interested to start PrEP. Ten MSMW, 11 MSME, and 7 TGW participated in three separate FGD. MSME felt PrEP offered protection for receptive anal sex, MSMW perceived less need for taking PrEP, and TGW felt that PrEP may encourage condomless transactional sex. GBMSM and TGW criticized the integration of PrEP services in public hospital HIV clinics as undesirable due to stigma.
Conclusion: We demonstrated PrEP interest among GBMSM and estimated a very high HIV-1 incidence in a small group of TGW, who have received no attention in PrEP programming in Kenya. TGW may have been misclassified as MSME in previous HIV-1 incidence reports. Tailored PrEP messages and adherence support is needed for specific key population sub-categories.

1041 SEROCONVERSION ON PrEP: A PROTOCOL FOR UNTANGLING ADHERENCE VS RESISTANCE FAILURE

Joshua T. Thaden[1], Monica Gandhi[2], Karen Kuncze[2], Alexander Louie[2], Hideaki Okochi[2], Christopher B. Hurt[3], **Mehri McKellar**[1]
[1]Duke University, Durham, NC, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: PrEP with emtricitabine (FTC)/tenofovir (TFV) disoproxil fumarate (TDF) reduces risk of HIV acquisition with adequate adherence. Here, we describe a case of seroconversion with multidrug resistant (MDR) HIV despite good adherence, complicated by inappropriate prescribing practices and follow-up.
Methods: History was obtained from patient and records. PrEP adherence was assessed via self-report, pharmacy records, and measuring TFV/FTC levels with LC-MS/MS in plasma and hair. Segmental hair analysis was performed to assess PrEP adherence over prior months. Genotypic resistance was evaluated.
Results: A 34 year-old white MSM started daily FTC 200 mg/TDF 300 mg in 2/2016 after a non-reactive antigen/antibody test in 12/2015; he had no interim sexual activity. He reported full adherence to FTC/TDF from February to May 2016. He self-discontinued PrEP from May-July due to perceived lack of risk, and restarted 7/2016-4/2017. At PrEP initiation, he was prescribed 30 days of FTC/TDF with 11 refills by an ID specialist. He was told to return in 1 month and 6 months for HIV and renal testing, but no visits occurred. In 3/2017, he developed fevers, chills, myalgias and had a negative rapid influenza A/B test at an urgent care site. No HIV test was performed. In 4/2017, an antigen/antibody HIV test was reactive at an evaluation for anal condylomata (day 0). He was seen in an HIV clinic on day 2. FTC/TDF was stopped; no additional therapy was yet started. HIV-1 RNA was 27,316 copies/mL and genotyping revealed M184V, K65R, and K103N mutations. Day 2 plasma revealed TFV and FTC levels of 75 ng/mL and 281 ng/mL, respectively, consistent with recent dosing. To evaluate adherence over preceding months, a hair sample was collected at day 27 and segmental analysis of TFV/FTC levels performed in 1 centimeter segments from the scalp. Hair drug levels were commensurate with consistently high PrEP adherence over the last 3 months (Figure).
Conclusion: Acquisition of MDR HIV despite excellent PrEP adherence has been described in 3 prior reports. Though exact time of acquisition is unknown, our case acquired a virus with at least K103N; subsequent development of K65R and M184V from consistent FTC/TDF use is epidemiologically most likely. This study employs segmental analysis of PrEP drug levels for the first time to assess adherence over preceding months. Proper PrEP prescribing and follow-up would have allowed for quicker identification of HIV and possible prevention of further drug resistance in this individual.

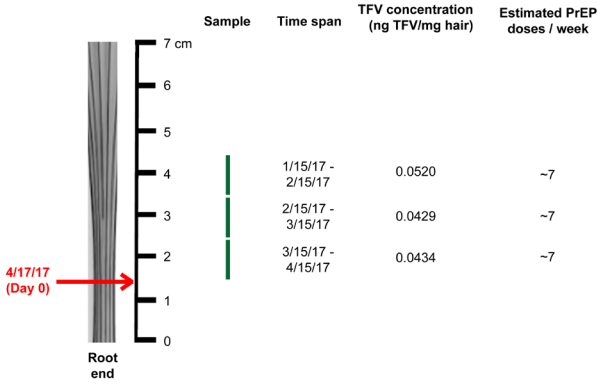


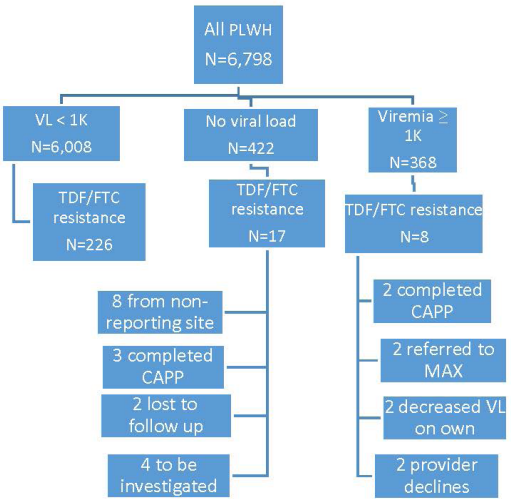
Figure. Segmental hair analysis in patient on TDF-FTC-based PrEP who seroconverted. Dates show first positive HIV test (Day 0), as well as time over which adherence assessed by hair concentrations in the UCSF Hair Analytical Laboratory (HAL). Data from a dose-concentration study called STRAND (Liu A, et al. PLOS ONE 2014) allows us to estimate number of doses per week from TFV levels in hair.

1042 A PUBLIC HEALTH APPROACH TO VIREMIC INDIVIDUALS WITH PrEP-RESISTANT VIRUS

Susan E. Buskin[1], Richard Lechtenberg[1], Matthew R. Golden[2], Mark J. Fleming[1], Julia C. Dombrowski[2]
[1]Public Health–Seattle & King County, Seattle, WA, USA, [2]University of Washington, Seattle, WA, USA

Background: King County public health HIV control efforts include tracking viremia and drug resistance, and promotion of antiretroviral adherence and reduction of viremia among people living with HIV (PLWH). A possible transmission of a tenofovir (TDF)/emtricitabine (FTC) resistant virus to a PLWH reporting good adherence to pre-exposure prophylaxis (PrEP, comprised of TDF and FTC) in 2016 initiated interventions with viremic PLWH with TDF/FTC resistant virus to help prevent transmission of an HIV strain potentially rendering PrEP ineffective.
Methods: HIV genotypic and viral load (VL) data from King County HIV surveillance were used to identify viremic PLWH with TDF/FTC resistant HIV. Resistance was defined by the Stanford database algorithm and based on any reported genotypic test. Resistance to TDF/FTC was defined by intermediate to high level resistance to both components. Viremia was defined as a most recent (within 2 years) plasma VL 1,000+ copies per mL. The Care and Antiretroviral Promotion Project (CAPP) investigated two prior viremic TDF/FTC resistant cohorts, working with individuals who are poorly engaged in HIV care to overcome barriers to care and antiretroviral adherence.
Results: Of 6,798 King County PLWH, genotypic sequences were reported for 3,892 (57%). Intermediate to high level TDF/FTC resistance was found for 251 (6%). We identified 368 PLWH (6% excluding 422 with no VL in 2 years) with viremia, and 8 had TDF/FTC resistance. Including 17 PLWH with no reported VL testing in two years and TDF/FTC resistance, 25 PLWH had TDF/FTC resistance and either viremia or no recent VL (corresponding to 0.4% of PLWH). Assuming the 43% of individuals with no reported genotype had similar levels of resistance we estimate that an additional 17 PLWH (42 total) may have no VL or viremia and TDF/FTC resistance, corresponding to 0.6% of PLWH. Investigation outcomes are summarized in the figure, and include (1) that nearly half of individuals without a VL were from a facility not reporting VL, all were virally suppressed or relocated and (2) at least 7 had previously completed the CAPP intervention and remained viremic or without VL, including 2 referred to a clinic providing extensive support to PLWH unable to achieve viral suppression.
Conclusion: FTC/TDF drug resistance among viremic PLWH in King County, WA remains rare, estimated in 0.4-0.6% of PLWH. We have developed outreach programs for these persons, designed to promote care and prevent transmission of HIV with TDF/FTC resistance.

People living with HIV (PLWH) King County, WA in 2017 by viral load status and resistance to TDF/FTC



PLWH=people living with HIV; VL = Plasma viral load copies/mL; CAPP=Care and antiretroviral Promotion Project; MAX = walk-in clinic that provides extensive support to persons with HIV who have been unable to achieve viral suppression; TDF=Tenofovir; FTC=Emtricitabine

1043 PATTERNS OF ORAL PrEP ADHERENCE AND HIV RISK AMONG EASTERN AFRICAN WOMEN

Maria Pyra[1], Elizabeth Brown[2], Jessica E. Haberer[3], Renee Heffron[1], Elizabeth A. Bukusi[1], Stephen Asiimwe[4], Connie L. Celum[1], Elly T. Katabira[5], Nelly R. Mugo[1], Jared Baeten[1]

[1]University of Washington, Seattle, WA, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Kabwohe Clinical Research Center, Kabwohe, Uganda, [5]Makerere University, Kampala, Uganda

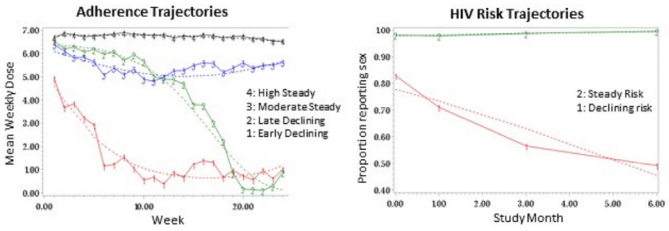
Background: Understanding when and how women use PrEP is important to developing successful implementation programs and adherence counseling. We sought to identify unique patterns of PrEP adherence, as well as predictors of these adherence patterns, and compare adherence patterns by HIV risk.

Methods: We used data from 233 HIV-uninfected women enrolled as members of serodiscordant couples in a PrEP demonstration project in Kenya and Uganda. Weekly PrEP adherence, assessed by daily electronic monitoring via MEMS Caps, and HIV risk, defined as any sex reported at study visits, over the first six months after PrEP initiation were modeled using group-based trajectory models.

Results: There were four unique adherence patterns identified (Figure 1): women with high steady adherence (55% of population); moderate steady adherence (29%); late declining adherence (8%); and early declining adherence (9%). No baseline characteristics, including age, marital status, education, or problem drinking, were significantly different across adherence patterns. Adherence patterns differed by average weekly doses (6.7 vs 5.4 vs 4.1 vs 1.5, respectively). Two risk groups were identified, steady HIV risk (78% of population) and declining HIV risk (22%). Women with steady HIV risk were more likely to have high steady adherence compared to women with declining HIV risk (61% vs 35%); women with steady HIV risk were also less likely to have early (6% vs 17%) or late (4% vs 19%) declining adherence compared to those with declining HIV risk.

Conclusion: Patterns of adherence to oral PrEP among women were associated with their concurrent HIV risk. Specifically, women with steady HIV risk were more likely to have high steady adherence and less likely to have declining adherence over the first six months of PrEP use compared to women with declining HIV risk.

Figure 1. Adherence and Risk Trajectories



1044 CHARACTERIZING THE HIV CONTINUUM OF CARE FOR TRANSGENDER WOMEN IN NORTH AMERICA

Tonia Poteat[1], David B. Hanna[2], Peter F. Rebeiro[3], Marina Klein[4], Michael J. Silverberg[5], Joseph J. Eron[6], Michael A. Horberg[7], Mari Kitahata[8], W. C. Mathews[9], Kristin Mattocks[10], Angel Mayor[11], Ashleigh Rich[12], Richard D. Moore[1], Keri N. Althoff[1]

[1]Johns Hopkins University, Baltimore, MD, USA, [2]Albert Einstein College of Medicine, Bronx, NY, USA, [3]Vanderbilt University, Nashville, TN, USA, [4]McGill University, Montreal, QC, Canada, [5]Kaiser Permanente Northern California, Oakland, CA, USA, [6]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [7]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [8]University of Washington, Seattle, WA, USA, [9]University of California San Diego, San Diego, CA, USA, [10]VA Central Western Massachusetts Healthcare System, Leeds, MA, USA, [11]Universidad Central del Caribe, Bayamon, Puerto Rico, [12]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

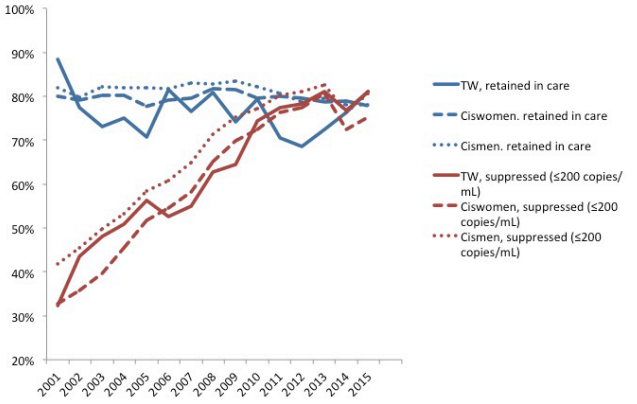
Background: Transgender women (women assigned male at birth), particularly Black TW, bear a disproportionate burden of HIV in the U.S. Prior studies suggest TW have lower viral suppression (VS) but similar retention in clinical care (RIC) compared with cisgender women (CW) and cisgender men (CM) with HIV. We sought to characterize the HIV Continuum of Care (CoC) over time, comparing TW to CW and CM participants, in the NA-ACCORD.

Methods: We analyzed CoC outcomes annually among adults from 9 clinical cohorts with longitudinal data (2001-2015) on transgender participants within the NA-ACCORD. CoC outcomes included retention (proportion >=2 visits >90 days apart), and viral suppression (proportion with HIV RNA <200 copies/mL at final measurement in the year). Log-binomial regression models were used to estimate adjusted prevalence ratios (aPR) and 95% confidence intervals ([,]) for retention and viral suppression by gender status in recent years (2013-14), adjusted for age, race, a history of injection drug use, and cohort.

Results: The study population includes TW (n=188), CW (n=5,469) and CM (n=22,722). Median age at baseline was higher for CM (40 interquartile range [IQR] 33-47 years) compared with CW (38 IQR 32, 46 years) and TW (37 IQR 30, 44 years) patients (p<0.001), with 37% of TW patients age >=40 years versus 44% of CW and 51% of CM (p=<0.001). Among TW, 39% were black compared with 62% of CW and 28% of CM (p<0.001). Although there was greater variability in estimates, TW had lower proportions retained in care than CW and CM; there was little change in retention over time for TW, CW, and CM (Figure). All three groups saw improvements in viral suppression, with CM showing the highest proportions and TW and CW having similar proportions over time. In 2014, the prevalence of retention in care and viral suppression did not differ by gender status (retention in care: TW vs. CM aPR=0.99 [0.88, 1.12] and CW vs CM aPR=1.02 [1.00, 1.05]; viral suppression: TW vs. CM aPR=0.96 [0.87, 1.06] and CW vs CM aPR=1.01 [0.98, 1.03]).

Conclusion: TW in the NA-ACCORD have successfully engaged in care; many of the 9 clinical care sites contributing data on transgender participants have instituted gender-affirming practices that are likely influencing the high proportions of TW retained and with viral suppression. The study is limited by use of a one-step method to identify transgender participants. Research into long-term health outcomes in TW with HIV are needed.

Figure: Retention in care and viral suppression among transgender women (TW) and cisgender women (ciswomen) and men (cismen) in the NA-ACCORD, 2001-2015



1045 PREDICTORS OF WILLINGNESS TO TAKE PrEP AMONG BLACK AND LATINA TRANSGENDER WOMEN

Tonia Poteat[1], Erin Cooney[1], Mannat Malik[1], Thespina Yamanis[2], Maren Lujan[2], Andrea L. Wirtz[1]

[1]Johns Hopkins University, Baltimore, MD, USA, [2]American University, Washington, DC, USA

Background: Black and Latina transgender women (BLTW) in the U.S. are at high risk for HIV with reported annual incidence rates as high as 3.2 per 100 person-years. While PrEP has demonstrated efficacy in multiple clinical trials and implementation projects, uptake and adherence among transgender women (TW) has been low. Adherence was only 18% among TW in the seminal iPrEx trial and did not correlate with HIV risk behavior. Efforts to promote PrEP among key populations have scaled up since FDA approval in 2012. The aims of this study were to estimate PrEP uptake and identify predictors of willingness to take PrEP among BLTW.

Methods: We recruited BLTW in Baltimore, MD and Washington, DC from April 2016 – May 2017, via community health centers, outreach, and network referrals. Each participant completed a face-to-face interview in English or Spanish, followed by OraQuick Rapid HIV 1/2 test and linkage to confirmatory testing, if positive. Interviews assessed psychosocial factors and HIV risk behaviors as well as PrEP awareness, willingness, and uptake. Bivariate and multivariable logistic regression models were used to test associations between legal gender affirmation (i.e. name or gender marker that matches current identity), transgender pride (measured via Likert scale), lifetime history of exchange sex, HIV risk perception, and PrEP willingness. Multivariable modeling controlled for age and survey language.

Results: Among 201 BLTW, 86% (n=174) had heard of PrEP. Of those, 80% (n=139/174) knew where to get it. Among self-reported HIV-negative or HIV-unknown BLTW who had not taken PrEP, 78% (n=59/76) were willing to take it, yet only 39% (n=30/76) had ever done so. The small number of participants on PrEP (n=30) limited the power to detect significant predictors of PrEP uptake. On bivariate analyses, greater transgender pride, history of exchange sex, and higher HIV risk perception were positively associated with PrEP willingness, while legal gender affirmation was negatively associated. History of exchange sex and legal gender affirmation remained significant in the multivariable model.

Conclusion: More than three-fourths of HIV-negative BLTW reported awareness and willingness to take PrEP. Nevertheless, uptake remains quite low. More research is needed to improve PrEP uptake as well as to explain potentially complex relationships between gender affirmation, exchange sex, and PrEP acceptability among BLTW.

Table. Predictors of PrEP Willingness among Self-reported HIV-negative Black and Latina Transgender Women (n=76)

Variable	Bivariate Associations with PrEP Willingness		Multivariable Model of PrEP Willingness	
	OR (95%CI)	p-value	aOR (95%CI)	p-value
Transgender Pride[1]	1.19 (1.05-1.36)*	p=0.007	1.08 (0.92-1.27)	p=0.326
Legal Gender Affirmation[2]	0.16 (0.03-0.78)*	p=0.023	0.07 (0.01-0.66)*	p=0.021
Lifetime History of Exchange Sex	3.81 (1.14-12.68)*	p=0.029	4.49 (1.02-19.83)*	p=0.048
HIV risk perception[1]	1.90 (1.07-3.37)*	p=0.028	2.01 (0.97-4.18)	p=0.062
Age in years[1]	1.00 (0.96-1.05)	p=0.969	1.05 (0.98-1.13)	p=0.145
Language[3]	0.38 (0.10-1.51)	p=0.170	0.77 (0.12-4.85)	p=0.783

1. Measured as continuous variable.
2. Any name and/or gender marker change versus none.
3. English versus Spanish
* Significant at p<0.05

1046 PrEP AND EARLY ART FOR FEMALE SEX WORKERS IN SOUTH AFRICA: THE TAPS PROJECT

Robyn Eakle[1], Gabriela Gomez[2], Niven Naicker[1], Rutendo Bothma[1], Judie Mbogua[1], Maria A. Cabrera Escobar[1], Elaine Saayman[1], Michelle A. Moorhouse[1], **Willem D. Venter**[1], Helen Rees[1]

[1]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [2]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands

Background: Operational research is required to design delivery of pre-exposure prophylaxis (PrEP) and early antiretroviral treatment (early ART). This paper presents the primary analysis of the TAPS Demonstration Project, a demonstration project offering both interventions to female sex workers (FSWs) in two urban clinic sites in South Africa.

Methods: TAPS was a prospective, observational cohort study with two arms delivered in existing service settings: 1) PrEP for HIV-negative FSWs, and 2) early ART for HIV-positive FSWs. The main outcome was retention at 12 months. We also present uptake, adherence, key demographic characteristics, number of sero-conversions, virological failures and sexually transmitted infections (STIs), as well as changes in sexual behaviour among participants and cost of services.

Results: Of the 947 FSWs seen in clinic, 692 were HIV tested. HIV prevalence was 49%. Among those returning to clinic after testing and confirmed clinical eligibility, 98% (219/224) and 94% (139/148) took up PrEP and early ART, respectively. Of those enrolled, 22% on PrEP and 60% on early ART were seen at 12 months. The majority of women were married or had a stead partner, worked in brothels, and were born in Zimbabwe. Little change was seen over time in consistent condom use or the number of sexual partners, with high levels of consistent condom use with clients and low use with main partners in both study arms. There were no seroconversions on PrEP and seven virological failures on early ART. Total cost of service delivery was approximately $126 for PrEP and $406 for early ART per person-year.

Conclusion: PrEP and early ART services can be implemented within FSWs routine services in high prevalence, urban settings, with good uptake for both PrEP and early ART. Retention can be challenging among FSWs on PrEP, but those remaining in care can be consistent in attendance and reported adherence. Costs of the TAPS programme were higher than previously published, however there is potential for cost reduction at scale. The TAPS demonstration project results provided the basis for the first government PrEP and early ART guidelines and the roll out of a national sex worker plan in South Africa.

1047 HIGH PrEP UPTAKE AMONG KENYAN PREGNANT WOMEN OFFERED PrEP DURING ANTENATAL CARE

John Kinuthia[1], Jillian Pintye[2], Kenneth K. Mugwanya[2], Marline Serede[3], Joseph Sila[3], Felix Abuna[3], Harrison Lagat[3], Julia Dettinger[2], Tina Schuh[2], Jared Baeten[2], Grace John-Stewart[2]

[1]Kenyatta National Hospital, Nairobi, Kenya, [2]University of Washington, Seattle, WA, USA, [3]University of Washington in Kenya, Nairobi, Kenya

Background: Women in high HIV prevalence regions of sub-Saharan Africa have substantial risk of acquiring HIV during pregnancy and postpartum. The PrEP Implementation for Young Women and Adolescents (PrIYA) Project provides real-world evidence on delivering PrEP to pregnant women in Western Kenya.

Methods: We approached HIV-uninfected pregnant women seeking routine antenatal (ANC) services at 10 maternal and child health clinics in Kisumu County, Kenya from June to August 2017. Women were screened for behavioral risk factors and willingness for PrEP counseling according to national PrEP guidelines. Women who wanted to consider PrEP were counseled on PrEP and assessed for medical eligibility. Eligible women willing to initiate PrEP received oral PrEP.

Results: We screened 1,008 pregnant women for willingness to be counseled for PrEP. The median age was 23 years (interquartile range 20-28) and 57% of women were ≤24years. Overall, 347 (34%) women accepted PrEP counseling. Compared to women who declined PrEP counseling, women who accepted more frequently had a partner of unknown HIV status (81% vs 19%, p<0.001), engaged in transactional sex (3% vs 1%, p=0.02), were forced to have sex (2% vs 1%, p=0.02) and were diagnosed with STIs (6% vs 1%, p<0.001) in the last 6 months. Acceptance of PrEP counseling was similar among women ≤24 and >24 years (35% vs 33%, p=0.55). There were no differences in gestational age between women who accepted and declined PrEP counseling (median 28 [IQR 24-32] vs 28 [IQR 23-34] weeks, p=0.26). Of the 347 women counseled for PrEP, one woman (<1%) was medically ineligible, and 252 (73%) wanted to initiate PrEP and were prescribed PrEP the same day. Compared to women who did not choose to initiate PrEP, initiators more frequently had a known HIV-infected partner (9% vs 2%, p<0.001) and >1 sex partner (6% vs 1%, p=0.04). Women in polygamous marriages more frequently initiated PrEP than women in monogamous marriages (88% vs 71%, p=0.05). PrEP initiators less frequently reported any fears about starting PrEP than women who did not initiate (4% vs 59%, p<0.001). Among women who did not initiate PrEP, the most frequently reported fears were pill burden (28%) and stigma (13%).

Conclusion: It was feasible to implement PrEP during ANC in a high HIV prevalence region. A substantial proportion of pregnant women chose to initiate PrEP (25% overall, 73% of those counseled on PrEP). Pregnant women who chose to start PrEP more frequently had risk factors for HIV than those who did not.

1048 PREDICTORS OF PrEP ELIGIBILITY AMONG AT–RISK WOMEN IN THE SOUTHERN UNITED STATES

Anar S. Patel[1], Lakshmi Goparaju[2], Jessica M. Sales[1], Cyra Christina Mehta[1], Oni J. Blackstock[3], Dominika Seidman[4], Igho Ofotokun[1], Mirjam-Colette Kempf[5], Margaret Fischl[6], Elizabeth T. Golub[7], Adaora Adimora[8], Audrey French[9], Gina Wingood[1], Seble Kassaye[2], Anandi N. Sheth[1]

[1]Emory University, Atlanta, GA, USA, [2]Georgetown University, Washington, DC, USA, [3]Montefiore Medical Center, Bronx, NY, USA, [4]University of California San Francisco, San Francisco, CA, USA, [5]University of Alabama at Birmingham, Birmingham, AL, USA, [6]University of Miami, Miami, FL, USA, [7]Johns Hopkins Hospital, Baltimore, MD, USA, [8]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [9]Cook County Health & Hospitals System, Chicago, IL, USA

Background: Women of color in the South have disproportionately high rates of new HIV infections, but low use of HIV pre-exposure prophylaxis (PrEP). Mechanisms to best identify US women eligible for PrEP are lacking, which contributes to limited PrEP uptake. Identifying factors associated with PrEP eligibility could facilitate improved screening, offering, and uptake of PrEP among US women at risk for HIV.

Methods: We applied CDC criteria for PrEP use to at-risk HIV negative women enrolled in the Southern sites (Atlanta, Chapel Hill, Birmingham/Jackson, Miami) of the Women's Interagency HIV Study (WIHS) from 2014-15 to estimate PrEP eligibility. PrEP eligibility was determined using number of male sex partners, partner HIV status, condom use, and injection drug use in the past 6 months. Factors associated with PrEP eligibility were assessed using unadjusted odds ratios (OR) and 95% confidence intervals (CI). PrEP willingness and use was determined at baseline visit.

Results: Of 225 women, 187 (83%) identified as African-American, median age was 45 years, and 120 (53%) had health insurance. In the past 6 months, 43% reported ≥ 2 partners, 7.1% had a partner with HIV, and 11.1% reported a sexually transmitted infection. Overall, 72 (32%) women met CDC criteria for PrEP; the most common PrEP indicator was condomless sex (25.5%). Education of ≤ high school (OR 2.66, CI 1.45, 4.85); experienced physical violence (OR 2.56, CI 1.07, 6.13), sexual violence (OR 4.74, CI 1.56, 14.44) or engaged in transactional sex (OR 3.99, CI 1.76, 9.06) in the last 6 months; non-injection drug use in the last 6 months (OR 2.07, CI 1.15, 3.72); and any previous incarceration (OR 1.87, CI 1.05, 3.36) were associated with PrEP eligibility (Table 1). Further, self-perception of HIV risk (medium vs low/none OR 3.46, CI 1.52, 7.88; high vs low/none OR 16.44, CI 5.28, 51.18) was highly predictive of PrEP eligibility. At baseline, 24 (11%) women previously heard of PrEP, and only 1 reported prior use. Overall, 189 (84%) were willing to take PrEP, including the majority of PrEP-eligible women (86%).

Conclusion: Nearly one-third of Southern HIV negative WIHS women were eligible for PrEP. Extremely low PrEP awareness and use despite high acceptability signify a critical need to enhance PrEP delivery for women in this region. Supplementing CDC eligibility criteria with questions about violence, transactional sex, incarceration, non-injection drug use and HIV risk self-assessment may enhance PrEP screening and uptake among US women.

Table 1. Factors associated with PrEP eligibility in HIV-negative WIHS women enrolled in Southern US sites (n=225)

Model predictor	Not PrEP eligible n = 153 N (%)	PrEP eligible n = 72 N (%)	Odds Ratio (95% Confidence Interval)
Age (years), median (Q1, Q3)	44.7 (35.3, 51.4)	44.4 (34.5, 50.9)	1.01 (0.98, 1.04)
Race			
Non-African American	23 (15.0%)	15 (20.8%)	ref
African American	130 (85.0%)	57 (79.2%)	0.67 (0.33, 1.38)
Health insurance			
No	68 (44.4%)	37 (51.4%)	1.32 (0.75, 2.32)
Yes	85 (55.6%)	35 (48.6%)	ref
Household income			
≤ $24,000	113 (77.4%)	58 (85.3%)	1.69 (0.78, 3.68)
> $24,000	33 (22.6%)	10 (14.7%)	ref
Marital status			
Married	54 (35.3%)	18 (25.4%)	ref
Not married[1]	99 (64.7%)	53 (74.7%)	1.61 (0.86, 3.01)
Education			
≤ High school	73 (47.7%)	51 (70.8%)	2.66 (1.46, 4.85)
> High school	80 (52.3%)	21 (29.2%)	ref
Alcohol use			
Abstain	64 (41.8%)	27 (37.5%)	ref
0-7 drinks/week	59 (38.6%)	21 (29.2%)	0.84 (0.43, 1.65)
>7 drinks/week	30 (19.6%)	24 (33.3%)	1.90 (0.94, 3.82)
Self-reported STI[2]			
No	140 (91.5%)	60 (83.3%)	ref
Yes	13 (8.5%)	12 (16.7%)	2.15 (0.93, 4.99)
Currently employed			
No	94 (61.8%)	54 (75.0%)	1.85 (0.99, 3.46)
Yes	58 (38.2%)	18 (25.0%)	ref
Physical violence[3]			
No	141 (92.8%)	60 (83.3%)	ref
Yes	11 (7.2%)	12 (16.7%)	2.56 (1.07, 6.13)
Sexual violence[3]			
No	147 (96.7%)	62 (86.1%)	ref
Yes	5 (3.3%)	10 (13.9%)	4.74 (1.56, 14.44)
Transactional sex[3]			
No	142 (92.8%)	55 (76.4%)	ref
Yes	11 (7.2%)	17 (23.6%)	3.99 (1.76, 9.06)
Ever incarcerated			
No	74 (48.4%)	24 (33.3%)	ref
Yes	79 (51.6%)	48 (66.7%)	1.87 (1.05, 3.36)
Seen a healthcare provider[3]			
No	42 (27.5%)	21 (29.2%)	1.09 (0.59, 2.02)
Yes	111 (72.6%)	51 (70.8%)	ref
Non-injection drug use[4]			
No	112 (73.2%)	41 (56.9%)	ref
Yes	41 (26.8%)	31 (43.1%)	2.07 (1.15, 3.72)
Depressed[5]			
No	90 (58.8%)	33 (45.8%)	ref
Yes	63 (41.2%)	39 (54.2%)	1.69 (0.96, 2.97)
Self-perception of HIV risk			
No to low risk	135 (88.2%)	39 (54.2%)	ref
Medium risk	14 (9.2%)	14 (19.4%)	3.46 (1.52, 7.88)
High risk	4 (2.6%)	19 (26.4%)	16.44 (5.28, 51.18)

[1] Individuals were classified as not married if never married, divorced, widowed, or separated [2] Sexually transmitted infection including gonorrhea, chlamydia, trichomonas, or syphilis since last semiannual visit [3] Since last semiannual visit [4] Including crack/cocaine, marijuana, hallucinogens, club drugs, and methamphetamines since last semiannual visit [5] Defined as Center for Epidemiological Studies-Depression (CES-D) score ≥ 16

1049 RISK BEHAVIOR, PERCEPTION, AND REASONS FOR PrEP AMONG YOUNG AFRICAN WOMEN IN HPTN 082

Connie L. Celum[1], Sinead Delany-Moretlwe[2], Sybil Hosek[3], Bonnie J. Dye[4], Linda-Gail Bekker[5], Nyaradzo Mgodi[6], Wonderful Mabuza[2], Goodness Zoh Mvuyane[5], Shorai Mukaka[6], Deborah J. Donnell[7], Subash Pathak[7], Heather Noble[7], Denni Lennon[8], Jessica M. Fogel[8], Peter L. Anderson[9]

[1]University of Washington, Seattle, WA, USA, [2]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [3]Stroger Hospital of Cook County, Chicago, IL, USA, [4]FHI 360, Durham, NC, USA, [5]University of Cape Town, Cape Town, South Africa, [6]University of Zimbabwe, Harare, Zimbabwe, [7]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [8]Johns Hopkins Hospital, Baltimore, MD, USA, [9]University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Background: Oral pre-exposure prophylaxis (PrEP) is highly effective when used consistently, and recommended for people at substantial risk of HIV infection. Young women in sub-Saharan Africa are an important population who could benefit from PrEP, but may experience barriers to consistent use. Strategies are needed to support PrEP uptake and adherence in this population.

Methods: HPTN 082 is an open label PrEP study in Cape Town and Johannesburg, South Africa and Harare, Zimbabwe, enrolled sexually active HIV-negative women ages 16-25 using the VOICE risk score and a PrEP readiness

scale. Women interested in PrEP were enrolled regardless of initial decision to initiate PrEP. PrEP 'acceptors' were randomized to standard adherence support (cognitive behavioral counseling, 2-way SMS, and adherence clubs) or enhanced adherence support based on drug level feedback at 8 and 13 weeks plus standard adherence support, with follow-up for one year.
Results: Of 434 enrolled, 396 initiated PrEP at and 13 after enrollment (94%) and 25 (6%) declined PrEP. Median age was 21 years. The median VOICE risk score was 7 in both acceptors and decliners (maximum score=10; score ≥5 associated with 6-8% HIV incidence in prior cohorts). 84% of acceptors reported a primary sex partner-60% were thought to be HIV negative, 19% of unknown status, and 1% HIV positive (21% missing data). Most acceptors thought their partners had other partners (24%) or were not sure (60%). Most acceptors reported risk behaviors - 66% inconsistent or infrequent condom use, 22% transactional sex in the past 3 months, and 50% intimate partner violence in the past year. STI prevalence was high: 30% C.trachomatis, 8% N. gonorrhoeae, and 7% T. vaginalis. 41% had depression based on a CES-D-10 score ≥11. Motivation for pregnancy prevention was high; 80% reported it was very important to them to not become pregnant in the next year and 71% were using contraception other than condoms. Only 16% reported a moderate or high chance of acquiring HIV in the next year. Of acceptors, 62% had a friend encourage them to take PrEP, 94% reported they were ready to start PrEP, 81% planned to tell family and friends about PrEP use, 94% thought they could take it daily, and 39% anticipated side effects.
Conclusion: Uptake of PrEP is very high among young African women participating in HPTN 082. A majority felt they could take PrEP daily and planned to disclose PrEP use. Women in HPTN 082 are appropriate for PrEP, given risk behaviors and high STI prevalence.

1050 HIV BIOMEDICAL PREVENTION AMONG US WOMEN: KNOWLEDGE, BELIEFS, AND PRACTICES

Seble Kassaye[1], Lakshmi Goparaju[1], Amanda D. Castel[2], Lari Warren-Jeanpiere[1], Anandi N. Sheth[3], Adaora Adimora[4], Margaret Fischl[5], Elizabeth T. Golub[6], Kathleen M. Weber[7], Jennifer Cohen[8], Oluwakemi Sosanya[9], Anna Rubtsova[3], Deborah Konkle-Parker[10], Tracey Wilson[11], Chenglong Liu[1]
[1]Georgetown University, Washington, DC, USA, [2]George Washington University, Washington, DC, USA, [3]Emory University, Atlanta, GA, USA, [4]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [5]University of Miami, Miami, FL, USA, [6]Johns Hopkins University, Baltimore, MD, USA, [7]Cook County Health & Hospitals System, Chicago, IL, USA, [8]University of California San Francisco, San Francisco, CA, USA, [9]Montefiore Medical Center, Bronx, NY, USA, [10]University of Mississippi, Jackson, MS, USA, [11]SUNY Downstate Medical Center, Brooklyn, NY, USA

Background: Though biomedical HIV prevention measures including post-exposure prophylaxis (PEP), pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP) are now available, U.S. women's knowledge, attitudes, and behavior (KAB) about PEP, PrEP and TasP are limited. We sought to identify important barriers and disparities to women's access.
Methods: A nested cross sectional survey among 2406 participants (1690 HIV+ and 716 HIV-) in the Women's Interagency HIV Study (WIHS) assessed PEP, PrEP and TasP KAB. Data collected in 2014-2015 included questions about HIV testing and risk perception, sexual partners, current medication adherence, PEP, PrEP and TasP awareness and experience, stigma, and prevention beliefs. We used logistic regression to assess factors associated with willingness to use PEP, PrEP or TasP, respectively, and only included those variables statistically significant in univariate analyses into multivariate models.
Results: Mean age of the sample was 47 years, and the majority (72%) were Black. Only 20% of women had heard of PEP and 14% had heard of PrEP. In multivariate analyses, HIV(-) women who would recommend PEP to others (Odds Ratio (OR): 20; 95% confidence interval (CI): 11-37; $P < 0.0001$) or thought they were at higher risk of HIV infection (OR: 2.2; 95% CI: 1.2-4.2; $P = 0.015$), were more willing to take PEP. Whereas older women (OR:0.95; 95%CI: 0.92-0.98; $P = 0.001$) and Black women (OR: 0.34; 95% CI: 0.12-0.96; $P = 0.042$) were less willing to use PrEP, women with casual sexual partners (OR:0.36; 95% CI:0.14-0.91; $P = 0.030$), those who believed PrEP will prevent HIV (OR:7.28; 95% CI: 1.92-27.68; $P = 0.004$), and those willing to recommend PrEP to others (OR; 95%CI; $P<0.001$) reported willingness to take PrEP themselves. No women in the sample were on PrEP at the time of the study. Interest in learning more about TasP was independently associated with willingness to take PEP/PrEP to prevent transmission to others (OR: 3.09; 95% CI: 1.1-8.7; $P = 0.033$) among HIV+ women.
Conclusion: Knowledge and use of PEP/PrEP was limited among women in the study. Many factors may affect use of PEP, PrEP and TasP among women. Reporting higher risk was associated with willingness to use these biomedical prevention modalities. Further studies are needed to identify modifiable factors to improve uptake of biomedical interventions for high risk women.

1051 DEPRESSION AND PrEP ADHERENCE AMONG HIGH-RISK HIV-UNINFECTED WOMEN IN EAST AFRICA

Jennifer Velloza[1], Jared Baeten[1], Jessica E. Haberer[2], Kenneth Ngure[3], Elizabeth M. Irungu[3], Nelly R. Mugo[3], Connie L. Celum[1], Renee Heffron[1]
[1]University of Washington, Seattle, WA, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]Kenya Medical Research Institute, Nairobi, Kenya

Background: Oral pre-exposure prophylaxis (PrEP) is highly efficacious but low adherence undermines its efficacy. PrEP implementation programs are working to identify modifiable factors to improve product adherence, especially for young women. Mental health factors, particularly depression, could be associated with lower PrEP adherence.
Methods: We analyzed data from 334 Kenyan and Ugandan HIV-uninfected female participants in the Partners Demonstration Project, an open-label study of integrated PrEP and ART delivery for HIV serodiscordant couples. HIV-uninfected participants completed quarterly visits over two years and were encouraged to use PrEP until their HIV-infected partners had ≥6 months of ART use. PrEP adherence was measured daily with electronic MEMS caps. Participants were considered "adherent" if MEMS data indicated that ≥80% of expected doses were taken between quarterly study visits. Depressive symptoms were assessed at enrollment, 12-month, and 24-month visits using the 16-item Hopkins Symptoms Checklist (HSCL-D); mean score ranges from 1-4 and scores >1.75 indicate "probable depression". We used linear methods to estimate the mean HSCL-D scores between annual visits and generalized estimating equations to determine whether depressive symptoms influenced PrEP adherence.
Results: The median age was 29 years (IQR: 24-35 years). At enrollment, 39 (11.7%) women reported symptoms indicating probable depression, decreasing to 9 (3.1%) at month 24 (p-value for trend <0.001). Almost all women initiated PrEP at enrollment (96.7%) and more than half stopped PrEP by their 12-month visit because of their partners' sustained ART use (N=196; 58.7%). Low adherence to PrEP was detected at 26.9% of 1,433 quarterly study visits and occurred more often during periods when women reported probable depression (41.1% of visits) relative to periods without depression (25.9% of visits). Probable depression during follow-up was significantly associated with reduced PrEP adherence after adjusting for site, age, pregnancy status, any unprotected sex acts, and relationship satisfaction with their study partner (aRR=0.70; 95% CI=0.50-0.98; p-value=0.04). Continuous HSCL-D score was similarly associated with reduced PrEP adherence (aRR=0.75; 95% CI=0.56-0.99; p-value=0.05).
Conclusion: Depression was relatively uncommon and was associated with lower PrEP adherence in this sample. Integration of depression screening and treatment into PrEP delivery programs may improve PrEP effectiveness among African women.

1052 REPORTED PrEP USE AMONG HIV-NEGATIVE PARTNERS OF US MSM RECEIVING HIV MEDICAL CARE

Linda Beer, R. L. Shouse, **Dawn K. Smith**, Amy R. Baugher, Jennifer Fagan
CDC, Atlanta, GA, USA

Background: Pre-exposure prophylaxis (PrEP) is efficacious for reducing HIV transmission and has the potential to drastically reduce HIV incidence. Lower PrEP use among groups most vulnerable to HIV may reduce PrEP's impact, especially for the partners of HIV-positive persons who are not virally suppressed. However, population-based data are lacking.
Methods: The Medical Monitoring Project (MMP) is a surveillance system that produces representative estimates of HIV-positive adults receiving medical care in the United States. Using weighted interview and medical record data collected 6/2014-5/2015, we examined the prevalence of reported partner PrEP use in discordant HIV status sexual partnerships among 918 HIV-positive MSM, and the association of partner PrEP use with viral suppression of the HIV-positive person. We examined partner-level factors associated with PrEP use among 1912 HIV-negative/unknown status ("HIV-negative") partners; among partners not on PrEP, we evaluated associations with HIV-positive MSM partners having durable viral suppression using Rao-Scott $\chi 2$ tests.

Results: In all, 10% (95% confidence interval [CI] 8-13) of MSM with HIV-negative partners in the past 12 months reported having ≥1 partner on PrEP. MSM reported that 6% (CI 4-7) of their partners were on PrEP, 67% (CI 63-71) were not on PrEP but the HIV-positive person was virally suppressed, and 27% (CI 23-31) were not on PrEP and the HIV-positive person was not virally suppressed. MSM reported that PrEP use was more prevalent among white compared with black and Hispanic/Latino partners, and among partners with whom they had condomless receptive anal intercourse (Table). Reported partner PrEP use was not associated with viral suppression of the HIV-positive person or partner age. Among HIV-negative partners not on PrEP, black and younger persons were more likely to be the partner of a person who was not virally suppressed. Among HIV-negative partners not on PrEP, condomless receptive anal intercourse was more common when the HIV-positive person was virally suppressed.

Conclusion: Reported PrEP use by partners of MSM in HIV care in the US was low, and over ¼ were not on PrEP and were the partners of a person who was not virally suppressed. Reported PrEP use was lower among blacks and Hispanics, and among younger and black partners of MSM who were not virally suppressed. These data may help inform efforts to increase viral suppression among MSM and expand PrEP use in partnerships.

Table. Characteristics of HIV-negative or unknown status partners of HIV-positive MSM receving HIV care, by PrEP use and durable viral suppression, United States—Medical Monitoring Project, 2014-2015

	All HIV-negative/unknown status partners					HIV-negative/unknown status partners not taking PrEP				
	PrEP (n=117)		No PrEP (n=1,795)			Durable viral suppression (n=1,275)		No durable viral suppression (n=520)		
Partner characteristics	n	Row % (95% CI)	n	Row % (95% CI)	Rao-Scott $\chi 2$ p -value	n	Row % (95% CI)	n	Row % (95% CI)	Rao-Scott $\chi 2$ p -value
Total	117	5.7 (4.4–7.0)	1795	94.3 (93.0–95.6)		1275	71.2 (66.9–75.4)	520	28.8 (24.6–33.1)	
Age										
<=29	42	5.6 (3.4–7.8)	662	94.4 (92.2–96.6)	0.898	425	65.6 (58.4–72.8)	237	34.4 (27.2–41.6)	0.003
30-49	59	5.9 (4.4–7.5)	893	94.1 (92.5–95.6)		659	73.5 (69.2–77.7)	234	26.5 (22.3–30.8)	
50+	15	6.6* (2.3–11.0)	178	93.4 (89.0–97.7)		142	79.1 (72.5–85.7)	36	20.9 (14.3–27.5)	
Race/Ethnicity										
Black, non-Hispanic/Latino	21	3.8 (2.2–5.4)	539	96.2 (94.6–97.8)	0.004	311	57.9 (50.5–65.4)	228	42.1 (34.6–49.5)	<.0001
Hispanic	22	4.6 (2.3–6.9)	524	95.4 (93.1–97.7)		395	77.5 (72.1–82.8)	129	22.5 (17.2–27.9)	
White, non-Hispanic/Latino	63	7.7 (5.0–10.3)	614	92.3 (89.7–95.0)		479	76.5 (72.3–80.7)	135	23.5 (19.3–27.7)	
Other	10	14.5* (4.3–24.6)	62	85.5 (75.4–95.7)		46	72.2 (54.2–90.1)	16	27.8 (9.9–45.8)	
Condomless receptive anal intercourse, past 12 months										
Yes	39	12.1 (7.8–16.3)	264	87.9 (83.7–92.2)	<.0001	207	78.0 (72.8–83.3)	57	22.0 (16.7–27.2)	0.011
No	77	4.6 (3.4–5.7)	1504	95.4 (94.3–96.6)		1043	69.6 (64.8–74.3)	461	30.4 (25.7–35.2)	
HIV-positive person was durably virally suppressed										
Yes	88	6.2 (4.5–7.8)	1275	93.8 (92.2–95.5)	0.242	-	-	-	-	-
No	29	4.6 (2.6–6.5)	520	95.4 (93.5–97.4)		-	-	-	-	

MSM, gay, bisexual, and other men who have sex with men; CI, confidence interval; all percentages are weighted; all variables measured by interview self-report from the HIV positive person except viral suppression, which was abstracted from medical records; durable viral suppression defined as all viral loads in the past 12 documented as undetectable or <=200 copies/mL; analysis was limited to the last 5 partners in the 12 months prior to interview and partners whose PrEP status was unknown were excluded; P -values of <0.05 were considered significant; *coeffient of variation is greater than 0.30, estimate may be unstable.

1053 RAPID SCALE-UP OF PrEP FOR HIV SERODISCORDANT COUPLES IN HIV CARE CLINICS IN KENYA

Elizabeth M. Irungu[1], Kenneth K. Mugwanya[2], Nelly R. Mugo[2], Elizabeth A. Bukusi[1], Kenneth Ngure[2], Josephine Odoyo[1], Elizabeth Wamoni[3], Sarah Masyuko[4], Jennifer F. Morton[2], Lara Kidoguchi[2], Gena Barnabee[2], Gabrielle O'Malley[2], Jared Baeten[2]

[1]Kenya Medical Research Institute, Nairobi, Kenya, [2]University of Washington, Seattle, WA, USA, [3]Partners in Health Research and Development, Thika, Kenya, [4]National AIDS and STD Control Programme, Nairobi, Kenya

Background: In 2016, the Kenya Ministry of Health released guidelines recommending pre-exposure prophylaxis (PrEP) for persons at risk of acquiring HIV. As part of Kenya's national roll-out of PrEP, we are conducting a national scale up of PrEP for HIV uninfected members of HIV serodiscordant couples, integrated into antiretroviral treatment (ART) clinics (the Partners Scale-Up Project).

Methods: Between January and July 2017, we trained health providers using a 2-day, case-based interactive curriculum and began PrEP implementation in 24 high volume HIV care clinics in Western and Central Kenya in a phased manner, using a randomized stepped wedge design and following Kenya national PrEP program measures and training. At baseline and monthly thereafter, program indicators for numbers undergoing couple HIV testing and initiating PrEP and ART were obtained from all clinics. We compared the frequency of PrEP initiation prior and after clinics started implementation, using generalized mixed models adjusted for clustering and time trends.

Results: Over the first ~6 months of the project, the number of HIV-uninfected partners initiating PrEP in HIV treatment clinics significantly increased from 146 prior compared to 1372 after clinics started implementation ($p<0.01$), and the number initiating per month increased each month of the period. Of those initiating PrEP, 52% were female and their median age was 32 years (IQR, 27 to 39). Overall, 716 public health staff, including nurses, clinical officers and HIV counsellors in 24 clinics were trained.

Conclusion: Delivering PrEP at scale for HIV serodiscordant couples in public HIV clinics in Kenya is feasible, with >1000 PrEP initiations done in 6 months at 24 clinics.

1054 NO RISK COMPENSATION BUT HIV EXPOSURE PERSISTS IN HETEROSEXUAL COUPLES USING PrEP

Kenneth K. Mugwanya[1], Renee Heffron[1], Nelly R. Mugo[2], Elizabeth A. Bukusi[2], Elly T. Katabira[3], Stephen Asiimwe[4], Kenneth Ngure[5], Connie L. Celum[1], Jared Baeten[1]

[1]University of Washington, Seattle, WA, USA, [2]Kenya Medical Research Institute, Nairobi, Kenya, [3]Makerere University College of Health Sciences, Kampala, Uganda, [4]Kabwohe Clinical Research Center, Kabwohe, Uganda, [5]Kenyatta University, Nairobi, Kenya

Background: Wide-scale implementation of pre-exposure prophylaxis (PrEP) for HIV prevention is underway in several settings but concerns remain about the potential for increased HIV risk taking in persons using PrEP. We evaluated sexual behavior in heterosexual HIV serodiscordant couples enrolled in a programmatic PrEP demonstration project in Kenya and Uganda.

Methods: Data were from the Partners Demonstration Project, an open label implementation study of integrated PrEP and antiretroviral treatment among 1013 high risk African heterosexual HIV serodiscordant couples conducted between November 2012 and June 2016. HIV uninfected partners were followed 3-monthly for up to 24 months with HIV testing, adherence and behavioral risk assessments, and comprehensive HIV prevention counseling.

Results: Overall, 985 HIV-uninfected partners initiated PrEP: 33% (329) were female and median age was 29 years (IQR 26-36). The proportion of HIV-uninfected partners reporting any condomless sex declined during follow-up from 67% at baseline to 37% at month 3 ($p<0.01$), thereafter remaining relatively stable through 12 months; behavior as reported by the HIV-infected partners revealed a similar pattern: 68% at baseline to 32% at month 3 ($p<0.01$). A similar pattern occurred for both women and men and for younger and older persons (i.e., ≤25 vs >25 years of age), although the frequency of sex without condoms tended to be higher among younger persons compared to older persons: 47% vs 33% at month 3, and 48% vs 31% at month 6, 46% vs 32% at month 12 ($p<0.05$ for all).

Conclusion: In this PrEP demonstration project in African HIV serodiscordant couples, self-reported condomless sex was common at PrEP initiation and declined by half during follow-up. Risk was higher at baseline and more likely to persist among younger HIV-uninfected partners.

1055 TDF/FTC PrEP, LUBRICANT USE, AND THE RECTAL MUCOSAL MICROBIOTA AMONG HIV-NEGATIVE MSM

Colleen F. Kelley[1], Jeffrey Fountain[2], Angela Holder[2], Chuong Dinh[2], LaShonda Hall[1], Sheila Heeke[1], Yingtian Hu[1], Colleen S. Kraft[1], Nicole A. Pescatore[1], Yijuan Hu[1], Clyde Hart[2], Richard Haaland[2]

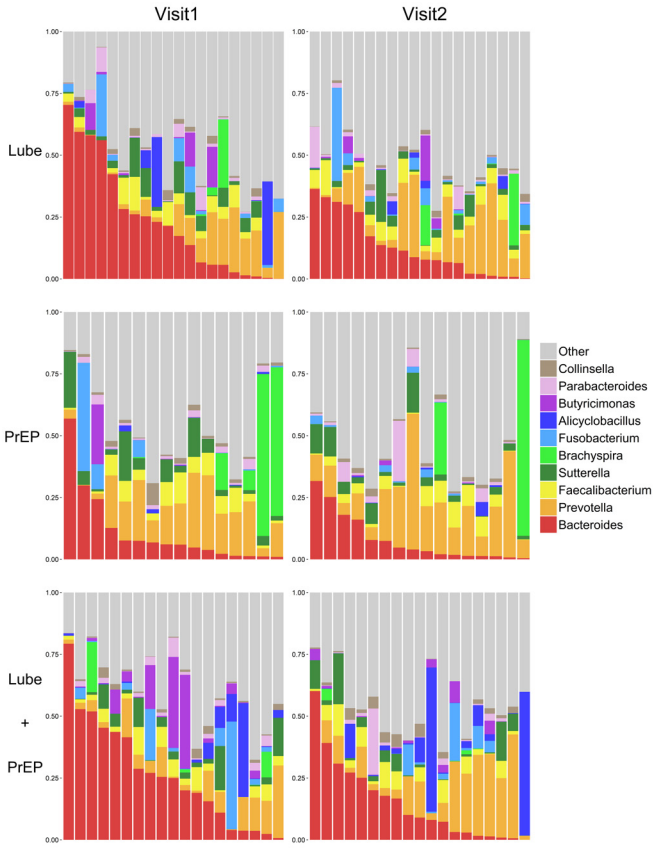
[1]Emory University, Atlanta, GA, USA, [2]CDC, Atlanta, GA, USA

Background: We previously reported that the rectal mucosal (RM) microbiota of men who have sex with men (MSM) engaging in receptive anal intercourse was enriched for Prevotellaceae; the mechanism for this enrichment and effect on clinical outcomes are unclear. We evaluated the effect of hyperosmolar lubricant and oral TDF/FTC on the RM microbiota among HIV-negative MSM.

Methods: HIV-negative MSM engaging in receptive anal intercourse were randomly assigned to take daily, oral Tenofovir/Emtricitabine (TDF/FTC) (n=20), apply 4 ml of hyperosmolar lubricant to the rectum (n=16), or both (n=20) for 7 days. RM secretions were collected via rigid sigmoidoscopy before product use and on day 8 for 16s rRNA sequencing by Illumina MiSeq and clustered into Operational Taxonomic Units. Levels of tenofovir (TFV) and FTC in rectal secretions and intracellular tenofovir-diphosphate, emtricitabine-triphosphate in blood and rectal biopsies were measured by HPLC-mass spectrometry. Shannon index (a diversity measure) and microbiota composition were evaluated before and after product use, and changes were compared across different products via linear regression modeling. Associations of diversity and microbiota composition with TDF/FTC drug levels were also evaluated.

Results: Rectal application of hyperosmolar lubricant was associated with increased RM microbiota diversity as measured by Shannon Index (median before 2.48 vs. after 2.64; p=0.006), a decrease in the relative abundance of the Bacteroides genus (median before 21.4% vs. after 8.9%; p=0.02), and a trend toward increased Prevotella genus (median before 4.8% vs. after 11.3%; p=0.09) (Figure). Oral TDF/FTC dosing was not associated with differences in

diversity or composition of the microbiota. Shannon index and the relative abundance of Bacteroides and Prevotella before study product start were not associated with any drug level in secretions, biopsies, or blood at day 8.
Conclusion: Application of hyperosmolar lubricant to the RM favors the relative abundance of Prevotella over Bacteroides and likely contributes to the enrichment for Prevotella among MSM reported previously. However, the diversity and composition of the RM microbiota do not appear to affect TFV and FTC levels in blood or RM tissues with oral dosing. Future research will be necessary to elucidate other contributing mechanisms for shifts in the microbiota, such as enema use, and whether other clinically relevant prevention outcomes are affected, such as RM susceptibility to HIV infection.



1056 GENDER-SPECIFIC RECTAL PROTEOME CHANGES WITH ORAL AND TOPICAL MARAVIROC USE AS PrEP

Sarah Mutch[1], Laura Noël-Romas[1], Jarret C. Engstrom[2], Rhonda M. Brand[3], Aaron Siegel[2], Ross Cranston[3], Ian McGowan[3], Adam Burgener[1]
[1]University of Manitoba, Winnipeg, MB, Canada, [2]Magee–Womens Research Institute, Pittsburgh, PA, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA

Background: Maraviroc (MVC) is an antiretroviral drug used in HIV therapy and is being explored for use in pre-exposure prophylaxis (PrEP); however, limited mucosal safety data exists on its use. Here we utilized a proteomics approach to study rectal mucosal immune changes in individuals using MVC in oral tablet, rectal gel or vaginal gel form in the CHARM-03 trial.
Methods: CHARM-03 is a Phase 1 randomized, open label, crossover trial of the CCR5 inhibitor, MVC. The drug was administered as a 300mg oral tablet, 1% rectal gel and vaginal gel (N=18; 10 males, 8 females). Rectal tissue samples, taken prior to administration and 2 hours after the 8th and final dose, were analyzed by label-free mass spectrometry (MS). Intrapersonal changes in protein expression associated with drug use were analyzed by paired t-tests and considered trending at P<0.05, and significant at an FDR=5%. IPA software was used to annotate protein functions.
Results: A total of 2447 human proteins and 179 bacterial proteins across 9 genera were detected by MS. Differential expression analysis identified the largest proteome alterations in participants using rectal gel (241 (9.8%) and 182 (7.4%) proteins in males and females, respectively); but none passed multiple hypothesis testing correction. Although there was minimal (4.4%) overlap in proteins associated with rectal gel use between genders, pathway analysis identified activation of leukocyte recruitment pathways in both arms (Z>2.4, P<0.05). Oral tablet use was associated with trending protein alterations in males (226 (9.2%)), including factors involved in the activation of myeloid cells (Z=2.65, P=1.9E-4) and lymphocyte migration (Z=2.61, P=5.86E-8). Oral and vaginal formulations did not influence rectal protein expression in women. Microbial proteome analysis was overshadowed by high levels of Xanthamonas proteins, which was linked physician sampling gel that contained xantham, precluding microbiome comparisons.
Conclusion: Oral and vaginal MVC use in women did not demonstrate an impact on rectal proteome expression in this study. Gender-specific trends were observed with rectal MVC gel use in all participants, oral tablet use in males, and suggested alterations in proteins involved in innate inflammatory processes. These findings suggest MVC topical gel use should be monitored in future safety trials and that gender differences in drug-host interactions may exist, warranting further study.

1057 MICROBIOME AND PROTEOME ALTERATIONS WITH DAPIVIRINE RING USE IN ADOLESCENT GIRLS

Christina Farr Zuend[1], **Laura Noël-Romas**[1], Jeanne Marrazzo[2], Sharon L. Hillier[3], Charlene S. Dezzutti[3], Kathleen E. Squires[4], Katherine Bunge[3], Adam Burgener[1]
[1]University of Manitoba, Winnipeg, MB, Canada, [2]University of Alabama at Birmingham, Birmingham, AL, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA, [4]Thomas Jefferson University, Philadelphia, PA, USA

Background: The antiretroviral-based dapivirine-containing vaginal ring has been shown to be effective at reducing HIV-1 acquisition, however, limited data exist on the impact of these products on the vaginal microbiome and mucosal environment in adolescents, a high risk group for HIV acquisition. Here we assessed host proteome and microbiome changes with dapivirine ring use in adolescent women enrolled in the MTN-023 trial using a comprehensive metaproteomics approach.
Methods: MTN-023 was a Phase 2a randomized, double-blind placebo-controlled trial assessing the safety of a dapivirine vaginal ring in 96 U.S. women, ages 15-17. Participants were randomized 3:1 to a dapivirine or placebo ring to be inserted monthly for 6 months. Cervicovaginal lavage samples were collected monthly and a subset of longitudinal samples from 35 participants were analyzed for host and microbial proteome alterations by mass spectrometry. Differential protein expression was analyzed using t tests, IPA software and hierarchical clustering, and microbial taxa differences by Mann-Whitney U-test.
Results: A total of 2046 bacterial proteins were identified belonging to 13 unique genera. Overall, the majority (82%) of the women had a microbiome dominated by Lactobacillus species, while 12% were Gardnerella dominant, and 6% were dominated by other anaerobic bacteria. In paired analysis the levels of L. crispatus increased over time in the trial (p=0.0007) while L. iners decreased (p=0.0003), and this did not differ by study arm. The 405 human proteins identified belonged to many functional pathways including innate immunity, inflammation, barrier function, and leukocyte recruitment. When stratified by study arm, 14 (3.5%) and 29 (7.2%) human proteins were differentially abundant (p<0.05) between baseline and follow-up in the placebo arm and dapivirine arms, respectively, but none passed multiple comparison correction. Interestingly, lack of condom usage in the last 30 days was linked to increases in neutrophil associated factors including PERM, MMP8, and ELNE. Changes in neutrophil factors were also associated with vaginal sex and Lactobacillus dominant microbiome (p<0.0001).
Conclusion: Dapivirine ring use in adolescents was not associated with changes to the mucosal proteome or microbiome. During the 6 months of ring use, L. crispatus increased, which may reflect behavioral changes during protocol participation. These data support the mucosal safety profile of dapivirine vaginal ring in adolescents.

1058 ACTIVITY OF GRIFFITHSIN-M78Q-AN HIV ENTRY INHIBITOR-IN THE RECTAL ENVIRONMENT

Henry Nabeta[1], Sanet Steyn[1], Amanda Lasnik[1], Ian McGowan[2], Joshua Fuqua[1], Joseph C. Kouokam[1], Kenneth E. Palmer[1]
[1]University of Louisville, Louisville, Kentucky, USA, [2]University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Background: Griffithsin (GRFT), a 121- amino acid dimeric lectin from Griffithsia sp. (red algae), is a recently discovered protein with potent antiviral activity against both CXCR4- and CCR5-tropic HIV-1. It binds tightly to HIV envelope glycoproteins, preventing viral entry into cells as well as cell-to-cell virus transmission. We are developing an oxidation-resistant variant of GRFT (Griffithsin-M78Q/ Q-GRFT) as a topical microbicide to protect people at risk due to condomless receptive anal intercourse (CRAI) Because of its protein nature, Griffithsin may be susceptible to protease enzymatic degradation and its activity may be affected by host- and microbiome-derived compounds in the rectum. The activity of Q-GRFT in the rectal environment remains unknown.
Methods: Six mouse and six human (HIV negative) rectal fluid samples were assessed for pH using MColorpHastTM strips, protein concentration by the bicinchoninic acid (BCA) assay, and protease activity by the casein colorimetric method. Q-GRFT activity (gp120 binding) was evaluated in rectal fluid and seminal plasma samples by enzyme-linked immunosorbent assay (ELISA). The growth inhibitory effects of Q-GRFT on the rectal microbiome components L. acidophilus, L. casei, and E. coli K12 were assessed by growth in broth media. Minimum Inhibitory Concentrations (MICs) were determined for Q-GRFT activity against C. trachomatis ATCC# VR348B Serovar E and N. gonorrhea ATCC#19424.
Results: The human rectal fluid had pH 7-8, protein concentration of 730-1211 µg/mL and protease activity of 0.237-1.069µg/mL trypsin. In the mouse rectal fluid, protein concentration was 275-1565 µg/mL while protease activity was 0.443-30.15µg/mL trypsin. Q-GRFT remained active in rectal and seminal fluids. Q-GRFT at 0-0.2 mg/mL did not inhibit growth of L. acidophilus, L. casei or E. coli. It was inactive against C. trachomatis and N. gonorrhea at concentrations of up to 50µg/mL in contrast to the control antibiotics doxycycline and penicillin, respectively (MIC of both, 0.03µg/mL).
Conclusion: Griffithsin-M78Q is stable in the rectal environment despite the protease activity detected in rectal fluids. It does not inhibit the rectal microbiome components L. acidophilus, L. casei and E. coli, or the pathogenic bacteria N. gonorrhea and C. trachomatis. Overall, Q-GRFT maintains its ability to bind and inactivate HIV in the presence of rectal fluids and seminal plasma while preserving the resident microbiome population.

1059LB EARLY TERMINATION OF A PHASE 1 TRIAL OF TENOFOVIR DISOPROXIL FUMARATE VAGINAL RING

Marla J. Keller[1], Laurie Ray[2], Jessica M. Atrio[2], Lilia Espinoza[1], Shada Sinclair[1], Jessica Goymer[1], Mark A. Marzinke[3], Bruce Frank[4], Peter L. Anderson[5], Jeanne Marrazzo[6], Nelly R. Mugo[7], Craig W. Hendrix[3], Betsy Herold[1]
[1]Albert Einstein College of Medicine, Bronx, NY, USA, [2]Montefiore Medical Center, Bronx, NY, USA, [3]Johns Hopkins University, Baltimore, MD, USA, [4]Particle Sciences, Bethlehem, PA, USA, [5]University of Colorado, Aurora, CO, USA, [6]University of Alabama at Birmingham, Birmingham, AL, USA, [7]Partners in Health Research and Development, Thika, Kenya

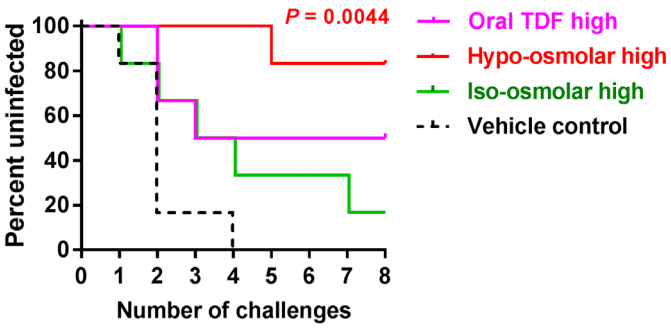
Background: A tenofovir disoproxil fumarate (TDF) polyurethane reservoir intravaginal ring (IVR) provided complete protection against SHIV in macaques and was well tolerated in sexually abstinent women with 2 weeks (wks) of continuous use. The objectives of this single blind, two-site, placebo controlled trial were to evaluate safety and PK of 3 months (mos) use of TDF IVR in sexually active (minimum of 4 sex acts/mo) women who were using contraception.
Methods: Women were randomized 3:1 to TDF or placebo with ring changes monthly and study visits every 2 wks. DAIDS grading tables were used to assess adverse events (AEs). Drug concentrations were measured in cervicovaginal fluid (CVF) obtained by swab, cervical tissue, plasma, dried blood spots (DBS) and in rings after use. Cytokines/chemokines were quantified in CVF and compared between baseline and Day 28-30 in each group.
Results: 17 of 40 planned women were enrolled (12 TDF, 5 placebo) before study termination. Only 2 TDF participants completed the study; 8 stopped ring use early due to Grade 1 vaginal ulceration near the ring, which occurred on average (avg) 32 days after ring use (range 23-56) and we elected to remove rings early in the other 2 (day 20 and 23) due to the AEs observed in 8 participants. 4 of the 8 women were symptomatic and 3 had bilateral ulcers. All of the ulcers resolved. None of the women in the placebo arm developed ulcers and 4 of 5 completed the study; 1 stopped early (day 67) due to travel. Contraceptive method and frequency of sex did not differ between the groups or in women with or without ulcers. Median (IQR) CVF TFV, tissue TFV-DP and DBS TFV-DP at Day 28-30 were 9 x 10^4 ng/mL (4 x 10^4, 1 x 10^5), 301 fmol/mg (203, 347) and 669 fmol/punch (473, 883). CVF TFV levels did not differ at 2 versus 4 wks after ring use and were similar to levels observed in the previous 2-wk study in sexually abstinent women. Avg in vivo TDF release rate was 7 ± 1.3 mg/day based on residual drug levels in rings. 10 of 14 CVF inflammatory mediators were significantly higher at Day 28-30 compared to baseline in the TDF arm; no placebo arm changes were observed ($p<0.05$, paired t-test).
Conclusion: Genital ulceration was observed with sustained TDF, but not placebo ring use, in sexually active women. Sustained levels of intracellular TFV-diphosphate or other metabolites may interfere with epithelial repair and/or induce inflammation, which in the setting of microabrasions associated with ring use and/or sex may predispose to ulceration.

Cytokines/chemokines median, pg/ml	TDF			Placebo		
	Day 0	Day 28-30	p-value	Day 0	Day 28-30	p-value
CVF IL-1α	75	1029	0.03	96	47	0.99
CVF IL-1β	1	1456	0.02	23	40	0.32
CVF IL-8	712	6378	<0.01	782	1071	0.18
CVF IP-10	161	8481	0.01	89	106	0.51
CVF MIG	338	60723	0.02	34	47	0.49
CVF MIP-1β	3	99	<0.01	9	8	0.62
CVF RANTES	2	140	0.03	3	2	0.52
CVF GM-CSF	2	56	0.03	2	2	0.39
CVF IL-17	2	11	0.03	2	4	0.24
CVF TNF-α	2	188	0.02	2	2	0.39

1060LB HYPO-OSMOLAR RECTAL ENEMA TFV FORMULATION PREVENTS SHIV ACQUISITION

Peng Xiao[1], Sanjeev Gumber[2], Mark A. Marzinke[3], Abhijit Date[3], Thuy Hoang[3], Justin Hanes[3], Laura Ensign[3], Lin Wang[4], Lisa C. Rohan[4], Richard Cone[3], Edward J. Fuchs[3], Craig W. Hendrix[3], **Francois Villinger**[1]
[1]University of Louisiana at Lafayette, Lafayette, LA, USA, [2]Emory University, Atlanta, GA, USA, [3]Johns Hopkins University, Baltimore, MD, USA, [4]Magee–Womens Research Institute, Pittsburgh, PA, USA

Background: Oral pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC) has been approved for prophylaxis of HIV-1 transmission, but is associated with systemic adverse effects, high cost, and low adherence in some populations. Protection from rectal transmission of HIV using topical microbicides that are congruent with sexual behavior, e.g., medicated lubricants and douches, offer the promise of improved adherence and lower cost while limiting systemic toxicity. Sodium based hypo-osmolar enemas have been shown to protect the colon epithelium while at the same time promote the uptake of hydrophilic drugs by the tissue. We have therefore incorporated tenofovir (TFV) into two enema formulations and tested whether these formulations protect macaques from rectal SHIV acquisition.
Methods: Daily oral TDF (22 mg/Kg) and two enema formulations (5.28 mg/mL in iso-osmolar [IOsm] or hypo-osmolar [HOsm] saline) were compared for TFV pharmacokinetics and efficacy at preventing rectal SHIV acquisition by rhesus macaques following repeated weekly challenges with ~103 TCID50 SHIV162p3. Macaques were challenged one hour following the weekly enema dose or oral daily dose.
Results: Oral TDF achieved similar peak plasma TFV levels (~110 ng/mL) as rectal HOsm. One hour after rectal HOsm dosing, mean colorectal tissue homogenate TFV-DP was 4,784 fmol/mg (+/- 1366) at one hour, >6 times the IOsm dose at 1 (714+/-378) and 24 hours (448+/-133), the estimated steady-state daily oral TDF colorectal TFV-DP concentrations being 849 fmol/mg. When evaluated for efficacy after 8 weekly SHIV challenges, the greatest protection was seen with the HOsm TFV enema which protected 5/6 monkeys ($p=0.004$, when comparing HOsm to all other survival curves). Oral TDF protected 3/6 macaques, IOsm TFV protected 1/6 macaques, and none of the controls were protected (Figure).
Conclusion: A single dose TFV HOsm enema delivered one hour before rectal SHIV challenge provided a high level of protection, superior to oral TDF and an IOsm enema of similar dose. In an ongoing clinical study of the same TFV HOsm formulation, colorectal tissue TFV-DP concentrations overlap monkey concentrations throughout 24 hours after dosing. This macaque study demonstrates the protective effect of a topically applied, episodic form of PrEP for clinical evaluation as a potential alternative to oral PrEP.



1061 A PHASE I DOSE-ESCALATION STUDY OF MONOCLONAL ANTIBODY VRC07-523LS IN HEALTHY ADULTS

Martin R. Gaudinski[1], Katherine V. Houser[1], Grace Chen[1], Ro Shauna Rothwell[1], Pamela Costner[1], Lasonji Holman[1], Ingelise Gordon[1], Robert Bailor[1], Margarita G. Lorenzo[1], Richard A. Koup[1], Edmund V. Capparelli[2], Barney S. Graham[1], John R. Mascola[1], Julie Ledgerwood[1]

[1]NIH, Bethesda, MD, USA, [2]University of California San Diego, La Jolla, CA, USA

Background: Human monoclonal antibodies that potently and broadly neutralize HIV-1 (bnMAbs) are under development for prevention and treatment of HIV-1 infection. The VRC01 class of bnMAbs targets the CD4-binding site of the HIV-1 envelope protein. VRC01, the first member of this antibody class, is currently being evaluated for prevention of HIV infection in two phase 2b efficacy trials. VRC07-523LS is an engineered clonal variant of VRC01 that is approximately 10 fold more potent than VRC01 and active against 96% of diverse HIV-1 strains, including clade C. The -LS mutation in the antibody Fc region is designed to lengthen its half-life by increasing binding affinity to the neonatal Fc receptor. This change extended terminal half-life and improved protection in the NHP challenge model. These qualities make VRC07-523LS an attractive candidate for a bnMAb prevention strategy.

Methods: VRC07-523LS was administered to healthy adults in an ongoing phase 1 trial (clinicaltrials.gov NCT03015181) to determine its safety, tolerability, and pharmacokinetics (PK). VRC07-523LS has been infused once at doses of 1mg/kg, 5mg/kg, 20mg/kg, and 40mg/kg intravenously (IV) or 5mg/kg subcutaneously (SC), and will be administered three times at 12 week intervals to a subset of subjects receiving 20mg/kg IV or 5mg/kg SC. Serum neutralization activity and detection of anti-drug antibodies will also be examined.

Results: A total of 25 subjects have enrolled in the study. Local and systemic reactogenicity was mild to moderate when reported. No serious adverse events or dose-limiting toxicities have occurred to date. Herein we report PK data through 4 weeks post-infusion for 18 subjects who have received a single administration of VRC07-523LS. Maximum (Cmax) and 4 weeks post-infusion serum concentrations increased proportionally with antibody dose (Table 1). At 4 weeks post-infusion, subjects who received 1mg/kg IV, 5mg/kg IV, 20mg/kg IV, or 5mg/kg SC had mean (±SD) serum concentrations of 14±8 mcg/mL (n=3), 57±12 mcg/mL (n=3), 207±69 mcg/mL (n=6), and 32±8 mcg/mL (n=6), respectively.

Conclusion: VRC07-523LS has been safe and well-tolerated at all doses and routes examined to date. Serum concentrations 4 weeks post-infusion demonstrated greater persistence and were more than 4 times higher than levels from prior studies of wildtype VRC01. The potent neutralizing activity, breadth, and extended half-life of VRC07-523LS make this antibody a leading candidate for inclusion in HIV-1 prevention and therapeutic strategies.

Table 1. VRC07-523LS mean pharmacokinetic parameters by group

Group and dose	C_{MAX}	AUC	4 weeks post-infusion conc.
	Mean (SD)		
Intravenous Dosing			
1 mg/kg (n=3)	49 (15)	682 (264)	14 (8)
5 mg/kg (n=3)	240 (35)	2369 (488)	57 (12)
20 mg/kg (n=6)	1076 (235)	8506 (1893)	207 (69)
Subcutaneous Dosing			
5 mg/kg (n=6)	57 (17)	1108 (232)	32 (8)

Pharmacokinetics parameters include: C_{MAX}= maximum serum concentration (mcg/mL); AUC= area under the curve, 0-4 weeks (mcg x day/mL); 4 week post-infusion concentration (mcg/mL); SD= standard deviation

1062 A PHASE 1 TRIAL OF THE COMBINATION OF 3BNC117 AND 10-1074 IN HIV-UNINFECTED ADULTS

Yehuda Z. Cohen[1], Allison Butler[1], Rebeka Levin[1], Katrina Millard[1], Maggi Pack[1], Shiraz A. Belblidia[1], Juan P. Dizon[1], Irina Shimeliovich[1], Kelly Seaton[2], Nicole L. Yates[2], Georgia Tomaras[2], Marshall Zingg[3], Michael S. Seaman[3], Michel Nussenzweig[1], Marina Caskey[1]

[1]The Rockefeller University, New York, NY, USA, [2]Duke Human Vaccine Institute, Durham, NC, USA, [3]Beth Israel Deaconess Medical Center, Boston, MA, USA

Background: Broadly neutralizing anti-HIV-1 antibodies are currently being developed for the treatment and prevention of HIV infection. It has been postulated that effective broadly neutralizing antibody therapy or prophylaxis will necessitate the combination of multiple antibodies, akin to the use of multiple drugs in antiretroviral therapy. This trial was designed to evaluate the safety and pharmacokinetic profile of the combination of the broadly neutralizing antibodies 3BNC117 and 10-1074, which target different epitopes on the HIV-1 envelope.

Methods: This placebo-controlled, double blind, randomized trial (NCT02824536) consisted of 3 groups of 8 participants. Group 1 received a single dose of both antibodies at 10 mg/kg. Groups 2 and 3 received 3 doses of both antibodies 8 weeks apart at 3 mg/kg and 10 mg/kg, respectively. Participants in each group were randomized 3:1 to receive the study products or placebo, administered by intravenous infusion.

Results: Twenty-four participants were enrolled. The infusions were generally well tolerated, with no serious adverse events considered related to infusion. Overall, the safety profile of the antibody combination was similar to the safety profile of either antibody administered individually. Serum 3BNC117 and 10-1074 levels were measured by anti-idiotype ELISA, and serum neutralizing activity was evaluated by TZM.bl assay. Preliminary pharmacokinetic measurements performed by non-compartmental analysis demonstrate a half-life for 3BNC117 and 10-1074 of 18 and 24 days, respectively. These results are similar to previously published half-lives for each antibody administered alone. Serum neutralizing activity against selected viral strains correlated with measured antibody levels.

Conclusion: The broadly neutralizing antibodies 3BNC117 and 10-1074 were well tolerated when administered in combination. Additionally, no reduction in half-life was observed for either antibody. These results support the continued development of combinations of broadly neutralizing antibodies for the treatment and prevention of HIV-1 infection.

1063 PHASE 1 TRIAL TO ASSESS SAFETY AND ANTIVIRAL ACTIVITY OF MB66 VAGINAL FILM

Susan Cu-Uvin[1], Kenneth H. Mayer[2], Thomas Moench[3], Karen T. Tashima[1], Jai G. Marathe[4], Joseph A. Politch[4], Tara J. Nyhuis[5], Larry Zeitlin[3], Hans M. Spiegel[6], Kevin Whaley[3], Deborah Anderson[4]

[1]Brown University, Providence, RI, USA, [2]Harvard University, Cambridge, MA, USA, [3]Mapp Biopharmaceutical, Inc, San Diego, CA, USA, [4]Boston University, Boston, MA, USA, [5]University of Colorado Boulder, Boulder, CO, USA, [6]NIH, Bethesda, MD, USA

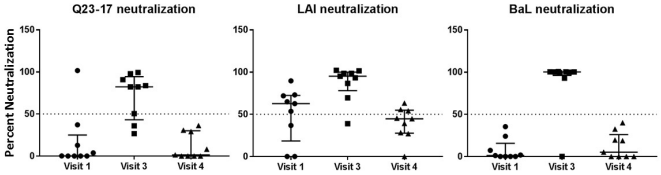
Background: Monoclonal antibodies (mAbs) show promise as multipurpose prevention technology because their specificity and diversity enable broad-spectrum activity. The MB66 product comprises a combination of anti-HIV and anti-HSV mAbs, produced in Nicotiana (N), to provide protection against two incurable viral infections with high and synergistic morbidity. We sought to assess in women the safety and antiviral effects (ex vivo) of MB66 film antibodies when delivered vaginally.

Methods: The MB66 film contains 10 mg of VRC01-N (anti-HIV-1 mAb) and 10 mg of HSV8-N (anti-HSV-2 mAb). Eight healthy and sexually abstinent women without evidence of genital tract infections were enrolled. A study clinician manually inserted the MB66 film in the clinic. Visits and clinical sampling occurred at baseline, 1, 4, 24 hrs and 6-10 days post dose. Adverse events were documented based on DAIDS adverse event grading. Aliquots of cervicovaginal lavage samples (CVLs) were assayed by Luminex for 15 cytokines that have been associated with HIV transmission, by TZM-bl assay for HIV neutralization [HIV strains: Q23-17 (R5 clade A, transmitter/founder strain), BaL (R5 clade B), and LAI (X4 clade B)], and by Plaque Reduction Neutralization Test for HSV-2 neutralization [HSV-2 strain G].

Results: There were four reported adverse events: Grade 1 (cramping, spotting and rash on chest) and Grade 2 (vaginal itching). Only the spotting was deemed related to product. Levels of proinflammatory or other cytokines were not significantly increased in CVLs from the 24hr and 6-10 day time points compared

to baseline. Significant HIV neutralization was observed for Visit 3 CVLs (24 hrs after film insertion) for all 3 HIV strains and for HSV-2. Neutralizing activity in Visit 4 CVLs (6-10 days post film use) was not significantly different from Visit 1 (baseline) CVLs.

Conclusion: Single dose vaginal application of MB66 film was safe and well-tolerated. Significant HIV-1 and HSV-2 neutralization (ex vivo) was observed at 24 hours post-film insertion.



1064 ACCEPTABILITY OF TETANUS TOXOID VACCINE PRIOR TO SAFE MALE CIRCUMCISION

Anna Lawino, Richard A. Mangwi, Christopher G. Orach
Makerere University College of Health Sciences, Kampala, Uganda

Background: Uganda has experienced cases of tetanus in the safe male circumcision (SMC) program for HIV prevention. Gulu district begun implementation of tetanus toxoid (TT) vaccination of men prior to SMC in 2015. However, there is concern that the introduction of the vaccine in SMC may lead to reduced uptake of circumcision. This study aimed to assess the level and factors associated with acceptability of TT vaccine by adult men prior to SMC in Gulu district, Uganda.

Methods: This was a cross sectional study conducted from May to June 2017. A total of 685 uncircumcised men aged 18 years and above were interviewed using semi-structured questionnaires. Key informant interviews were conducted with 10 health workers and 2 district focal persons for immunization and HIV. Quantitative data analysis was done using STATA version 13. Qualitative data were analyzed using thematic content analysis.

Results: Two thirds (66.1%) and 52.1% of respondents accepted TT vaccine for SMC and expressed willingness to get circumcised respectively. Good overall knowledge of tetanus and TT vaccination stood at 80.2% while only 11.3% knew the recommended vaccine doses. Factors significantly associated with acceptability of TT vaccine were: good overall knowledge of tetanus and TT vaccination (AOR: 2.05, 95% CI: 1.29-2.94), positive vaccine perception (AOR: 0.45, 95% CI: 0.24-0.82), TT vaccination community outreaches (AOR: 1.78, 95% CI: 1.05-2.99), ever received TT vaccination (AOR: 2.64, 95% CI: 1.76-3.97) and rural residence (AOR: 1.93, 95% CI: 1.14-3.29). Implementation challenges were: losses to follow up, limited funds, vaccine stock outs, lack of awareness on benefits of TT vaccination among community members and health workers.

Conclusion: Acceptability of TT vaccine prior to SMC was moderately high and willingness to get circumcised was 52.1%. The factors significantly associated with acceptability of TT vaccine before circumcision included good knowledge about tetanus and TT vaccine, positive vaccine perception, TT vaccination community outreaches, rural residence and ever received TT vaccine. The district health office and key implementing partners of SMC need to (1) Develop strategies for community sensitization on TT vaccination of men, (2) Conduct in service training and supervision of health workers on new policy changes, (3) Scale up SMC and strengthen community education on it's benefits, and (4) Target use of community based approaches of vaccine delivery to improve accessibility and uptake.

1065 PERCEPTIONS OF AND MOTIVATIONS FOR VMMC AMONG ADOLESCENTS: A MULTICOUNTRY STUDY

Eshan U. Patel[1], Michelle R. Kaufman[1], Kim H. Dam[1], Lynn M. Van Lith[1], Karin Hatzold[2], Arik V. Marcell[1], Webster Mavhu[3], Catherine Kahabuka[4], Lusanda Mahlasela[5], Emmanuel Njeuhmeli[6], Kim S. Ahanda[6], Getrude Ncube[7], Gissenge J. Lija[8], Collen Bonnecwe[9], Aaron Tobian[1]
[1]The Johns Hopkins University, Baltimore, MD, USA, [2]Population Services International, Harare, Zimbabwe, [3]Centre for Sexual Health and HIV/AIDS Research Zimbabwe, Harare, Zimbabwe, [4]CSK Research Solutions, Ltd, Dar es Salaam, Tanzania, United Republic of, [5]Centre for Communication Impact, Pretoria, South Africa, [6]United States Agency for International Development, Washington, DC, USA, [7]Ministry of Health and Child Welfare, Harare, Zimbabwe, [8]Tanzania Ministry of Health, Community Development, Gender, Elderly, and Children, Dar es Salaam, Tanzania, United Republic of, [9]South African National Department of Health, Pretoria, South Africa

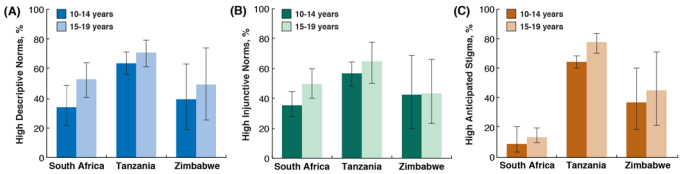
Background: The WHO and UNAIDS have set a Fast-Track goal to achieve 90% coverage of voluntary medical male circumcision (VMMC) among males aged 10-29 years in priority settings by 2021. Little is known about age-specific facilitators of VMMC uptake among adolescents.

Methods: Younger (10-14 years; n=967) and older (15-19 years; n=559) adolescent males completed structured interviews prior to receiving VMMC counseling at 14 service provision sites across South Africa (4 sites; n=446), Tanzania (4 sites; n=540), and Zimbabwe (6 sites; n=540) about perceptions of and motivations for VMMC. Adjusted prevalence ratios (aPR) were estimated by multivariable modified Poisson regression with generalized estimating equations and robust standard errors to account for site-level clustering.

Results: The majority of adolescents in both age groups reported a strong desire for VMMC. Compared to older adolescents, younger adolescents were less likely to cite HIV/STI protection (aPR=0.77 [95%CI=0.66-0.91]) and hygienic reasons (aPR=0.77 [95%CI=0.66-0.91]) as their motivation to undergo VMMC, but were more likely to report being motivated by advice from others (aPR=1.88 [95%CI=1.54-2.29]). While most adolescents believed that undergoing VMMC was a normative behavior, younger adolescents were less likely than older adolescents to perceive that the majority of their peers were already circumcised (i.e., higher descriptive norms; aPR=0.79 [95%CI=0.71-0.89]), higher injunctive norms (aPR=0.86 [95%CI=0.73-1.00]), and higher anticipated stigma from peers/girls for being uncircumcised (aPR=0.79 [95%CI=0.68-0.90]). Younger adolescents were also less likely than older adolescents to correctly cite that VMMC offers males partial HIV protection (aPR=0.73 [95%CI=0.65-0.82]). Irrespective of age, adolescents' main concern about undergoing VMMC was pain (aPR=0.95 [95%CI=0.87-1.04]). Among younger adolescents, fear of pain was negatively associated with desire for VMMC (aPR=0.89 [95%CI=0.83-0.96]).

Conclusion: Age-specific strategies are important to consider for sustainable VMMC demand generation. Programmatic efforts to create and sustain VMMC demand should consider building on the social norms surrounding VMMC and aim to alleviate fears about pain. There is also a need to correct the misperceptions surrounding the level of HIV protection VMMC offers.

Figure. Normative perceptions of VMMC among adolescents seeking the procedure in South Africa, Tanzania, and Zimbabwe.



1066 NOTIFIABLE ADVERSE EVENTS ASSOCIATED WITH MEDICAL MALE CIRCUMCISION IN KENYA

Elijah Odoyo-June[1], Kawango Agot[2], Nandi Owuor[3], Cristine Kisia[4], Boaz Otieno-Nyunya[5], Paul K. Musingila[5], Vincent Ojiambo[6], Norah Talam[7], Hellen Muttai[5], Kennedy Serrem[8], Martin Sirengo[8]
[1]US CDC Nairobi, Kisumu, Kenya, [2]Impact Research and Development Organization, Kisumu, Kenya, [3]Jhpiego–Kenya, Kisumu, Kenya, [4]WHO Kenya Office, Nairobi, Kenya, [5]US CDC Kisumu, Kisumu, Kenya, [6]USAID/Kenya and East Africa, Nairobi, Kenya, [7]KEMRI/Walter Reed Proj, Kericho, Kenya, [8]Ministry of Health, Nairobi, Kenya

Background: Since 2008, Kenya has implemented medical male circumcision for HIV prevention, with passive reporting of moderate and severe adverse events (AE) to monitor program safety. With PEPFAR support, an additional reporting system was introduced in 2014 in which an AE is classified as notifiable if it occurs within 30 days of medical circumcision (MC) and is tetanus or leads to death, complete or partial amputation of the penis, hospitalization for >3 days or probable permanent disability or deformity. We report Kenya's experiences with reporting notifiable AEs.

Methods: Building on PEPFAR's notifiable AE (NAE) reporting protocol, Kenya has implemented a robust NAE investigation and follow-up system that is reported through standardized forms. The system incorporates taking photographs of AE lesions to monitor healing and evaluate effectiveness of management; these also serve as records of the final outcomes and as case studies for learning. Incidence of penile glans injuries in boys 10-14 years and

tetanus are used as proxy indicators of non-compliance as most are preventable by following program guidelines.

Results: Of 661,653 MCs performed in Kenya from August 2014 to August 2017, a total of 25 NAEs were reported. The spectrum of NAEs recognized and reported is growing and includes 4 infant deaths (3-due to non MC conditions); 1 adolescent death (15yrs due to tetanus); 3 non-fatal tetanus (1 related to PrePex); 5 penile glans injuries during forceps guided MC in boys 10-12 yrs; 1 penile glans injury during Mogen clamp infant MC; 3 urethral fistulae in boys 10-12 years; and 8 conditions (including 2 severe bleeding, 1 necrotizing fasciitis, and 5 previously undiagnosed medical conditions) leading to hospitalization for ≥3 days. Cases associated with non-compliance (24%) were 5 penile glans injuries and 1 case of tetanus following MC through PrePex device where the second requisite dose of tetanus toxoid was not given.

Conclusion: NAE reporting system has enhanced understanding of AEs and revealed cases of serious AEs associated with non-compliance or undiagnosed underlying medical conditions. MC programs should implement enhanced NAE reporting systems to monitor lapses in compliance with program safety standards and for learning purposes. Programs introducing new methods of MC should expand their scope of NAEs to include previously undescribed AEs.

1067 SAFETY AND ACCEPTABILITY OF PREPEX CIRCUMCISION AMONG ADOLESCENTS IN KISUMU, KENYA

Kawango Agot, **Julie Ambia**, Risper Bosire, David Muhuaya, Joshua Juma, Abraham Bitok, Spala Ohaga, Benard Ayieko, Maurice Onyango
Impact Research and Development Organization, Kisumu, Kenya

Background: Non-surgical methods of male circumcision (MC) that are simpler to use are required to accelerate uptake of voluntary medical male circumcision in sub-Sahara Africa. We aimed to assess safety and acceptability of PrePex device, a non-surgical MC method, among adolescent boys aged between 10 and 12 years in Kisumu, Kenya.

Methods: We implemented two PrePex procedures: day 0 foreskin removal procedure (FRP) and standard PrePex where the foreskin is left to self-detach. Questionnaires were administered to study participants and parents/legal guardians by clinicians after device placement. All study participants are being followed for 56 days; however, we report until day 42 for which follow-up is complete. Percentages were used to summarise acceptability and safety of the PrePex device. Chi-square test was used to assess the association between the PrePex procedure and safety.

Results: Between April and August 2017, 214 adolescent males were enrolled; 41% (88/214) underwent the standard PrePex procedure. Of those enrolled, 44% had contraindications to PrePex circumcision; 65 had preputial adhesions and 30 had a narrow foreskin, with 21 having both conditions. Overall, 59% (56/95) of those with contraindications underwent day 0 FRP procedure. By day seven, 96% (192/201) kept penile hygiene as instructed, 79% (156/198) reported no pain and 96% (191/200) reported no difficulties in passing urine. However, these attributes were not associated with the type of PrePex procedure. Four of those who underwent day 0 FRP and five of those who underwent standard procedure reported missing school due to pain. Poor hygiene was associated with reporting pain ($p<0.001$). By day 21, 79% (151/193) had experienced epithelialization and 77% (148/193) granular tissue formation. Adolescents who underwent standard procedure were more likely to experience epithelialization and granular tissue formation ($p<0.001$) compared to those who underwent day 0 FRP. By day 42, all participants had experienced epithelialization and granular tissue formation. Only one moderate adverse event occurred during device placement. All participants found the procedure to be quite safe or very safe and were willing to recommend it to their peers.

Conclusion: Non-surgical circumcision using the PrePex device was safe and acceptable among adolescent males ages 10-12 years. Most participants reported no pain post device placement. Only one moderate intra-operative adverse event occurred.

1068 INTEGRATION OF FAMILY PLANNING INTO HIV CARE AND TREATMENT PROGRAM IN KENYA

Wangui Muthigani[1], Emily R. Begnel[2], **Dunstan Achwoka**[3], Tai Ho Chen[3], John Kinuthia[4], Christine J. McGrath[2], Alison L. Drake[2]
[1]Ministry of Health, Nairobi, Kenya, [2]University of Washington, Seattle, WA, USA, [3]US CDC Nairobi, Nairobi, Kenya, [4]Kenyatta National Hospital, Nairobi, Kenya

Background: Integration of family planning (FP) services in HIV care can improve uptake of FP and prevent mother-to-child HIV transmission. We characterized FP use and integration of FP services in HIV care by county-level HIV prevalence.

Methods: We conducted a cross-sectional survey of sexually active, HIV-infected women aged 15-49 years from 109 HIV care and treatment facilities with ≥1000 patients on antiretroviral therapy (ART) in Kenya. Facilities were classified as integrated if HIV and FP care were delivered in the same building, and as high or low HIV burden (average county prevalence 12% and 4%, respectively). Modern FP included tubal ligation, vasectomy, intrauterine devices (IUDs), implants, injectables, oral contraceptives (OCs), vaginal rings, condoms, and emergency contraception. Women who did not desire pregnancy within 2 years and were not using modern FP were defined as having unmet FP need. Analyses were adjusted to account for facility-level clustering.

Results: Overall, 4805 HIV-infected women were enrolled; 3746 from 85 facilities in high burden counties and 1059 from 24 facilities in low burden counties. Median age was 34 years (IQR 28-39), 60% were married, and 89% were on ART. Integrated services were offered at 74% of facilities; 90% of unintegrated facilities provided FP referrals. FP consultations during HIV care were uncommon (8%), and more likely in low (16%) than high (6%) burden counties ($p<0.01$). Among 4014 (84%) women who did not receive FP services during their most recent HIV care visit, 56% were already using a non-barrier modern method. Of the 791 (16%) women who received FP services, 69% only received consultation and 1% planned to initiate FP following consultation. The majority (85%) of women used modern FP; 70% used condoms with (37%) or without (32%) another modern FP method. Other modern method use included injectables (32%), implants (25%), OCs (5%), and IUDs (5%). Method mix was similar by HIV burden ($p>0.05$). Desire for pregnancy prevention during the next 2 years was slightly higher (85%) in low than high (82%) burden counties ($p=0.04$); however, unmet need was similar (13% for low vs. 10% for high burden, $p=0.3$).

Conclusion: Despite low FP counseling rates at HIV care visits, integrated FP services and contraceptive use were high among HIV-infected women, largely driven by high rates of condom use. Offering FP counseling at each HIV care visit may improve dual method use, reduce unmet need, and prevent unintended pregnancies among HIV-infected women.

1069 MISSED OPPORTUNITY FOR FAMILY PLANNING IN HIV-INFECTED WOMEN ON ART IN TOGO

Shino Arikawa[1], Cécile Cazes[1], Anne Thomas[2], Thierry Tiendrebeogo[1], Benjamin G. Kariyiare[2], Vincent Pitche[3], Didier K. Ekouevi[1], Renaud Becquet[1]
[1]INSERM, Bordeaux, France, [2]Centre Africain de Recherche en Épidémiologie et en Santé Publique, Lomé, Togo, [3]Conseil National de Lutte contre le SIDA, Lomé, Togo

Background: Increased access to prevention of mother-to-child transmission services with expanded antiretroviral eligibility have led to dramatic reduction in HIV vertical transmission, but evidence on women's childbearing desire in relation to antiretroviral treatment (ART) is sparse, showing increased likelihood in some settings but not in others. Previous assessment often lacked comparative group of uninfected women and concerns remain over high prevalence of unplanned pregnancy among HIV+ women. We investigated whether HIV infection in the era of universal ART influences childbearing desire and behavior of HIV+/- women in order to inform programmatic priorities.

Methods: A cross-sectional survey was conducted in three rural and urban health facilities in Togo in 2016. Eligible HIV+ women were non-pregnant, aged 18-49 years and on ART regardless of timing of initiation. HIV- women were recruited from those accompanying patient at a non-HIV service in the same health facilities. Non-infection to HIV was self-declared. The outcomes were childbearing desire and unmet need for family planning. Health-seeking behaviors were analyzed in respect to women's childbearing desires. Logistic regression models were used to assess the associations between the outcomes and women's HIV status with adjusted odds ratios (aOR) and 95% confidence intervals (CI).

Results: Of 1,189 women included in the study (706 HIV+, 483 HIV-), 60.5% declared having childbearing desire. Adjusted for age, study site, presence of a male partner and the number of living children, women's HIV status was not associated with the likelihood of reporting childbearing desire (aOR: 0.8, 95%CI: 0.5-1.1). Of those having immediate desire (N=276), only one in three reported having fertility-related dialogue with health providers, with no difference by HIV status ($p=0.4$). Overall, use of modern contraceptives was 21.1%, and 25.3% in HIV+ and HIV- women respectively ($p=0.1$). Among sexually active women wanting to avoid or delay pregnancy, unmet need for family planning

was 62.4% and 68.9% in HIV+ and HIV- women respectively (aOR:1.3, 95%CI: 0.9-1.9).

Conclusion: Childbearing desire in HIV+ women on ART was as high as that of HIV- women. Despite regular contacts with health personnel, contraceptive needs and fertility concerns of HIV+ women remained unaddressed. HIV care should better integrate reproductive health services with appropriate counselling and provision of a full-range of contraceptive methods to allow safe conception in HIV+ women.

1070 CONTRACEPTION AND PrEP IN SOUTH AFRICAN HAIR SALONS: OWNER, STYLIST, AND CLIENT VIEWS

Ingrid V. Bassett[1], Ai Xu[1], Sabina Govere[2], Hilary Thulare[2], Simone C. Frank[1], Christina Psaros[1], Robert A. Parker[1]

[1]Massachusetts General Hospital, Boston, MA, USA, [2]AIDS Healthcare Foundation, Durban, South Africa

Background: Nearly half of unintended births in sub-Saharan Africa occur among women ages 15-24, who also have high HIV incidence. Women congregate regularly without partners in community hair salons; these may be useful venues for family planning and HIV prevention services. We assessed the acceptability and feasibility of offering contraception and PrEP for HIV in hair salons in South Africa.

Methods: We surveyed hair salon owners, stylists, and female clients (≥18y) at hair salons in and around Umlazi Township about comfort with a nurse offering health services, including contraception, HIV testing, and PrEP. To assess feasibility of offering services, we asked clients about frequency and time spent at salons. We assessed the relationship between salon features and clients' attitudes towards receiving health services at the salon using Fisher's exact test.

Results: We visited 12 township and 5 Durban salons, with a median of 235 unique monthly clients (IQR 110, 425). 9 salons (53%) had a private room useable for health services. Most owners (11/17, 65%) were female and comfortable (94%) with a nurse offering health services in their salon. Most stylists (75/92, 82%) were women and 98% reported that if trained they would be willing to talk to clients about health topics and refer to a nurse for services. Among 326 female clients, median age was 28 (IQR 24-33) and 73% currently use contraception; the majority (97%) visit the salon at least every 2 months, attend the same salon for most visits (80%) and spend >1 hour (83%). 91% reported willingness to receive injectable contraception, 93% oral contraceptive pills, 74% HIV testing and 77% PrEP at the salon. Clients from salons in townships compared to in Durban were more likely to be willing to get contraception ($p<0.001$) and PrEP ($p=0.001$) in the salon. Access to a private salon room was also significantly related to client willingness to receive health services ($p=0.005$). Women already on contraception were more likely to agree to contraception in the salon ($p=0.028$); contraceptive use was not related to willingness to receive PrEP ($p=0.82$).

Conclusion: Most owners, stylists and clients were willing to receive contraception and PrEP from a nurse in hair salons in South Africa. Clients regularly attend salons in intervals compatible with injectable contraception and PrEP use. Hair salons represent an innovative venue for reaching young women at high risk for unintended pregnancy and HIV infection.

1071 PREGNANCY INTENTION AND CONTRACEPTIVE USE IN MALAWI'S PMTCT PROGRAM

Deus Thindwa[1], Megan Landes[2], Monique van Lettow[2], Annie Kanyemba[3], Ernest Nkhoma[3], Thokozani Kalua[4], Happy Phiri[3], Joep J. van Oosterhout[5]

[1]Imperial College London, London, UK, [2]University of Toronto, Toronto, ON, Canada, [3]Management Sciences for Health, Lilongwe, Malawi, [4]Malawi Department of HIV and AIDS, Lilongwe, Malawi, [5]Dignitas International, Zomba, Malawi

Background: Avoiding unintended pregnancies through family planning is a WHO strategy in preventing mother to child transmission of HIV (PMTCT) and maternal morbidity/mortality. We investigated factors associated with recent unintended pregnancy, unmet contraceptive need, future pregnancy intention and current contraceptive use among Malawian women living with HIV in the Option B+ era.

Methods: Women living with HIV were enrolled at 4-26 weeks postpartum into a cohort study at the Under-5 clinics of three high-volume government hospitals. Structured baseline interviews included questions on socio-demographics, HIV knowledge, partner's HIV status/disclosure, ART use, pregnancy intention and contraceptive use. Logistic regression was used to determine factors associated with pregnancy intention and contraceptive use.

Results: We enrolled 578 HIV-positive women between May 2015 – May 2016; median maternal age was 28 years (IQR: 23-32), median parity was 3 deliveries (IQR: 2-4) and median infant age was 7 weeks (IQR: 6-12). Overall, 41.8% women had a recent unintended pregnancy, of whom 35.0% had unmet contraceptive need and 65.0% had contraceptive failure, from ineffective, or incorrect use, prior to conception. In multivariable analysis, recent unintended pregnancy was higher in women ≥35 years vs. 14-24 years (aOR: 2.1, 95%CI: 1.0-4.2) and in women with parity >3 vs. primiparous (aOR: 2.9, 95%CI: 1.5-5.6). Unmet contraceptive need was higher in women 14-24 years vs. ≥35 years (aOR: 4.2, 95%CI: 1.8-9.9), primiparous vs. parity >3 (aOR: 8.3, 95%CI: 1.8-39.5), and women whose partner's HIV-status was unknown (aOR: 2.2, 95%CI: 1.2-4.0). Current contraceptive use was associated with being on ART during index pregnancy (aOR: 2.5, 95%CI: 1.5-3.9). Finally, future pregnancy intention was higher among women non-affiliated to a Christian religion (aOR: 2.8, 95%CI: 1.1-6.8).

Conclusion: High rates of recent unintended pregnancy and unmet need for contraceptives among women living with HIV highlight the need for improved access to contraceptive services. To help achieving elimination of MTCT of HIV in Malawi family planning programs should also address contraceptive failure, from ineffective and incorrect use.

1072 HIV-1 RESERVOIR DYNAMICS IN MENOPAUSAL WOMEN DURING HORMONE THERAPY

Stephanie Banning[1], Olivia Roberts-Sano[1], Emanuele Mazzola[2], Qianjing He[1], Stacey Chapman[3], Rebecca Gelman[2], Susan Cu-Uvin[3], **Athe Tsibris**[1]

[1]Brigham and Women's Hospital, Boston, MA, USA, [2]Dana–Farber Cancer Institute, Boston, MA, USA, [3]The Miriam Hospital, Providence, RI, USA

Background: Recently presented data suggested that estrogen might block HIV reactivation in cells isolated from premenopausal women. We tested the effects that systemic hormone therapy (HT) had on reservoir dynamics in menopausal women living with HIV. The scientific premise of our study was that estradiol limits HIV-1 latency reversal.

Methods: We conducted a non-randomized, open label pilot study in 12 treated HIV-infected, virologically suppressed (>1 year) menopausal women who were experiencing vasomotor symptoms. Three women without a uterus received transdermal estrogen patch (patch HT), 6 women with a uterus received conjugated estrogens and medroxyprogesterone acetate (oral HT), and 3 women received no treatment (no HT). HT was given for 4 weeks. HIV-1 total DNA and cell-associated RNA (caRNA) levels in PBMC, along with latency reversal agents (LRA)-induced virus reactivation in resting CD4+ T cells (rCD4), was assessed using blood samples obtained at entry and weeks 1, 4, and 8. Plasma levels of estradiol (E2) and estrone (E1) were measured by mass spectrometry. The primary endpoint was the change in HIV-1 caRNA levels between weeks 0 and 4.

Results: Mean $\log_{10}$ levels of HIV-1 DNA and caRNA at week 0 were 2.5 and 3.0 copies/106 PBMC, respectively, in the patch HT group, 2.3 and 3.2 in the oral HT group, and 2.4 and 3.1 in the no HT group. In the oral HT group, E2 and E1 levels increased from entry (8.9 pg/mL and 30.2 pg/mL, respectively) to week 4 (17.9 and 110). A statistically significant difference in the differences of HIV-1 $\log_{10}$ caRNA was observed between the oral and no HT groups when comparing weeks 0 and 4 ($p=0.024$); caRNA levels in the HT group were higher. No other statistically significant differences were observed between weeks 0 and 4 when comparing the patch, oral and no HT groups. HIV-1 differences of $\log_{10}$ DNA levels were similarly unchanged. Greater magnitudes of HIV-1 caRNA increases were observed in rCD4 treated with RMD when compared to either PHA/IL-2 or bryostatin in all HT groups, an effect that was not inhibited by fulvestrant. No association of LRA response with HT group or duration of HT was observed.

Conclusion: In this pilot study, HT did not decrease HIV levels in PBMC or ex vivo LRA-induced virus reactivation in rCD4. Increases in estradiol concentrations were modest. RMD was a more potent LRA than PHA/IL-2 or bryostatin in the samples we tested. A larger study is required to more definitively address the association between HT and HIV-1 reservoir dynamics.

1073 ASSOCIATION OF HIV STATUS WITH SEXUAL FUNCTION IN WOMEN AGED 45-60

Nasreen Toorabally[1], Cath Mercer[1], Kirstin Mitchell[2], Fiona Burns[1], Caroline Sabin[1], Richard Gilson[1], **Shema Tariq**[1]
[1]University College London, London, UK, [2]University of Glasgow, Glasgow, UK

Background: Reproductive aging is associated with decreased sexual function, although there is a paucity of data in women living with HIV (WLWH). Using two national UK datasets, we explore the association of HIV status with sexual function in women aged 45-60.

Methods: An analysis of cross-sectional data of sexually active women aged 45-60 drawn from Britain's 3rd National Survey of Sexual Attitudes & Lifestyles (Natsal-3, HIV- women), and PRIME, a study of HIV and menopause (WLWH). Self-reported sexual function was captured using the validated Natsal sexual function measure (Natsal-SF) in those sexually active in the past year, with the highest quintile defined as having low sexual function. Samples were compared using multivariable logistic regression with adjusted odds ratios (AOR) controlled for age, ethnicity, relationship status, depression and number of chronic conditions.

Results: 1699/2101 (89.1%, weighted) HIV- women from Natsal-3 and 336/594 (56.6%) WLWH from PRIME reported sexual activity in the past year (p=0.001). Median age of HIV- women and WLWH was 51 and 49 years respectively (p<.001); a greater proportion of HIV- women were postmenopausal (56.3% vs 28.3%, p<.001). Almost 90% of HIV- women were White British; 70% of WLWH were Black African (p<0.001). WLWH were more likely to report depression and other chronic conditions, and less likely to be in a relationship (all p<0.05). Amongst WLWH, 71.7% had CD4≥500 cells/mm^3 and 90.3% had an undetectable HIV viral load. Relative to HIV- women, WLWH were more likely to report ≥1 sexual problem lasting ≥3 months in the past year (AOR 2.61 [1.54-4.45]; p<0.001), almost all of the specific sexual problems the surveys asked about (all p<0.01, table), and were more likely to have low sexual function (AOR 3.87 [2.35-6.38]; p<0.001). Low sexual function was more common in postmenopausal WLWH (only), although of borderline statistical significance (AOR:1.78 [0.94-3.38]; p=0.08).

Conclusion: We report an association between HIV status and low sexual function in women aged 45-60. Although we cannot eliminate the possibility of residual confounding and reporting bias, this analysis highlights the burden of sexual problems among midlife WLWH. Further research is required to elucidate potential biological mechanisms underlying low sexual function in women aging with HIV, and we recommend that assessment of sexual function be integrated into routine care for this group.

Table: Univariable and multivariable associations between sexual function and HIV status (reference group HIV- women [Natsal-3 sample])[a]

	Natsal-3 (HIV-) n=1228[b], 1677[c] %	PRIME (HIV+) n=312 %	Odds ratio (95% confidence interval)	*p*-value	Adjusted odds ratio[d] (95% confidence interval)	*p*-value
Overall sexual function[e]						
Low sexual function	20.4	42.6	2.90 (2.20-3.84)	<0.001	3.87 (2.35-6.38)	< 0.001
Lacked interest in sex	38.3	52.2	1.76 (1.26-2.46)	0.001	2.79 (1.50-5.16)	0.001
Lacked enjoyment in sex	13.1	32.7	3.21 (2.43-4.23)	< 0.001	4.19 (2.08-8.41)	< 0.001
Felt anxious during sex	3.5	17.3	5.84 (3.83-8.89)	<0.001	4.90 (2.55-9.42)	< 0.001
Physical pain as a result of sex	7.5	16.7	2.48 (1.88-3.27)	< 0.001	2.92 (1.91-4.46)	<0.001
No excitement/ arousal during sex	8.7	28.8	4.25 (3.09-5.85)	< 0.001	3.42 (1.98-5.91)	<0.001
No orgasm/ took a long time to reach orgasm despite arousal	14.9	31.1	2.59 (1.93-3.47)	<0.001	2.92 (1.78-4.75)	< 0.001
Reached orgasm too quickly	2.4	7.4	3.20 (1.68-6.10)	< 0.001	1.79 (0.33-9.66)	0.497
Vaginal dryness	17.2	27.6	1.83 (1.39-2.41)	<0.001	2.27 (1.37-3.77)	0.002
Experienced at least one problem	54.3	68.9	1.86 (1.47-2.37)	< 0.001	2.61 (1.54-4.45)	< 0.001

[a]Restricted to those who were sexually active in the past year and had available data on sexual function; [b]Unweighted denominator; [c]Weighted denominator (to account for study design); [d]Adjusted for age, ethnicity, number of chronic conditions, depression and ongoing relationship status; [e]Using the Natsal sexual function score, standardised to account for those who had not been in a relationship for the whole of the past year, score≥13.44 (80th percentile) indicates low sexual function.

1074 MENOPAUSAL SYMPTOMS ARE ASSOCIATED WITH PSYCHOLOGICAL DISTRESS IN HIV+ WOMEN

Shema Tariq, Fiona Burns, Lorraine Sherr, Richard Gilson, Alexandra Rolland, Caroline Sabin
University College London, London, UK

Background: Despite increasing numbers of older women accessing HIV services, there remains a paucity of data on HIV and the menopause. We explore the association of severe menopausal symptoms with psychological distress in women living with HIV (WLWH).

Methods: An analysis of data on 710 women recruited to the PRIME Study; an observational study of WLHIV aged 45-60 in England in 2016-17. Psychological distress was measured by PHQ-4 (score≥3 indicating distress). The Menopause Rating Scale was used to capture severe somatic (score≥9) and urogenital (score ≥4) symptoms.

Results: Median age was 49 years (interquartile range: 47-52).The majority were Black African (n=489, 70.9%), with low rates of drug use (n=19, 2.8%). Almost all (n=669, 97.4%) were on antiretroviral therapy; a minority had a CD4 count<200 cells/mm^3 (n=49, 8.2%) or detectable HIV viral load (n=70, 10.7%).The majority were either peri- (n=311,44.3%) or post- (n=246, 35.0%) menopausal. Use of systemic and vaginal estrogen was low (n=31, 6.8% and n=28, 4.4% respectively) Nearly half of WLWH reported psychological distress (n=326, 45.9%); 28.9% scored above the cut-off for anxiety (205/710) and 25.1% (178/710) for anxiety. Women reported high levels of somatic symptoms (n=615, 88.6%) of which 18.7% were severe (115/615). Two thirds had urogenital symptoms (n=463); 42.8% were severe (183/463). Psychological distress was associated with demographic factors, and severe somatic and urogenital symptoms (table). Women with severe somatic menopausal symptoms were five times more likely than those without to report psychological distress (adjusted odds ratio [AOR] 4.90; 95% confidence interval [CI] 2.71,8.88; p<0.001). Those with severe urogenital symptoms were over twice as likely to report psychological distress (AOR 2.66; 95% CI 1.74,4.01; p<0.001).

Conclusion: In one of the first studies to explore the association of menopausal symptoms with psychological distress in midlife WLWH, we report high levels of somatic and urogenital symptoms. Severe symptoms in both domains were significantly associated with psychological distress, although we cannot assess the direction of this relationship, highlighting the need for longitudinal data. Of note, use of systemic and vaginal estrogen was low in this population. Midlife WLWH with severe menopausal symptoms are a group requiring particular psychosocial support and who may benefit from management of somatic and urogenital symptoms.

Table: Characteristics of women with and without psychological distress

	No psychological distress n=384	Psychological distress n=326	*p*-value[a]
Median age in years, (interquartile range)	50 (47-53)	49 (47-52)	0.37
Ethnicity			
Black African	275 (73.9)[b]	214 (67.3)	
White UK	36 (9.7)	30 (9.4)	
White Other	8 (2.2)	18 (5.7)	
Black Other	32 (8.6)	32 (10.1)	
Other	21 (5.7)	24 (7.6)	<0.1
Employment			
Employed full time	236 (63.3)	106 (37.7)	
Employed part time	71 (19.0)	51 (16.2)	
Unemployed	66 (17.7)	158 (50.2)	<0.001
Education			
Did not complete school	30 (8.1)	47 (15.4)	
'O' level[c]	76 (20.5)	76 (24.9)	
'A' level[d]	70 (18.9)	69 (22.6)	
University	194 (52.4)	113 (37.1)	<0.001
Enough money for basic needs			
All the time	195 (50.8)	68 (21.1)	
Most of the time	98 (25.5)	92 (28.5)	
Some of the time	68 (17.7)	110 (34.1)	
No	23 (6.0)	53 (16.4)	<0.001
High risk alcohol use[e]			
No	331 (92.5)	268 (88.2)	
Yes	27 (7.5)	36 (11.8)	<0.1
Most recent CD4 count (cells/mm^3)			
≥500	218 (66.7)	177 (65.3)	
200-500	82 (25.1)	72 (26.6)	
<200	27 (8.3)	22 (8.1)	0.92
Most recent HIV viral load			
Undetectable	321 (89.7)	263 (88.9)	
Detectable	37 (10.3)	22 (11.2)	0.74
Menopausal status			
Pre-menopausal	84 (22.2)	61 (18.9)	
Peri-menopausal	161 (42.5)	150 (46.4)	
Post-menopausal	134 (35.4)	112 (35.7)	<0.001
Somatic symptoms			
None/Mild/Moderate	343 (94.2)	205 (68.6)	
Severe	21 (5.8)	94 (31.4)	<0.001
Urogenital symptoms			
None/Mild/Moderate	276 (78.0)	158 (56.8)	
Severe	78 (22.0)	120 (43.2)	<0.001

[a] χ^2 or Kruskal-Wallis test; [b] data are expressed as n (%);[c] equivalent to completing US Grade 10; [d] equivalent to completing US Grade 12; [e] using the Alcohol Use Disorders Identification Test (AUDIT-C) screening tool

1075 REPRODUCTIVE TRACT INFECTION RISK-BASED SCREENING FOR IUD INSERTION IN HIV+ WOMEN

Nontokozo Langwenya[1], Catherine Todd[2], Heidi Jones[3], Donald R. Hoover[4], Agnes Ronan[1], Landon Myer[1]
[1]University of Cape Town, Cape Town, South Africa, [2]FHI 360, Durham, NC, USA, [3]City University of New York, New York, NY, USA, [4]Rutgers University, Newark, NJ, USA

Background: Intrauterine devices (IUDs) are safe and effective contraception but IUD use in HIV+ women is limited by concerns about reproductive tract infections (RTI) and possible ascending infection. As RTI testing is a challenge in resource-limited settings, we assessed the performance of an existing screening tool intended to determine RTI risk and guide IUD insertion.

Methods: The tool scoring was based on (i) age under 25 years, (ii) cohabitation with partner, (iii) secondary education, (iv) bleeding between periods and (v) the number of sex partners without condom use (minimum score 0, maximum score 5). Women's risk was categorized as low (score=0), moderate (score=1-2) and high (score>=3). In a clinical trial of IUD use among HIV+ women in Cape Town, South Africa (NCT01721798), a nurse administered the screening tool prior to RTI testing for Neisseria gonorrhoea (NG) and Chlamydia trachomatis (CT) via GeneXpert® nucleic acid amplification testing; Trichomonas vaginalis (TV) and bacterial vaginosis (BV) via OSOM® BV Blue and Trichomonas for genital tract specimens; and Treponema pallidum (TP) with Alere® Determine Syphilis rapid diagnostic tests for whole blood. The sensitivity, specificity, and likelihood ratio of both positive and negative results for any RTI, as well as for NG/CT/TV and for NG/CT were calculated. We also explored categorizing the score as 0 vs 1-5, 0-1 vs. 2-5 and 0-2 vs. 3-5.
Results: Of 302 women included, 47% (n=144) were antiretroviral treatment (ART) naïve and the mean age was 31.2 years (range, 18-41). The overall prevalence of any RTI was 37% (NG=8%, CT=10%, TV=11%, BV=16% and TP=2%; 7% of women with multiple infections). RTI prevalence was higher for ART-naïve women compared to women using ART (Table 1). Overall, 4%, 27% and 69% of women had screening tool scores of 0, 1 or 2+, respectively; mean scores did not differ by RTI (infected=1.97 vs uninfected=1.93, p=0.727) but were significantly higher in ART-naïve women vs those on ART (2.17 vs 1.7, p<0.001). At the recommended threshold of 1+, the tool demonstrated high sensitivities but very low specificities; at a threshold of 2+ and 3+, the tool demonstrated high negative predictive values. The performance of the tool did not differ by ART use or specific type of RTI.
Conclusion: This risk screening tool provided little value in distinguishing women with RTI. Given the high prevalence of RTI in HIV+ women in this setting, there is an urgent need for low-cost diagnostic testing technologies.

Table 1: Prevalence of RTIs and Performance of RTI screening tool

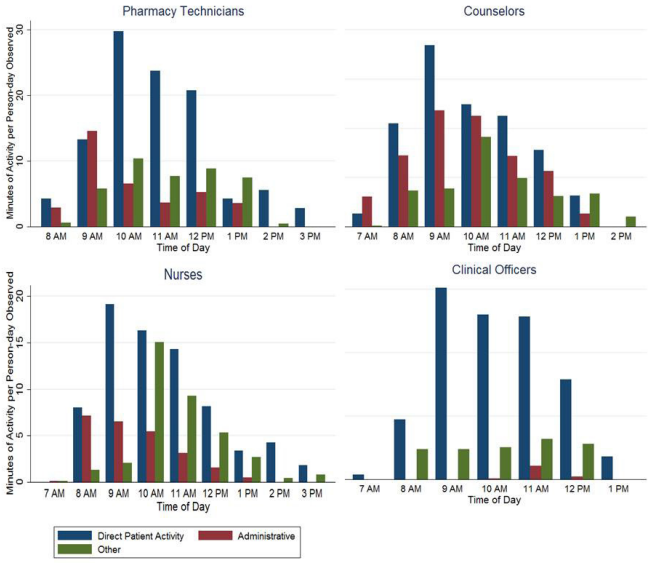
	NG	CT	TV	BV	TP	Any STI
All women (n=302)	8%	10%	11%	16%	2%	37%
ART-naïve (n=144)	7%	12%	13%	20%	5%	42%
On ART(n=158)	5%	8%	10%	13%	0%	32%
p-value	0.451	0.261	0.473	0.126	0.008	0.091
Scale performance in predicting RTI	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**LR+**	**LR-**
Score=0 vs 1+ (recommend[1])						
NG+CT+TV+BV+TP	95%	3%	50%	50%	0.978	1.667
NG+CT+TV	97%	4%	23%	83%	1.101	0.670
NG+CT	95%	4%	14%	83%	0.994	1.130
Score 0 or 1 vs 2+						
NG+CT+TV+BV+TP	66%	29%	35%	60%	0.930	1.168
NG+CT+TV	72%	32%	24%	89%	1.060	0.848
NG+CT	72%	32%	15%	87%	1.073	0.872
Score 0 , 1 or 2 vs 3+						
NG+CT+TV+BV+TP	31%	74%	45%	63%	1.229	0.921
NG+CT+TV	36%	78%	33%	80%	1.641	0.818
NG+CT	44%	78%	25%	89%	1.996	0.716

PPV = positive predictive value / NPV = negative predictive value / LR+ = likelihood ratio positive / LR- = likelihood ratio negative
[1] Morrison CS, Murphy L, Kwok C, Weiner DH. Identifying appropriate IUD candidates in areas with high prevalence of sexually transmitted infections. Contraception. 2007;75(3):185–192

1076 IDENTIFYING OPERATIONAL CHALLENGES IN ZAMBIAN ART CLINICS: A TIME AND MOTION STUDY

Radhika Tampi[1], Taniya Tembo[2], Arianna L. Zanolini[2], Anjali Sharma[2], David Dowdy[1], Charles B. Holmes[1], Mpande Mukumbwa-Mwenechanya[2], Carolyn Bolton Moore[2], Izukanji Sikazwe[2], Austin Tucker[1], **Hojoon Sohn**[1]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]Center for Infectious Disease Research in Zambia, Lusaka, Zambia

Background: The mass scale-up of antiretroviral therapy (ART) in Zambia has taken place in the context of limited infrastructure and human resources resulting in many operational side-effects. In this study, we aimed to empirically measure current workload of ART clinic staff and patient wait times and service utilization.
Methods: We conducted time and motion (TAM) studies from both the health care worker (HCW) and patient perspectives at 10 ART clinics in three provinces (Lusaka, Southern, and Eastern) in Zambia. A team of trained personnel recorded times for consecutive discrete activities based on direct observation of clinical and non-clinical activities performed by counselors, clinical officers, nurses, and pharmacy technicians. For patient TAM, we recruited consecutive consenting patients and recorded their times of arrival and departure and major ART services utilized. Data from the 10 clinics were pooled to evaluate median time per patient spent for each activity and total duration of stay in the clinic.
Results: The percentage of observed clinical time spent on direct patient interaction (median time per patient encounter) was 43.1% for ART counselors (4 minutes, interquartile range [IQR] 2-7), 46.1% for nurses (3 minutes, IQR 2-4), 57.2% for pharmacy technicians (2 minutes, IQR 1-2), and 78.5% for clinical officers (3 minutes, IQR 2-5). Direct patient workloads for the HCWs were heaviest between 8AM and 12PM with little or no clinical activities observed after 2PM (Figure). The length of patient clinic visits was inversely associated with arrival time – patients arriving prior to 8AM spent nearly twice as much time at the clinic as those arriving after 8AM (277 vs. 171 minutes). Overall, patients spent 219 minutes on average for non-clinical visits, and 244 minutes for clinical visits, but this difference was not significant in rural clinics. In comparison, total time patients spent directly with clinic staff were 9 and 12 minutes on average for non-clinical and clinical visits.
Conclusion: Current Zambian ART clinic operations include substantial inefficiencies for both patients and HCWs, with workloads heavily concentrated in the first few hours of clinic opening, limiting HCW and patient interaction time. Redistributing workloads throughout operational hours and preventing backlogs of patients waiting for hours before clinic opening may substantially improve ART delivery in the Zambian context.



1077 EFFECT OF UNDISCLOSED HIV+ STATUS ON LINKAGE TO AND RETENTION IN CARE

Neena M. Philip[1], Yingfeng Wu[1], Margaret McNairy[2], Averie B. Gachuhi[1], Matthew R. Lamb[1], Harriet Nuwagaba-Biribonwoha[1], Veli M. Madau[3], Sean Burke[3], Zandile Mnisi[4], Wafaa M. El-Sadr[1]
[1]ICAP at Columbia University, New York, NY, USA, [2]Weill Cornell Medicine, New York, NY, USA, [3]ICAP at Columbia University–Swaziland, Mbabane, Swaziland, [4]Ministry of Health, Mbabane, Swaziland

Background: Link4Health, a cluster randomized controlled trial in Swaziland, found that a combination intervention strategy (CIS) versus standard of care (SOC) was associated with a 50% increase in linkage to care and 12-month retention after a HIV-positive (HIV+) test. CIS comprised five interventions: point of care CD4 count, accelerated ART initiation, health educational packages with disclosure support messaging, SMS reminders, and non-cash financial incentives. We assessed predictors of HIV disclosure and its effect on linkage and retention outcomes.
Methods: Adults ≥18 years, newly testing HIV+ were recruited. Demographics, psycho-social factors, and disclosure of HIV+ status were collected at baseline, month 1 (M1) and month 12 (M12). The primary outcome was a combined measure of linkage to care within one month plus retention in care at 12 months after HIV testing. Hierarchical Poisson regression models with random effects of study sites were used to estimate adjusted relative risk ratios and 95% confidence intervals (CI) (Table).

Results: A total of 2197 participants were enrolled from Aug 2013-Nov 2014 and followed for 12 months. Median age was 32 years (IQR 26-40); 59% were female. Participants in CIS versus SOC had significantly lower undisclosed HIV+ status at M1 and M12. Among all participants, undisclosed HIV+ status decreased 61.5% from M1 to M12; only 5.7% reported undisclosed HIV+ status at M12. There were no associations between undisclosed HIV+ status at M12 and sex, marital status, education, employment, number of close friends, mental health, stigma, or HIV knowledge. In adjusted analysis, undisclosed HIV+ status at M12 was more than four-fold higher among 18-24 year olds vs persons 50 years and older and more than two-fold higher among those very concerned vs not concerned with unintended disclosure at baseline. Among 18-24 year olds with undisclosed HIV+ status at M12, half reported being very concerned about unintended disclosure. Those with undisclosed HIV+ status at M1 [aRR 1.5, 95% CI 1.2-1.7] and M12 [aRR 1.7, 95% CI 1.4-2.2] were significantly less likely to achieve the primary outcome. Among 18-24 year olds with undisclosed HIV+ status at M12, 84.4% failed to achieve the primary outcome.
Conclusion: Undisclosed HIV+ status may hinder linkage and retention in care. Interventions are needed to assist HIV+ persons in disclosure. Screening for disclosure fears and addressing disclosure concerns among 18-24 year olds is particularly important.

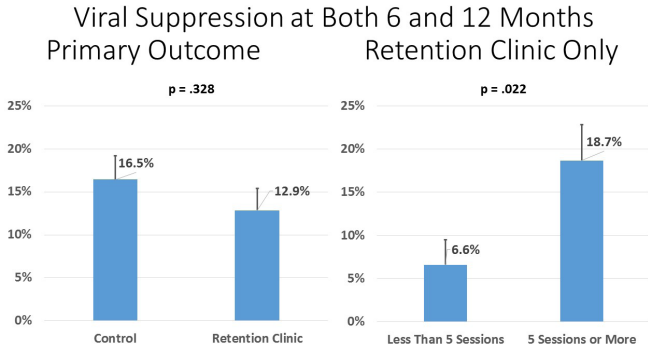
Predictor		Disclosure status at month 1 (n=1901)			Disclosure status at month 12 (n=1953)		
		n (col%)	Undisclosed n (row%)	Adjusted risk ratio (95% CI)	n (col%)	Undisclosed n (row%)	Adjusted risk ratio (95% CI)
		1901 (100)	281 (14.8)		1953 (100)	111 (5.7)	
Study arm	CIS	972 (51.1)	112 (11.5)	**0.5 (0.3, 0.9)**	997 (51.0)	37 (3.7)	**0.4 (0.3, 0.8)**
	SOC	929 (48.9)	169 (18.2)	ref	956 (49.0)	74 (7.7)	ref
Age	18-24y	384 (20.2)	68 (17.7)	1.3 (0.8, 2.1)	391 (20.0)	32 (8.2)	**4.3 (1.3, 14.0)**
	25-49y	1322 (69.5)	187 (14.1)	1.2 (0.7, 1.9)	1364 (69.9)	74 (5.4)	2.8 (0.9, 9.0)
	50+y	195 (10.3)	16 (13.3)	ref	198 (10.1)	5 (2.5)	ref
Concern about unintended disclosure	Very concerned	642 (34.0)	125 (19.5)	**1.9 (1.4, 2.5)**	660 (34.0)	53 (8.0)	**2.1 (1.3, 3.4)**
	A little concerned	488 (25.9)	57 (11.7)	1.2 (0.8, 1.7)	510 (26.3)	25 (4.9)	1.4 (0.8, 2.4)
	Not at all concerned	758 (40.2)	96 (12.7)	ref	770 (39.7)	33 (4.3)	ref

Risk ratio at M1 adjusted for study arm, age, marital status, prior HIV+ diagnosis, and concern about unintended disclosure.
Risk ratio at M12 adjusted for study arm, age, concern about unintended disclosure.

1078 INTEGRATED COCAINE & MENTAL HEALTH TREATMENT WITH NAVIGATION RCT FOR HIV+ OUTPATIENTS

Lisa Metsch[1], Daniel Feaster[2], Lauren Gooden[1], Christin Root[3], Pedro C. Castellon[1], Jonathan Colasanti[3], Eugene W. Farber[3], Gabriel Cardenas[2], Terri Liguori[1], Wendy S. Armstrong[3], Allan Rodriguez[2], Carlos del Rio[3]
[1]Columbia University Medical Center, New York, NY, USA, [2]University of Miami, Miami, FL, USA, [3]Emory University, Atlanta, GA, USA

Background: HIV+ cocaine users are less likely to be virally suppressed (VS, <200 copies/mL) due to poor engagement in care. We tested the efficacy of an integrated substance use treatment (SUT), mental health, and outpatient HIV care intervention on improving viral suppression in non-suppressed HIV-infected cocaine users.
Methods: Project RETAIN recruited 360 cocaine-using HIV+ patients who were not VS between 1/28/2013 and 3/9/2016 in Miami, FL and Atlanta, GA. Patients were randomized to treatment as usual (TAU) or to a Retention Clinic (RC) which included 11 sessions of strengths-based patient navigation, 9 sessions of SUT (2 of motivational enhancement therapy and 7 of cognitive-behavioral therapy) and mental health services over 6-months. The a-priori outcome was treatment success (viral suppression at both 6 and 12-month follow-up) versus failure (viral non-suppression at one or both, death or drop out).
Results: Patients were 63% male, 84% black, 9% Hispanic, with a mean age of 46 and most (94%) had incomes under $10,000. Median HIV viral load and CD4 count were 30,588 copies/mL and 157 cells/uL, respectively. There was no difference in treatment success across arms (TAU=16%, RC=13%, p=.328). There was not a significant gender by treatment interaction (p=.061). Although not significant, women in the RC arm tended to have more treatment success (20%) than men (10%). The RC group had significantly more individuals participate in SUT (87%) than did the TAU group (9%, p<001). RC participants attending 5 or more SUT sessions had higher rates of viral suppression (19%) than those with 4 or fewer (7%, p=.022). Urine tested substance use decline from baseline (85%) to 6- (74%, p<.001) and 12-months (65%, p<.001) was not different by study arm (p=.187). Finally, severe psychological distress in 32% of the sample at baseline declined differentially at 6 months (TAU=25%, RC=16%, p=.049). There were 33 deaths during the trial (9%) with no difference between TAU (10%) and RC (8%, p=.607).
Conclusion: Only a minority of HIV+ cocaine-using patients became VS over the 12-month study and there was no effect of the integrated SUT, mental health services and patient navigation intervention on viral suppression. Patients in the integrated intervention did have reduced psychological distress after completing the intervention. Despite more SUT in the RC arm, both groups declined equally in substance use. Interventions that improve retention in care and viral suppression are needed for this population.

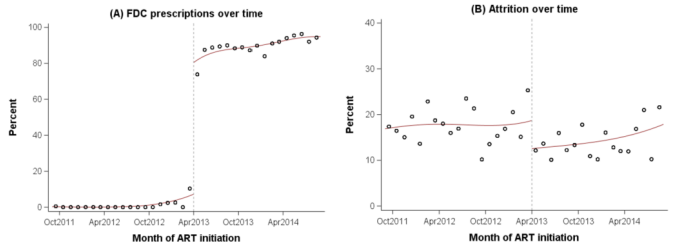


1079 SINGLE-PILL ART AND RETENTION IN CARE: A REGRESSION DISCONTINUITY STUDY IN S. AFRICA

Sheryl Kluberg[1], Matthew P. Fox[1], Michael LaValley[1], Denise Evans[2], Kamban Hirasen[3], Mhairi Maskew[2], Lawrence Long[1], Jacob Bor[1]
[1]Boston University, Boston, MA, USA, [2]University of the Witwatersrand, Johannesburg, South Africa, [3]Health Economics and Epidemiology Research Office, Johannesburg, South Africa

Background: Single-pill fixed-dose combination (FDC) antiretroviral therapy (ART) is recommended by the World Health Organization (WHO) because of its potential to improve patient quality of life, as well as adherence and retention on therapy. However, the causal effect of FDCs on clinical retention in sub-Saharan Africa has not been investigated. In April 2013, South Africa adopted WHO recommendations to use FDCs for first-line ART in the public sector. We assessed whether this policy had an impact on retention in HIV care using a quasi-experimental regression discontinuity design.
Methods: We analyzed data on 1124 patients initiating ART at Themba Lethu clinic, a large public-sector HIV clinic in Johannesburg, South Africa. The sample was limited to patients starting ART between October 2012 and September 2013, the 6 months before and after FDCs were introduced. We estimated the intention-to-treat effect of the FDC policy change on the risk of attrition, defined as a ≥3-month lapse in care within the first 12 months, using a regression discontinuity analysis that compared outcomes for patients starting ART just before and just after the policy change. We also assessed sensitivity of our results to other definitions of retention and assessed effect heterogeneity by age, sex, and measures of baseline health status.
Results: The percentage of patients starting FDC increased from 2.5% in the 6 months before the guideline change to 85.7% in the 6 months afterwards. The FDC policy change was associated with an 11.3 percentage point decrease in attrition within the first year (95% CI: -22.0; -0.6). In instrumental variables analysis, starting FDC led to an 18.0 percentage point drop in attrition compared to multiple pills (95% CI: -33.6; -2.4) among patients induced to start FDC because of the policy change. Results were robust to other attrition outcomes. The greatest decreases in attrition were among the healthiest patients (i.e., those without anemia, with early WHO clinical stage disease, or higher CD4 counts).
Conclusion: South Africa's switch to FDC for first-line ART substantially reduced attrition among patients starting therapy in this large public-sector cohort. The effect was greatest among healthier patients, who represent a growing share of ART initiators under universal test-and-treat.

Figure. Effect of FDC policy on (A) percent starting FDC and (B) percent lost from care in first year.



1080 HIV CARE DELIVERY BY ID PHYSICIANS, OTHER PHYSICIANS, AND ADVANCED PRACTICE PROVIDERS

John Weiser[1], Guangnan Chen[2], Wendy S. Armstrong[3], Linda Beer[1]
[1]CDC, Atlanta, GA, USA, [2]ICF International, Atlanta, GA, USA, [3]Emory University, Atlanta, GA, USA

Background: The United States is facing a shortage of HIV care providers. Ensuring workforce stability requires knowledge of the demographics, clinical practices, and work satisfaction of infectious disease (ID) physicians, other physicians, nurse practitioners (NPs) and physician assistants (PAs) who provide HIV care.

Methods: We surveyed 1,234 HIV care providers between 6/2013-1/2014. Providers were eligible if practicing in a facility sampled for the Medical Monitoring Project, a survey designed to produce nationally representative data about adults receiving HIV care in the United States. Data were weighted to represent all HIV care providers. We assessed associations between provider type and other characteristics.

Results: In the United States, 45% of HIV care providers were ID physicians, 35% other physicians (15% internal medicine, 13% family medicine, 1% pediatrics, 6% not board certified, other, or unknown), 15% NPs, and 5% PAs. Compared to ID physicians, larger percentages of other physicians provided primary care and care in a language other than English (Table). More NPs than ID physicians cared for >50 HIV patients and worked at Ryan White HIV/AIDS Program-funded facilities. Larger percentages of other physicians and NPs were black or Hispanic and were lesbian/gay/bisexual compared to ID physicians. There were no differences among providers in ordering of genotypes on all new patients or initiating antiretroviral therapy (ART) regardless of CD4+ T-lymphocyte cell count. Larger percentages of NPs than ID physicians provided comprehensive ART adherence counseling and reproductive counseling for women, and adequate sexual and substance use risk-reduction services. Nearly half of ID physicians provided HIV expert assistance to other providers. One-third of ID physicians and one-quarter of other physicians were satisfied with salary and with administrative burden.

Conclusion: Performance on most key HIV quality measures was comparable across provider types, although NPs outperformed ID physicians in several areas. ID physicians played a critical role in providing HIV expert assistance to NPs, PAs, and other physicians, nearly all of whom also provided primary care in addition to HIV treatment. Of concern, a large majority of physicians, particularly non-ID physicians, were dissatisfied with salary and administrative burden. Addressing concerns about provider remuneration could help retain and attract providers to the field of HIV care.

Table. Comparison of Provider and Practice Characteristics of Infectious Disease Physicians vs. Other Physicians, Nurse practitioners, and Physician Assistants who Care for HIV Patients, United States, 2013-2014, N = 1224

	Total	ID physicians	Other physicians[a]		Nurse practitioners		Physician assistants	
	% (95%CI)	% (95%CI)	% (95%CI)	Rao-Scott X^2 P-value	% (95%CI)	Rao-Scott X^2 P-value	% (95%CI)	Rao-Scott X^2 P-value
Age ≥ 50 years	58.6 (53.6-63.5)	53.3 47.0-59.5	66.4 57.7-75.0	<0.05	64.0 53.8-74.1	0.11	b	
Sex								
Male	56.7 (49.8-63.5)	59.6 (50.2-69.0)	71.9 (62.6-81.2)	0.04	15.1 (7.9-22.2)		b	
Female	43.3 (36.5-50.2)	40.4 (31.0-49.8)	28.1 (18.8-37.4)		84.9 (77.8-92.1)		b	
Race/Ethnicity								
White	62.9 (55.9-69.9)	65.3 (58.7-71.9)	55.8 (44.3-67.3)	<.0001	68.4 (52.9-83.9)	<.0001	b	
Black or Hispanic	21.4 (14.7-28.1)	13.3 (9.1-17.6)	30.4 (18.0-42.8)		27.5 (11.5-43.5)		b	
Other	15.7 (10.7-20.7)	21.4 (14.7-28.1)	13.8 (6.5-21.1)		b		b	
Sexual orientation								
Heterosexual or straight	85.0 (80.9-89.1)	92.0 (87.3-96.6)	78.8 (72.2-85.4)	<0.005	86.4 (79.9-92.8)	0.04	b	
Gay, lesbian, or bisexual	15.0 (10.9-19.1)	8.0 (3.4-12.7)	21.2 (14.6-27.8)		13.6 (7.2-20.1)		b	
HIV specialist (HIVMA criteria or AAHIV-S)	58.0 (51.3-64.7)	61.6 (55.7-67.5)	51.8 (39.3-64.3)	0.13	63.7 (46.2-81.1)	0.84	b	
Provides primary care	92.9 (78.2-97.7)	70.9 (61.9-79.9)	92.7 (88.0-97.5)	<0.0001	89.3 (78.4-100.0)	0.08	99.4 (99.0-99.7)	<0.0001
Provides care in language other than English	38.7 (31.3-46.1)	33.0 (25.7-40.4)	52.4 (39.5-65.2)	<0.005	28.3 (14.9-41.6)	0.54	b	
Provides continuous and direct care for >50 HIV patients	65.3 (58.9-71.7)	64.8 (56.6-73.0)	59.5 (47.6-71.4)	0.50	83.8 (77.4-90.3)	<0.0001	54.8 (27.8-81.8)	0.45
Provides HIV expert assistance to other HIV care providers	37.1 (30.7-43.4)	45.1 (34.5-55.6)	34.5 (26.0-42.9)	0.14	21.8 (10.2-33.5)	<0.005	b	
Practice facility receives Ryan White HIV/AIDS Program funding	47.3 (35.4-59.2)	36.9 (24.7-49.1)	46.0 (32.7-59.3)	0.24	74.7 (51.6-97.9)	<0.0005	59.5 (25.2-93.7)	0.19
Orders a genotype on all patients during initial evaluation	82.0 (77.3-86.8)	86.2 (80.2-92.2)	75.6 (65.9-85.3)	0.07	85.1 (71.9-98.3)	0.89	80.9 (60.7-100.0)	0.60
Prescribes ART initiation regardless of CD4 count	69.6 (62.4-76.8)	69.9 (58.7-81.1)	69.9 (61.3-78.6)	1.00	66.6 (52.7-80.5)	0.71	73.7 (53.1-94.3)	0.78
Comprehensive ART adherence counseling	69.8 (62.9-76.8)	63.8 (53.2-74.5)	71.0 (61.7-80.4)	0.24	85.1 (78.9-91.2)	<0.0005	68.8 (34.3-100.0)	0.80
Comprehensive reproductive health counseling for women	48.4 (41.3-55.4)	43.1 (33.0-53.1)	52.1 (40.2-64.1)	0.20	58.5 (51.6-65.4)	0.01	b	
Adequate sexual behavior risk reduction services[c]	36.7 (28.8-44.6)	29.1 (22.6-35.5)	38.0 (23.8-52.3)	0.14	57.3 (50.2-64.4)	<0.0001	29.7 (10.3-49.1)	0.95
Adequate substance use risk reduction services[c]	42.9 (35.0-50.7)	36.6 (26.9-46.3)	41.5 (30.7-52.2)	0.42	61.6 (53.3-70.0)	<0.0005	44.2 (26.2-62.1)	0.46
Satisfied or very satisfied with area of HIV practice:								
Salary and reimbursement	36.9 (30.5-43.3)	37.2 (28.9-45.4)	27.5 (21.0-33.9)	<0.005	51.1 (37.5-64.6)	0.04	52.9 (30.8-75.0)	0.19
Time for documentation / administrative work	32.6 (26.8-38.5)	34.6 (27.8-41.5)	26.7 (18.8-34.6)	0.04	42.6 (33.9-51.3)	0.12	b	

Abbreviations: ID, infectious disease; AAHIV-S, American Academy of HIV Medicine specialist; ART, antiretroviral therapy; CD4, CD4+ T-lymphocyte cell count
[a] Other physicians include internal medicine physicians, family medicine physicians, pediatricians, non-board certified physicians, other board certified physicians, and physicians with unknown board certifi
[b] Coefficient of variation >0.3, estimate is unstable and is not reported
[c] Performed at 70% on on delivery of 9 sexual behavior- and 7 substance use-related HIV transmission risk services

1081 BETTER RETENTION AMONG PATIENTS ON ART ARGUES FOR UNIVERSAL TREATMENT IN KENYA

Irene Mukui[1], Maureen Kimani[1], Samuel M. Mwalili[2], Agnes Natukunda[3], Evelyne Ngugi[2], Abraham Katana[2], Lucy Ng'ang'a[2], Peter W. Young[2], George Rutherford[3]
[1]Ministry of Health, Nairobi, Kenya, [2]US CDC Nairobi, Nairobi, Kenya, [3]University of California San Francisco, San Francisco, CA, USA

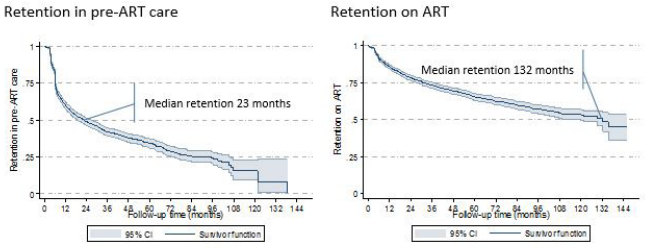
Background: Understanding outcomes of patients in HIV care and on antiretroviral therapy (ART) is critical in monitoring progress towards achieving the 90-90-90 treatment targets. The Longitudinal Surveillance of Care and Treatment in Kenya surveyed outcomes for retrospective cohorts of adult and adolescent patients in care

Methods: We studied a nationally representative random sample of HIV infected patients aged ≥15 years enrolled in care between 2003-2013 from 50 health facilities providing ART. We evaluated overall, pre-ART and ART retention, defined as being alive and not missing last appointment by >90 days. We analyzed baseline demographic, clinical and laboratory variables, ART initiation and retention using Kaplan-Meier analyses and log-linear modeling; data were weighted to account for survey design

Results: We sampled 3152 patients followed for a median of 30.3 months (IQR 6.5-65.8 months). Overall, 1161 (33.8%) were retained in care at the end of follow up, 187 (5.9%) died, 427 (14.5%) transferred out and 1,329 (44.3%) were lost to follow up. Baseline factors associated with overall retention were female sex (p<0.001), being married (p<0.001), higher enrollment CD4 (p<0.001) and enrollment under recent ART guidelines (CD4 based ART eligibility of ≥ 350 cells/μL versus eligibility at < 350 cells/μL) (p<0.001). Among all patients median pre-ART retention was 23 months (Figure); 2,152 (68.3%) began ART after a median of 2.0 months (IQR, 0.7-11.4) in care. Among those who started ART, 122 (5.9%) died, 276 (13.3%) transferred out, 576 (26.9%) were LTFU and 1131 (51.8%) were retained a median of 132 months. Factors associated with ART retention were being employed (p=0.006), higher enrollment CD4 (p=0.001) and enrollment during more recent guideline period (p<0.001). Those initiating ART versus those not were more likely to be older (>25 years, OR=1.8, 95% CI 1.4-2.2) and enrolled in care from 2010–2013 versus 2003–2005 (OR=1.5, 95% CI 1.1–2.1)

Conclusion: Data from the pre-universal ART era in Kenya demonstrate that almost one third of patients in pre-ART care had not started ART by the end of 2016, but once initiating ART, patients were retained a median of 11 years. Our study suggests that by encouraging early treatment initiation, new guidelines implementing universal ART should improve overall retention of PLHIV in care.

Figure 1: Average retention on antiretroviral treatment (ART) was longer than retention among those who had not started ART, Kenya, 2003-2016



Notes: For retention in pre-antiretroviral (pre-ART) care, failure defined as death or loss to follow-up (LTFU), censored at transfer out or antiretroviral (ART) initiation. For retention on ART, failure defined as death or LTFU, censored at transfer out.

1082 IS DIFFERENTIATED CARE IMPLEMENTED? ANALYSIS OF SEVEN AFRICAN TREATMENT PROGRAMS

Andreas D. Haas[1], Leigh F. Johnson[2], Izukanji Sikazwe[3], Nathan Ford[4], Matthew P. Fox[5], Hans Prozesky[6], Cleophas Chimbetete[7], Jonathan Euvrard[2], Matthias Egger[1]

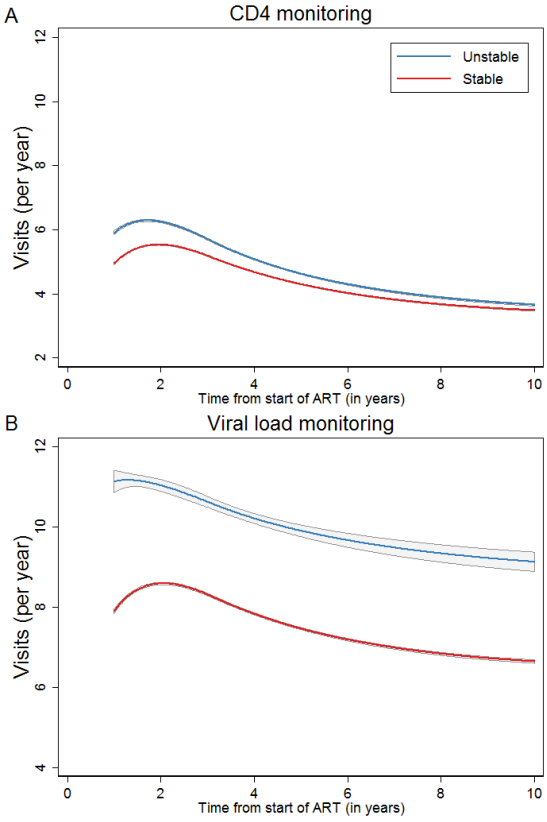
[1]University of Bern, Bern, Switzerland, [2]University of Cape Town, Cape Town, South Africa, [3]Center for Infectious Disease Research in Zambia, Lusaka, Zambia, [4]WHO, Geneva, Switzerland, [5]Boston University, Boston, MA, USA, [6]Stellenbosch University, Tygerberg, South Africa, [7]Newlands Clinic, Harare, Zimbabwe

Background: Since 2016, WHO has recommended differentiated HIV care models, which adapt the frequency of clinic visits to patients' needs. WHO recommends virological and immunological criteria to identify stable patients who qualify for less frequent clinic visits, but data on how these criteria are used in African routine care settings are scarce. We compare the frequency of clinic visits among patients classified as stable and unstable according to virological or immunological criteria and assess time trends in appointment spacing.

Methods: We included HIV-1 infected adults aged 16 years or older, starting ART between 2004 and 2015 in one of seven programs participating in the International Epidemiology Databases to Evaluate AIDS – Southern Africa (IeDEA-SA). Patients from South Africa (monitored with viral load testing) were classified as stable, if their viral load was <1,000 copies/mL. Patients from Zambia and Zimbabwe (monitored with CD4 cell counts) were classified as stable, if their CD4 cell count was >200 cells/μL and had increased since the last measurement. We analyzed visit times as multiple failure-time data in a survival analysis framework. Patients entered the analysis 1 year after start of ART and were censored at their last visit. We used univariable and multivariable flexible parametric survival models with restricted cubic splines to examine time-dependent effects of patient- and program-level characteristics and the rate of clinic visits.

Results: We included 152,338 patients: 71% (108,179) came from two programs with CD4 monitoring, and 29% (44,159) came from five programs with viral load monitoring. The figure shows the rate of clinic visits (per year) and 95% CIs (shaded areas) for stable and unstable patients on ART. In CD4 monitoring sites, the rate of clinic visits in stable patients and unstable patients was similar (Figure A). In viral load monitoring sites, the rate of clinic visits in stable patients was substantially lower than in unstable patients (Figure B). In more recent years, stable patients were followed-up less frequently than in earlier years. This time trend did not change in multivariate models adjusted for CD4 cell count at ART initiation.

Conclusion: Programs with viral load monitoring implemented differentiated care models and reduced the frequency of clinic visits in virologically suppressed patients. We found little evidence for differentiated appointment spacing in programs without access to viral load monitoring.



1083 LINKAGE, TREATMENT AND SUPPRESSION IN THE BOTSWANA COMBINATION PREVENTION PROJECT

Pamela J. Bachanas[1], Refeletswe Lebelonyane[2], Mary Grace Alwano[3], William Abrams[3], Baraedi W. Sento[4], Lisa Block[5], **Tendani Gaolathe**[6], Shahin Lockman[7], Shenaaz El Halabi[2], Janet Moore[1]

[1]CDC, Atlanta, GA, USA, [2]Botswana Ministry of Health, Gaborone, Botswana, [3]CDC Botswana, Gaborone, Botswana, [4]Tebelopele Voluntary Counseling and Testing Center, Gaborone, Botswana, [5]Intellectual Concepts, Atlanta, GA, USA, [6]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [7]Brigham and Women's Hospital, Boston, MA, USA

Background: Botswana has high rates of HIV diagnosis and treatment coverage, but substantial ongoing HIV incidence and high prevalence. Finding unidentified HIV-positive persons missed by the national testing programs and getting them on treatment is essential for reaching epidemic control. In the Botswana Combination Prevention Project (BCPP), we assessed the degree to which enhanced HIV testing, linkage to care, and universal ART increased HIV testing and treatment coverage, and whether age and gender were associated with differential rates of coverage.

Methods: BCPP is a community-randomized trial designed to evaluate the impact of a combination prevention package on population level HIV incidence in 30 communities. HIV testing in the 15 intervention communities included home-based and targeted mobile testing of residents age 16-64. Newly-identified and known HIV-positive persons not on ART were referred to the local HIV clinic for care and universal ART initiation, and linkage to care support was provided for referred individuals who did not register at the clinic.

Results: 3,554 HIV-positive persons were newly identified or were known to be HIV-positive but not on ART, and were referred for treatment. Ninety percent (3,184/3,554) of those referred linked to care, and 79% (2,791/3,554) initiated ART. Of those who initiated ART and had a viral load test, 98% (2,006/2,053) were virally suppressed (VL< 400 copies/mL) at > 6 months. Linkage to care rates were lower for males (86%) compared to females (92%), $\chi 2$ (1, N= 3,554) = 39.98, p<.0001, and a lower percentage of referred males (75%) initiated ART compared to females (81%), $\chi 2$ (1, N= 3,554) = 19.2, p<.0001. Age differences were also found; linkage to care rates were lower for younger persons 16-24 (82%) compared to persons ages 25 and older (91%), $\chi 2$ (1, N= 3,554) = 39.6,

p<.0001. ART initiation rates were also lower among the 16-24 (69%) age group compared to those 25 and older (80%), $\chi 2$ (1, N= 3,554) = 43.2, p<.0001 (see Table 1).

Conclusion: BCPP achieved high rates of linkage to care and ART initiation through a combination of community- and clinic-based interventions. In the context of a highly successful national program, BCPP was able to substantially increase uptake and coverage of treatment. Despite targeted efforts, young people 16-24 (particularly men) were less likely to link to care and initiate ART, compared to older persons. Interventions are needed that encourage and support young people to start and remain on treatment.

Table 1: Persons Identified and Referred, Linked to Care, Initiated on ART and Virally Suppressed by Age and Gender in BCPP Combination Prevention Communities 1-15

	Total	Females 16-24	Females 25-34	Females ≥35	Males 16-24	Males 25-34	Males ≥35
HIV+ Persons Not on ART Referred to HIV Clinic	N=3554 (Females = 2,154; Males = 1,400)	N=413	N=754	N=987	N=121	N=472	N=807
Total Referred who Linked to Care	3184 (90%)	350 (85%)	702 (93%)	934 (95%)	90 (74%)	394 (83%)	714 (88%)
Total Referred who Initiated ART	2791 (79% of Referred; 88% of Linked)	298 (72%)	602 (80%)	844 (86%)	73 (60%)	341 (72%)	633 (78%)
Total on ART who are Virally Suppressed at ≥6 months (who had VL test)	2006/2053 (98%)	196/207 (95%)	436/451 (97%)	688/695 (99%)	40/41 (98%)	213/218 (98%)	433/441 (98%)

1084 DISTRIBUTION OF ADVANCED HIV IN 3 HIGH HIV PREVALENCE COUNTRIES IN AFRICA

Menard L. Chihana[1], Helena Huerga[2], Gilles van Cutsem[3], Stephen Wanjala[4], Charles Masiku[5], Elisabeth Szumilin[6], Jean F. Etard[7], Mary-Ann Davies[8], David Maman[1]

[1]Epicentre, Cape Town, South Africa, [2]Epicentre, Paris, France, [3]MSF, Johannesburg, South Africa, [4]MSF, Nairobi, Kenya, [5]MSF, Lilongwe, Malawi, [6]MSF, Paris, France, [7]IRD, Montpellier, France, [8]University of Cape Town, Cape Town, South Africa

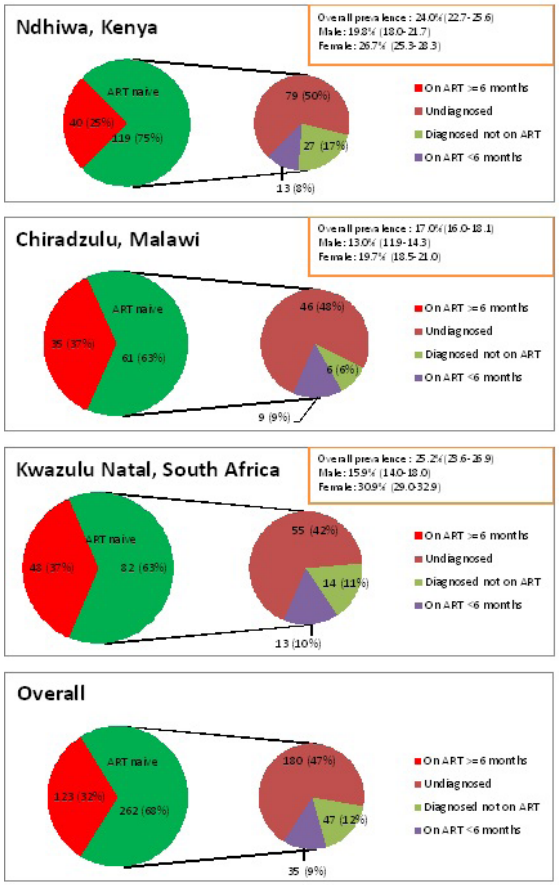
Background: Despite substantial increases in antiretroviral therapy (ART) access, a number of HIV-infected patients continue to experience advanced disease, contributing to ongoing HIV-related morbidity and mortality. To help reduce mortality, the WHO recently released guidelines for managing individuals with advanced HIV disease and their rapid initiation on ART. We quantified population level estimates of advanced HIV from three high HIV prevalence settings in Sub-Saharan Africa.

Methods: Three HIV cross-sectional surveys were conducted in Ndhiwa (Kenya); September-November 2012, Chiradzulu (Malawi); February-May 2013 and KwaZulu-Natal (South Africa); July-October 2013. Individuals aged 15-59 years were eligible for inclusion. Consenting individuals were interviewed at households using a structured questionnaire followed by rapid HIV testing and, among those who tested positive, home based CD4 testing for Kenya and Malawi and laboratory tested for South African and viral load testing were conducted. Advanced HIV was defined as CD4 count of <200 cells/µl.

Results: Among 18991(39.2% male) individuals, 4113(21.7%) tested HIV-positive; 385/3957 (9.7%; 95% Confidence Interval [CI]:8.8-10.7) had advanced HIV, ranging from 8.1%(6.6-9.9) in Malawi to 11.6%(9.9-13.5) in Kenya. Only 158/385 (41.0%) reported ever being on ART, with 32.0% on ART for at least 6 months; the rest were ART naive (figure). The proportion of ART naive individuals among those with advanced HIV was lower in Malawi and South Africa where criteria for ART initiation at the time were less restrictive than Kenya (63.3% vs 74.8%; p=0.04). Overall, 68.7% of ART naive had not previously been diagnosed with HIV, and this was similar across countries. Among those on ART for at least 6 months, 46.3% had viral load ≥1000 copies/µL; 60.2% were male and 65% were 35-59 years old.

Conclusion: Our estimates of advanced HIV in the population were lower than most clinical studies. More than half of patients with advanced HIV were ART naive, the majority not previously diagnosed as HIV-infected, suggesting the need for different testing strategies to identify and link these patients to care.

Fig 1 showing distribution of 385 advanced HIV individuals by period on ART



1085 CASCADE OF CARE AMONG SERODISCORDANT COUPLES IN 4 HIGH PREVALENCE SETTINGS IN AFRICA

Menard L. Chihana[1], Nolwenn Conan[1], Erica Simons[2], Cyrus Paye[2], Daniela B. Garone[3], Reinaldo Ortuno[4], Helena Huerga[2], Gilles van Cutsem[5], Stephen Wanjala[6], Charles Masiku[7], Elisabeth Szumilin[8], Jean F. Etard[9], Mary-Ann Davies[10], David Maman[1]

[1]Epicentre, Cape Town, South Africa, [2]Epicentre, Paris, France, [3]MSF, Harare, Zimbabwe, [4]MSF, Blantyre, Malawi, [5]MSF, Johannesburg, South Africa, [6]MSF, Nairobi, Kenya, [7]MSF, Lilongwe, Malawi, [8]MSF, Paris, France, [9]IRD, Montpellier, France, [10]University of Cape Town, Cape Town, South Africa

Background: Discordant couples are at high risk of HIV transmission. We quantified the prevalence of HIV discordant couples and evaluated each step of the cascade of care among HIV infected partners in four high prevalence settings in sub-Saharan Africa.

Methods: We used data from four HIV prevalence surveys conducted in Ndhiwa (Kenya); September-November 2012, Chiradzulu (Malawi); February-May 2013, Gutu (Zimbabwe) and Nsanje (Malawi); September-December 2016. Individuals aged 15+ years were eligible for inclusion. Consenting individuals were interviewed at home using a structured questionnaire and were asked to participate in voluntary rapid HIV testing. For participants who tested HIV-positive, viral load tests were done for all sites while CD4 tests were done for everyone in Ndhiwa and Chiradzulu and for only those not on ART in Gutu and were not done in Nsanje. Couples were people who themselves reported being married or living together with the partner in the same household at the time of the survey.

Results: Of eligible 25,861 individuals, 23,415 (90.5%) were included and of these 22,854 (97.6%) tested for HIV. Among 4,918 identified couples, HIV discordancy was found in 15.9% (95%CI 14.0-18.0) in Ndhiwa, 10.0% (8.6-11.5) in Chiradzulu, 5.6% (4.7-7.5) in Nsanje and 7.6% (6.0-9.6) in Gutu. Among couples with at least one HIV-infected partner, the proportion of HIV-discordancy was 44.8% in Ndhiwa, 40.9% in Chiradzulu 39.4% in Nsanje and 41.8% in Zimbabwe. Men were more likely to be the HIV-positive partner in

62.9% (56.0-69.3) of the discordant couples in Ndhiwa and 62.1% (50.0-73.0) in Gutu, but about half of HIV-positive partners were men in Chiradzulu (48.8%; 41.3-56.4) and Nsanje (52.3%; 40.2-64.1). HIV status awareness among HIV-positive partners in discordant couples ranged from 42.4% in Ndhiwa, to 72.7% in Gutu. VL suppression ranged from 34.2% in Ndhiwa to 69.5% in Nsanje. VL suppression was similar between men and women in three settings, Ndhiwa (38.4% vs 27.8%, p=0.14), Nsanje (65.6% vs 74.1%, p=0.49) and Gutu (54.1% vs 66.7%, p=0.96) but lower in men than women in Chiradzulu (44.4% vs 62.7%, p=0.02).

Conclusion: High rates of discordant couples with low status awareness among positive partners are one of the major gaps in this high risk group. The low rates of status awareness among HIV-positive partners must be addressed in order to promote timely initiation of ART and/or PREP to reduce transmission within this high-risk group.

1086 MULTI-MONTH SCRIPTING (MMS) AND RETENTION ON HIV ANTIRETROVIRAL THERAPY IN HAITI

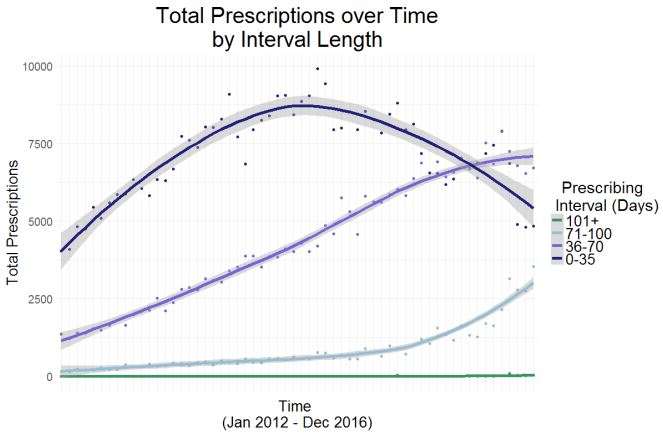
Nancy Puttkammer[1], Tricia Rodriguez[1], Ermane Robin[2], Gracia Desforges[2], Canada Parrish[1], Jean Gabriel Balan[3], Jean Guy Honore[3], Joelle Deas Van Onacker[2], Scott Barnhart[1], Jane M. Simoni[1], Kesner Francois[2]
[1]University of Washington, Seattle, WA, USA, [2]Ministry of Public Health and Population, Port-au-Prince, Haiti, [3]I-TECH, Petion-Ville

Background: Haiti's Ministry of Health recently endorsed a national initiative to lengthen prescribing intervals for HIV antiretroviral therapy (ART), known as multi-month scripting (MMS). With MMS, virally-suppressed patients on ART for >6 months are moved from monthly prescribing intervals to intervals of 2-6 months. This decreases patient travel and clinic waiting time, and reduces congestion in ART clinics. Differentiated models of HIV care seek to optimize quality and efficiency of HIV services; however, few studies have described results of MMS in resource-limited settings.

Methods: To describe the evolution of ART prescribing patterns in Haiti, we analyzed 867,449 ART prescription records from 65,460 patients in 82 health facilities from January 2012 to December 2016, drawn from the iSanté electronic medical record (EMR) system. We assessed the relationship between prescribing interval and being retained in care, defined as returning within 90 days of the next expected ART pick up date. The outcomes analysis used a subset of 45,604 ART patient records during 2015 – 2016. A multilevel logistic model was used to estimate the association between MMS and retention on ART, after adjustment for clinic site and for patient age, sex, baseline WHO stage, time on ART, and starting ART regimen.

Results: By March 2016, MMS intervals of 36 – 70 days were most common in Haiti (see Figure). Among patients on ART for at least 6 months, MMS accounted for at least half of prescriptions in 81% of sites by December 2016 (increasing from 66% of sites 1 year earlier). Patients receiving MMS tended to be older, have been on ART longer, and have more advanced WHO stage at baseline. Retention was highest (80.8%) among patients with MMS intervals of 71-100 days, and lower (63.4%) among patients with intervals of 0-35 days. After adjustment, longer MMS intervals were positively associated with retention. Odds of retention were 2.3 times higher for intervals of 36-70 days (p<.001), and 2.6 times higher for intervals of 71+ days (p<.001), compared to intervals of 0 -35 days.

Conclusion: Haiti has aggressively moved toward MMS across a majority of ART sites. The association between longer MMS intervals and improved retention on ART is promising, although these favorable results may reflect the preferential selection of stable patients for MMS, rather than a direct causal effect of the strategy. Nevertheless, the fact that no unintended negative relationship was observed between MMS and retention is important.



1087 ROUTINE RETENTION IN CARE AT HOWARD BROWN, 2012-2017: ARE QUARTERLY VISITS TOO MUCH?

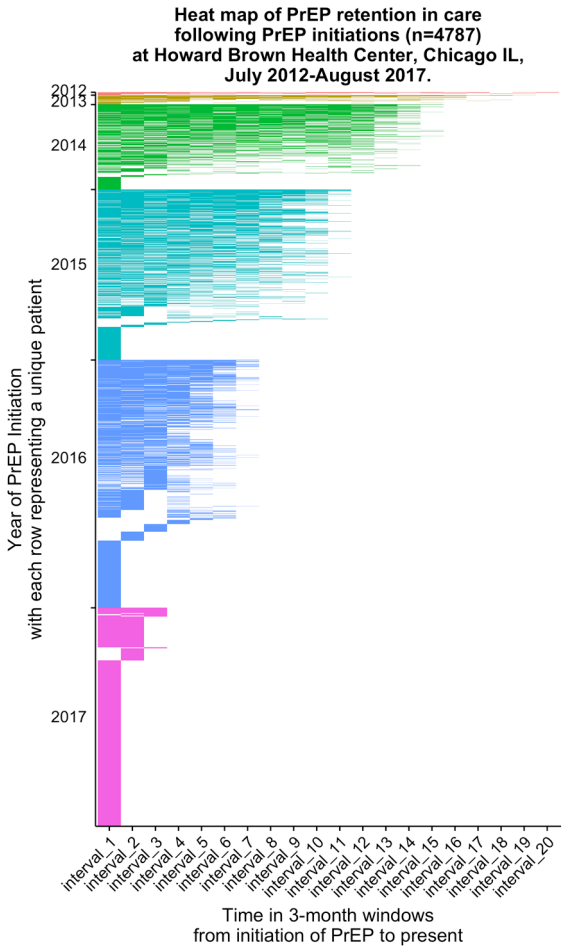
Laura Rusie[1], Carlos Orengo[1], Diane Burrell[1], Magda Houlberg[1], Arthi Ramachandran[2], Kristin Keglovitz-Baker[1], David Munar[1], John A. Schneider[2]
[1]Howard Brown Health Center, Chicago, IL, USA, [2]University of Chicago, Chicago, IL, USA

Background: PrEP retention in care is a critical yet understudied component of the PrEP care continuum. Most PrEP retention in care analyses come from placebo-controlled and open-label studies, but data are limited on real-world PrEP use.

Methods: We conducted a retrospective cohort study from July 2012 through August 2017 of Howard Brown Health patients initiating PrEP in Chicago. We abstracted unique PrEP starts as well as other demographic, clinic visit and clinic history data and examined drivers of visit constancy. Multinomial regression models were built beginning with all associated predictors removing one variable at a time based on p-value.

Results: Overall the cohort included 4787 participants who initiated PrEP from January 2012 through August of 2017 accumulating 4058 person-years of PrEP use (see Figure 1). Cohort members are young with over half being under 30 years of age, 36% Latinx or Black and 24% uninsured. There were approximately 178 monthly PrEP starts in 2017, 858 (62%) of clients have been on PrEP for 24 months or more, 1687 (35%) had an STI during follow-up, and 30% had two or more other clinical diagnoses at PrEP initiation. With respect to PrEP retention in care, among those with the opportunity for at least 12 months of follow-up, 42.9% remained in care at 12 months, yet only 15% had high visit constancy of 4 out of 4 quarters with a PrEP visit during the first 12 months of PrEP care. In final multinomial regression models, factors associated with at least 1/4 quarters with a PrEP visit included number of other comorbidities. In addition with increasing visit constancy of 3/4 quarters and 4/4 quarters with a PrEP visit, uninsured clients were less likely to be retained (aOR, 0.53; 95% CI, 0.34-0.84) and (aOR, 0.36; 95% CI, 0.21-0.62) respectively.

Conclusion: While overall client engagement in PrEP was modest, adherence to CDC recommended guidelines for quarterly visits was low. Insurance status and prevalent co-morbidities were the main drivers of PrEP retention in care. It is unclear whether low rates of retention are due to need for longer gaps between scheduled visits for adherent patients, whether risk and perception of risk is dynamic or whether social and structural factors are impeding clinic visits. PrEP retention in care interventions are needed to realize the full potential of PrEP in the context of HIV elimination in the United States.

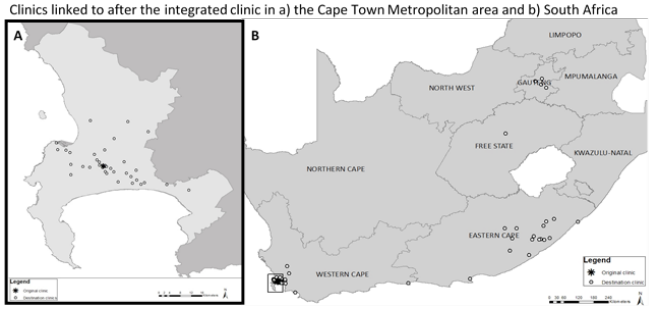


1088 POSTPARTUM MOBILITY AND TRANSFER OF CARE AMONG HIV+ WOMEN ON ART IN SOUTH AFRICA

Tamsin K. Phillips[1], Kate Clouse[2], Allison Zerbe[3], Catherine Orrell[1], Elaine J. Abrams[3], Landon Myer[1]
[1]University of Cape Town, Cape Town, South Africa, [2]Vanderbilt University, Nashville, TN, USA, [3]Columbia University, New York, NY, USA

Background: Women initiating antiretroviral therapy (ART) in pregnancy commonly require transfer of care postpartum. Transfer and mobility present a potential challenge to long-term retention in this vulnerable population.
Methods: Working with a routine primary care cohort, we used electronic health data (HIV-related laboratory tests, ART dispensing and clinic visits from the National Health Laboratory Services and Western Cape Department of Health) to asses HIV care access and mobility in women who initiated ART in an integrated antenatal-ART service in Cape Town, March 2013-June 2014. Transfer out of the integrated clinic was required by all women postpartum. We investigated any linkage to care after leaving the integrated clinic and calculated the number of new clinics attended up to 30m on ART. Among women who did link, we used Poisson regression to explore predictors of i) retention: accessing care at least once at both 6-18m and 18-30m on ART, and ii) viral suppression (VS): HIV viral load ≤1000 copies/ml (>12m on ART).
Results: Among 617 women, HIV care was accessed at 98 different facilities, with 11% of women moving out of Cape Town (Figure). Overall, 59% were retained; 21% never linked to care and 20% were lost after linking to a new clinic. Among 485 women who linked to care, 21% attended ≥2 (max 3) clinics. Women ≤25 years old or unemployed were more likely to attend ≥2 clinics (adjusted risk ratio [aRR] 1.10 95% confidence interval [CI] 1.02-1.18 and aRR 1.06 95% CI 0.99-1.12, respectively). Evidence of retention was found for 75% of women who linked (n=363). Those ≤25 years old or reporting unplanned pregnancies were less likely to be retained (aRR 0.87 95% CI 0.76-0.99 and aRR 0.86 95% CI 0.78-0.95, respectively). Among 338 retained women with viral load available, 87% were VS. Being >25 years old, employed or married predicted VS. Although not statistically significant, women who attended ≥2 clinics were slightly less likely to have VS (aRR 0.92 95% CI 0.82-1.03) and the distance they moved after transfer was not associated with VS.
Conclusion: Some women never linked to care after leaving the integrated clinic. Those who did spread to a large number of different facilities and a quarter were not retained in care. Younger age was a shared risk factor for non-retention, raised viral load and mobility. HIV programs should facilitate clinic transfers when needed and targeted interventions supporting young postpartum women warrant consideration.

Clinics linked to after the integrated clinic in a) the Cape Town Metropolitan area and b) South Africa



1089 LINKAGE TO CARE AFTER HIV TESTING IN THE COMMUNITY IN A HIGH HIV PREVALENCE SETTING

Sarah Jane Steele, Bernadette Gergonne, Liesbet Ohler, Ellie Ford-Kamara, Gilles van Cutsem, Amir Shroufi
MSF, Cape Town, South Africa

Background: In 2012, Médecins Sans Frontières, in partnership with the Department of Health (DOH), implemented community testing using mobile, fixed site (M&FS) and door to door (D2D) models, in a catchment area covered by 9 MSF-supported DOH health facilities (HF) in KwaZulu-Natal, South Africa (2016 population 127,611). We assess linkage to care at an MSF-supported HF among people who test positive in the community.
Methods: Routine data were analysed retrospectively (Jan 2013 – May 2017). Linkage was ascertained using two methods 1) All tests in the community were collected electronically and matched to facility-based data on individuals in HIV care (Tier.Net) using an algorithm based on name and date of birth; 2) referral slips provided after a positive HIV test in the community, and presented at a facility were encoded in Tier.Net. Time to linkage was available for individuals linked to care through matching, assessed by testing model and CD4 using Kaplan-Meir estimates and applied to the overall number linked.
Results: 6,005 individuals (67%, 4027 female) tested positive in the community. Median age among those testing positive was 27.3 years (Interquartile range: 21.9-35.8). 695 (12%) were known to be in HIV care and were excluded from further analyses. Of those not previously in care, 2493 (47%, 2493/5309) were identified as ever linked: 966 (18%) by referral slips only, 924 (17%) by merging only and 603 (11%) by both. Among those linked to care and for whom time to linkage was available (1507), 10.8% (95%CI: 9.4%-12.5%) linked to care on the same day as the community test, 42.3% (95%CI: 40.4-52.4%) within 1 week and 77.5% (95%CI: 75.4%-79.6%) within 6 months. Applying this to the 2493 known to be linked, we estimate overall linkage at 6 months to be 36% (1932/5309). Those with CD4<200 were more likely to link to care on the same day, as were those testing at M&FS but after six months of follow-up the differences no longer persisted (Table 1). Among linked, no differences in time to linkage were observed by sex or age.
Conclusion: We found that only half of those testing in the community link to care, however, this is likely to be under ascertained. Males who linked to care were similar to females, but males were under-represented among those testing positive. A high proportion of those who link to care do so early. Healthy individuals testing in the community were just as likely to access care at 6 months as those who were less healthy.

Table 1: Time to linkage to care, among those identified as linked at an MSF-Supported DOH health facility following a positive HIV testing in the community in KwaZulu-Natal South Africa (n=1507)

		Time to linkage among those linked to care							
		Same day		One week		One month		Six months	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
CD4 at presentation	<200	15.9	12.0-20.9	45.8	40.1-52.0	58.3	52.5-64.2	77.7	72.5-82.3
	200- <350	9.6	7.1-12.9	43.5	38.9-48.5	59.5	54.7-65.3	79.9	75.8-83.6
	350 - <500	10.3	7.6-13.9	42.2	37.3-47.5	56.4	51.3-61.5	76.9	72.5-81.2
	>500	9.7	7.2-13.2	40.1	35.4-45.2	56.5	51.5-61.5	76.8	72.4-80.9
Community testing model	Mobile and fixed sites	12.8	10.9-14.9	46.1	43.1-49.0	59.1	56.2-62.0	76.9	74.4-79.3
	Door to door	5.3	3.5-7.9	31.1	26.9-35.8	49.9	45.2-54.8	76.9	72.7-80.8

1090 PHONE CALL FROM CLINICAL OFFICER AT HIV TESTING/RE-CONTACT IMPROVES LINKAGE TO CARE

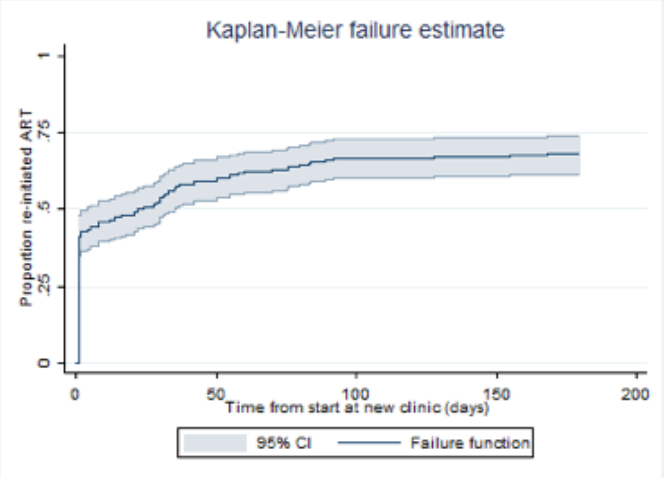
James Ayieko[1], Erick Wafula[2], Wilson Opudo[3], Craig R. Cohen[2], Elizabeth A. Bukusi[1], Tamara D. Clark[2], Laura B. Balzer[4], Moses R. Kamya[5], Edwin D. Charlebois[2], Maya L. Petersen[6], Diane V. Havlir[2]
[1]Kenya Medical Research Institute, Nairobi, Kenya, [2]University of California San Francisco, San Francisco, CA, USA, [3]Kenya Medical Research Institute, Kisumu, Kenya, [4]Harvard University, Cambridge, MA, USA, [5]Makerere University, Kampala, Uganda, [6]University of California Berkeley, Berkeley, CA, USA

Background: In the SEARCH HIV test-and-treat study, linkage to care rates declined after two years. After achieving "90-90-90", we noted that prior non-linkers and new infection cases were harder to link to care. We had separately observed that patients who linked but subsequently defaulted from care often re-engaged after a personal phone call from a clinical officer. We therefore tested whether a phone call to patients at time of initial HIV diagnosis or, among those not currently in care, at time of re-contact at community health campaigns (CHC) or home-based testing (HBT) could improve linkage.
Methods: We conducted a nested randomized controlled trial during year two of the SEARCH study (NCT01864603; August-December 2016). Previously diagnosed HIV+ adults currently not engaged in care (Never linked and Lost to follow up) and newly diagnosed HIV+ adults were randomized at CHC or HBT to receive an immediate phone call from a clinical officer or no phone call. All participants received ART messaging and a one-time transport voucher for linkage. Intervention participants also received a phone call establishing a personal connection, reinforcing ART messaging, discussing linkage barriers and scheduling appointment. Linkage was defined as clinic enrollment and completion of first clinic visit. We compared the proportion linking by 7 and 30 days after randomization between intervention and control arms using Pearson chi-square tests without continuity correction.
Results: A total of 130 participants were randomized (68 intervention, 62 control); 88 (68%) were newly diagnosed and 42 (32%) were not currently in care. Median age was 31 years (IQR 27-40), 26.9% were male. Participants in the intervention group were more likely than those in the control group to link to care by 7 days (24/68, 35.3% vs. 12/62,19.4%, p=0.043). The effect of the intervention was maintained at 30 days (28/68, 41.1% vs. 15/62, 24.2%, p=0.040).
Conclusion: A single phone call from a clinical officer to participants at the time of HIV testing or re-contact significantly improved linkage to care. However, overall linkage rates were low two years after initiation of universal test-and-treat. As the demographics of new diagnoses change and "hard to engage" patients comprise an increasing proportion of those not linked, additional innovative linkage interventions are needed.

1091 UNDERSTANDING PATIENT MOBILITY IN HIV +VE ADULTS ACROSS MULTIPLE CLINICS IN ZAMBIA

Kombatende Sikombe[1], Sandra Simbeza[1], Jillian L. Kadota[1], Ingrid Eshun-Wilson[2], Laura Beres[3], Carolyn Bolton Moore[4], Njekwa Mukamba[1], Charles B. Holmes[3], Izukanji Sikazwe[1], Elvin Geng[5]
[1]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, [2]Stellenbosch University, Cape Town, South Africa, [3]Johns Hopkins University, Baltimore, MD, USA, [4]University of Alabama at Birmingham, Birmingham, AL, USA, [5]University of California San Francisco, San Francisco, CA, USA

Background: Many patients in HIV care in Africa considered lost to follow up (LTFU) at one facility are report accessing care in another. To date, however, the success of these unofficial transfers – as measured by time to re-entry at the new facility, prevalence of treatment interruptions, speed of treatement re-initiation and preservation of identifiers – has not been characterized, but may reveal opportunities for improvement.
Methods: We traced a random sample of HIV infected patients in Zambia who were lost to follow-up. Among those found alive and reporting care at a new facility, we reviewed records at the receiving facility to verify transfer, assess whether treatment identifiers were preserved, identify the date of treatment re-initiation. We used the Kaplan-Meier methods to examine incidence of ART re-initiation after entry into new clinic.
Results: Among 350 patients who were lost to follow up and who reported care at a new facility when contacted through intensive tracing effrots , 209 (60%) were successfully verified through chart review at new clinic. Of the 209 verified, 54 (26%) were male, median age was 34.3 (IQR 29-40) and 86% were on ART at the time of last visit at original clinical. The median visit gap did not differ significantly between within (261.5 days, IQR 118-544) vs. cross province transfer (219, IQR 117-599; p=0.95). At the receiving site, 123 (59%) were registered under new ART IDs, 110 (54%) received a new HIV test. Overall, 40.7% initiated ART on the same day as presentation to new facility. The proportion who restarted ART at the receiving clinic increased to 54.1% (95% CI: 47.5%-60.9%) by 30 days, 66.0% (95% CI: 59.6%-72.4%) by 90 days, and 67.9% (95% CI: 61.6%-74.2%) by 180 days (Fig 1).
Conclusion: Movement from clinic-to-clinic involves both administrative as well as clinical inefficiencies. Many patients use new identifiers and names at new facilities. Re-entry into a new clinics among the silent transfer is often delayed and timely reiinitiation of treatment is inconcsistent, suggesting interruptions in treatment. Health systems innovations to ensure smooth and safe between-clinic transfers is needed to advance the public health response.



1092 RISK FOR ATTRITION IN HIV-INFECTED CLIENTS ON TREATMENT IN URBAN HIV CLINICS IN KENYA

Emily C. Koech[1], Sylvia Ojoo[2], Caroline Ngunu[3]
[1]University of Maryland, Baltimore County, Baltimore, MD, USA, [2]University of Maryland, Baltimore, MD, USA, [3]Ministry of Health, Nairobi, Kenya

Background: Despite efforts to scale-up antiretroviral therapy (ART) in Kenya, 12 month retention is around 80%. Lack of a national referral system impedes patient tracking worsened in urban settings by numerous HIV clinics and highly mobile populations. Through PEPFAR-CDC funding, the University of Maryland, Baltimore (UMB) collaborates with NCC to provide ART for over 22,000 patients in 32 facilities by June 2017. To minimize attrition, (transfer-out {TO}, lost-to-follow-up {LFTU} or death) UMB developed a retention system comprising: patient education for self-management, case-management for vulnerable patients, and a robust appointment management and tracking system. Understanding risk factors for attrition may support enhancement of our retention strategies
Methods: A retrospective analysis was undertaken of ART patient attrition between October 1, 2016 and June 30, 2017 from 25 facilities. Data was abstracted from both paper and electronic medical records, and statistical analysis conducted using Stata Version 13. Descriptive and bivariate analyses were used to determine statistical significance at 95% confidence interval (CI)
Results: A total of 1,576 attritions occurred during this period; 803 (51%) TO, 654 (42%) LTFU and 117 (7%) died with a median duration on ART of 8 months (0-199 months). The majority were female 1,121(71%) and aged 25-49 years 1,117 (71%). Overall, 74% of attritions were from the facility of ART initiation, while 26% transferred-in (TI) on ART. Odds of attrition among TI were 6.2 times

(CI: 5.4-7.1) more than if started on ART at the facility. Compared to adults >25 years, the odds of attrition among 0-9, 10-19 and 20-24 years was 1.6 (CI: 1.2-2.1), 1.9 (CI: 1.4-2.4) and 2.2 (CI: 1.8-2.6), respectively. Compared to those on ART for 0-12 months, odds of attrition for those on ART 13-24 months and >24 months was 0.39 (CI 0.34-0.45) and 0.21 (CI: 0.18-0.23) respectively. VL suppression were significantly lower amongst attritions, regardless of reason for attrition; Odds Ratios 0.32 (CI: 0.24-0.42), 0.40 (CI: 0.27-0.60) and 0.18 (CI: 0.09-0.38) among TO, LTFU and dead respectively

Conclusion: In a Kenyan urban population, age, being a transfer-in and duration on ART were strong predictors of attrition. Attritions had lower VL uptake and viral suppression rates compared to active patients. Patients transferring-in on ART had particularly poor outcomes suggesting vulnerabilities that should be considered in their care. The process of patient transfer also merits review

1093 TIME TO ART INITIATION IN KENYA, 2003-2013

Kenneth Masamaro[1], Jacques Muthusi[1], Maureen Kimani[2], Irene Mukui[2], Evelyne Ngugi[1], George Mgomella[1], Tai Ho Chen[1]

[1]US CDC Nairobi, Nairobi, Kenya, [2]Ministry of Health, Nairobi, Kenya

Background: Scale up of antiretroviral treatment (ART) in Kenya included three major guideline changes during 2003–13, prior to adoption of ART eligibility for all HIV-infected persons in 2016. We hypothesize that ART scale up reduced delays in ART initiation for eligible patients.

Methods: We conducted a retrospective chart review of HIV-infected patients aged ≥15 years enrolled in 50 health facilities in Kenya with ≥50 adults on ART during 2003–13. Primary outcomes included proportion of eligible patients with delayed ART initiation (defined as ART initiation >1month after enrolment) and median time to ART initiation. Guideline periods (AP) were adjusted to include a six month implementation period: Jan 2003–Jun 2006 (AP1, with ART recommended for patients with CD4 count <200 cells/mm^3), Jul 2006–Dec 2010 (AP2, ART for CD4 <250), and Jan 2011–Sep 2013 (AP3, ART for CD4 <350). We calculated weighted proportions and 95% confidence intervals (95% CI) as well median and inter-quartile range (IQR). We used Pearson chi-square to test for differences in proportion and Kruskal-Wallis statistics to test differences in the distribution of time to ART.

Results: Of 3152 sampled patients, 2103 (66.7%) were women; median age at enrolment was 36.5 years (IQR 30.6, 44.3) for men and 31.5 years (IQR 25.4, 38.8) for women. Among this cohort, 1624 (51.5%) patients were eligible for ART initiation at time of enrolment. During AP1, 65/184 of eligible patients (35.0%, 95% CI 27.3–42.8%) were started on ART <1 month after enrolment compared to 305/847 (36.7%, 95% CI 31.7–41.8%) and 271/593 (44.3%, 95% CI 37.9–50.7%) in AP2 and AP3, respectively. Median days from enrolment to ART initiation in eligible patients were 75 (IQR 21, 271), 56 (IQR 20, 229), and 40 (IQR 15, 179) in periods AP1, AP2, and AP3, respectively (p<0.001). Patients in national referral facilities were less likely to have delayed ART initiation than those in lower tier facilities during AP3, but not in earlier guideline periods. Patients with opportunistic infections or recent TB diagnosis were less likely to have delayed ART initiation.

Conclusion: Median time from enrolment to ART initiation decreased during successive guideline periods from 2003–2013. However, most patients eligible for ART at enrolment into HIV care experienced delays (≥1 month) in ART initiation during 2003–13 in Kenya. Treatment programs should continue to monitor for and address delays in ART initiation.

1094 YOUTH-FOCUSED CARE IN AN ADULT CLINIC IMPROVES RETENTION FOR YOUNG ADULTS WITH HIV

David C. Griffith[1], Shanna Dell[1], Jeremy Snyder[1], Samantha Greenblatt[2], Jeanne C. Keruly[1], Allison Agwu[1]

[1]Johns Hopkins University, Baltimore, MD, USA, [2]Johns Hopkins Hospital, Baltimore, MD, USA

Background: Young adults with HIV (YAHIV) are less likely to be retained in care or achieve viral suppression when seen in adult clinics. We assessed outcomes of YAHIV newly entering or transitioning from pediatric care into a youth-focused care model embedded in an adult HIV clinic.

Methods: The Accessing Care Early (ACE) program for YAHIV is embedded in a large adult HIV clinic. Providers are internal medicine/pediatrics trained; the support team includes a nurse, social worker, and peer navigator. Eligibility for ACE includes age 18-30 years with ≥1 criteria: transfer from pediatric care, mental illness, substance abuse, or known adherence issues. Ineligible patients receive standard of care (SOC) in the general adult clinic. We performed a retrospective analysis of patients 18-30 years old entering ACE vs SOC from 2012-2014. Multivariable logistic regression assessed retention, HIV viral suppression (VS) < 200 copies/mL, and the association between clinical services utilization (nurse visits and telephone calls, social work visits, psychiatry visits, and peer navigator communication) and retention and VS.

Results: 137 patients entered care (2012-2014), 61 ACE and 76 SOC. In ACE 23% had perinatal HIV vs 3% in SOC; 39% of ACE transitioned from pediatric care compared to 5% in SOC. ACE YAHIV were more likely to have substance abuse, mental health disorder, and less education. Overall ACE YAHIV were less likely to be lost to follow up compared to SOC (16% vs. 37%, p<0.01). At 24 months 49% in ACE vs. 26% in SOC met the retention measure, (P<0.01). Adjusting for age, gender, race, HIV risk, viral load, CD4, mental health, and substance abuse, ACE was associated with retention in care (AOR 3.26 [1.23-8.63]). For those who met the retention measure, 60% (15/25) of ACE versus 89% (16/18) of SOC were virally suppressed (AOR 0.63 [0.35-1.14]). Adjusting for ACE vs. SOC, more frequent social work visits and nurse phone calls was associated with retention. Appointments were less likely to be missed if peer navigator confirmed via a bi-directional communication (OR 2.69 [1.64-4.42]).

Conclusion: The youth-focused ACE program successfully identified YAHIV at high risk for attrition and viremia. Despite comprising higher risk YHIV, ACE had better retention compared to SOC for YAHIV in an adult clinic. Improved retention did not to lead to improved VS compared to the SOC, underscoring the challenges with adherence and need for additional interventions to optimize VS for YAHIV.

Table: Unadjusted and adjusted logistic regression of retention in care at 24 months using the U.S. Health and Human Services Health Resources and Services Administration (HRSA) HIV/AIDS Bureau Performance Measure for HIV medical visit frequency (one medical visit in each 6-month period of a 24 month period with a minimum of 60 days between the first medical visit in the prior 6-month period and the last medical visit in the subsequent 6-month period) and virologic suppression defined as HIV-1 RNA < 200 copies/mL.

	Retention in Care		Virologic suppression	
Variable	**Unadjusted OR (95% CI)**	**Adjusted AOR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted AOR (95% CI)**
ACE clinic	**2.67 (1.23-5.76)**	**3.26 (1.23-8.63)**	**0.56 (0.32-0.97)**	0.63 (0.35-1.14)
18-25 years	0.56 (0.26-1.19)	0.66 (0.27-1.60)	1.13 (0.65-1.97)	1.21 (0.66-2.22)
Black Race	0.66 (0.27-1.61)	0.47 (0.17-1.32)	0.67 (0.32-1.38)	0.62 (0.30-1.27)
Risk				
Heterosexual	1.0(ref)	1.0(ref)	1.0(ref)	1.0(ref)
MSM	1.07 (0.41-2.73)	5.40 (0.92-31.75)	1.87 (0.93-3.73)	1.98 (0.62-6.31)
Perinatal	1.42 (0.37-5.37)	1.65(0.26-10.21)	1.76 (0.60-5.18)	1.47 (0.35-6.08)
Other	0.76 (0.12-4.70)	0.79 (0.08-7.38)	0.83 (0.15-4.45)	0.41 (0.09-2.02)
Gender*				
Male	1.0(ref)	1.0(ref)	1.0(ref)	1.0(ref)
Female	1.76 (0.74-4.23)	**5.70 (1.07-30.21)**	0.50 (0.25-1.02)	0.85 (0.26-2.80)
Transgender	--	--	0.27 (0.03-2.09)	0.48 (0.07-3.16)
CD4 Baseline				
<200	1.0(ref)	1.0(ref)	1.0(ref)	1.0(ref)
200-349	0.60 (0.20-1.81)	0.43 (0.11-1.56)	0.93 (0.44-1.94)	0.71 (0.32-1.56)
350-499	0.85 (0.28-2.58)	0.62 (0.18-2.20)	1.71 (0.79-3.69)	1.45 (0.63-3.36)
>500	0.79 (0.40-2.13)	0.48 (0.14-1.61)	**2.76 (1.33-5.75)**	**2.50 (1.16-5.34)**
Viral load at entry <200 copies/mL	0.99 (0.43-2.27)	0.81 (0.27-2.36)	**3.07 (1.50-6.32)**	**3.33 (1.30-8.57)**
Mental Health Disorder	1.43 (0.67-3.00)	0.93 (0.37-2.32)	0.59 (0.34-1.02)	0.64 (0.35-1.22)
Substance Abuse	1.06 (0.50-2.24)	0.83 (0.33-2.01)	**0.50 (0.29-0.87)**	**0.50 (0.27-0.90)**

*no transgender retained, omitted from retention in care logistic regression. ACE=access care early; MSM=male-to-male sex; CD4 measured in cells/mm^3; viral load measured in copies/mL.

1095 CAN FOOD HELP RETENTION IN HIV CARE: A COHORT STUDY OF ADULTS INITIATING ART IN HAITI

Julie Reiff[1], Stanislas Galbaud[2], Akanksha Dua[1], Jean Edouard Mathon[2], Patrice Joseph[2], Adias Marcelin[2], Pierrot Julma[2], Serena Koenig[3], Pierre Cremieux[1], Jean W. Pape[2], Margaret McNairy[4]

[1]Analysis Group, Inc, Boston, MA, USA, [2]GHESKIO, Port-au-Prince, Haiti, [3]Brigham and Women's Hospital, Boston, MA, USA, [4]Weill Cornell Medicine, New York, NY, USA

Background: Attrition from HIV care is highest in the first 6 months after initiation of antiretroviral therapy (ART) in resource-poor settings. Food was distributed to adults after ART initiation for 6 months at GHESKIO in Haiti, with the goal to improve retention in care. We evaluated the association of food with early retention in care.

Methods: This retrospective observational cohort study included routinely collected data from HIV-infected, non-pregnant adults ≥ 18 years who initiated ART from March-December 2016. During this time, food was distributed in monthly packages of 10 lb rice, 5 lb beans, 1 litre cooking oil, 3 pasta boxes, 3 tomato paste cans, and 4 milk cans for 6 months per patient. Early retention in

care was defined as a clinic visit 3-9 months after ART initiation and compared between patients who picked up food vs patients who did not pick up food. Differences in demographics were compared using Wilcoxon and Chi-Square tests. Logistic regression was used to examine the effect of food pick-up on retention, controlling for age, gender, province, weight and CD4 count.

Results: 1,909 patients initiated ART and were eligible for food during the study period. 492 patients voluntarily picked up food (case cohort) and 1,417 did not (control cohort). Reasons for not picking up food were inconvenient wait times, unavailable food on day of HIV clinic, disinterest, and lack of knowledge of food availability. Cases were older (39.0 vs 37.1 years), weighed less (59.0 vs 61.2 kg), and more likely to be female (61.6% vs 55.9%) compared to controls ($p<0.001$). Residence (87% Port-au-Prince), annual income (77% ≤$1/day), CD4 count (mean 445 cells/uL), and ART regimen (97% 3TC+TDF+NVP/EFV) were not significantly different between the cohorts. Median time to first food pick-up after ART initiation was 14 days [IQR 12, 59], median time between pick-ups was 30 days [IQR 2, 64], and median number of pick-ups was 5 packages. Early retention in care was 86% in cases vs 67% in controls, with an adjusted OR 2.81 [95% CI: 2.05, 3.84]. There is a significant difference in the likelihood of being retained in care seen at ≥ 4 food pick-ups [Table 1].

Conclusion: Among HIV patients who newly initiated ART, there was a positive association between receiving food and early retention in HIV care. Causality is not established and the effect of longer term retention must be evaluated. However, these positive initial results suggest time-limited interventions, including food, may reduce early attrition in HIV care.

Table 1. Comparison of early retention in HIV care between ART patients who received food after ART initiation.

	Enrolled (N=492)			Control (N=1,417)		P-Value
Retained	421 (85.57%)			972 (68.60%)		<0.001 *
	Unadjusted Logistic Regression Model			Adjusted Logistic Regression Model		
	Odds Ratios (95% CI)		P-Value	Odds Ratios (95% CI)		P-Value
Retained	2.71	(2.06, 3.58)	<0.001 *	2.81	(2.05, 3.84)	<0.001 *
Dose of food (ref: 0 pick-ups)						
1 food pick-up (N = 66)	1.70	(0.93, 3.10)	0.083	1.56	(0.79, 3.10)	0.202
2 food pick-ups (N = 37)	0.60	(0.31, 1.16)	0.130	0.67	(0.31, 1.46)	0.314
3 food pick-ups (N = 34)	0.96	(0.46, 1.98)	0.906	0.95	(0.44, 2.04)	0.888
4 food pick-ups (N = 45)	2.49	(1.10, 5.61)	0.028 *	2.87	(1.11, 7.43)	0.030 *
5 food pick-ups (N = 93)	5.62	(2.58, 12.25)	<0.001 *	7.84	(2.83, 21.71)	<0.001 *
6 or more food pick-ups (N = 217)	5.75	(3.41, 9.69)	<0.001 *	5.42	(3.09, 9.50)	<0.001 *

1096 HIV CASCADE OF CARE IN GREECE: USEFUL INSIGHTS FROM ADDITIONAL STAGES

Giota Touloumi[1], Georgia Vourli[1], Vasileios Paparizos[1], Athanassios Skoutelis[2], Simeon Metallidis[3], Panagiotis Gargalianos[1], Antonios Papadopoulos[1], Maria Chini[4], Nikolaos Sipsas[1], Mina Psychogiou[1], Georgios Chrysos[5], Helen Sambatakou[1], Charalambos Gogos[6], Dimitra Paraskeva[7], Georgios Nikolopoulos[8]
[1]University of Athens, Athens, Greece, [2]Evaggelismos General Hospital, Athens, Greece, [3]Aristotle University of Thessaloniki, Thessaloniki, Greece, [4]Red Cross Athens General Hospital, Athens, Greece, [5]Tzaneio General Hospital of Piraeus, Piraeus, Greece, [6]University of Patras, Patras, Greece, [7]Hellenic Center of Disease Control and Prevention, Athens, Greece, [8]University of Nicosia, Nicosia, Cyprus

Background: Aiming to HIV infection elimination, UNAIDS set the 90-90-90 target by 2020. We aimed to construct a six-stages HIV Cascade of Care (CoC) in Greece (overall and by risk group) along with qualitative indicators, to depict the current situation towards the UNAIDS goal and to assess risk group and stage-specific weaknesses.

Methods: The CoC included: i) number of people living with HIV (PLHIV) by the end of 2013; ii) proportion of PLHIV ever diagnosed; iii) proportion of diagnosed linked to care iv) proportion of linked who ever initiated ART; v) proportion of treated retained in care vi) proportion of the retained in care who are virally suppressed (≤200 copies/mL) at last visit (01/07/2012-31/12/2013)]. It combined surveillance data from the Hellenic Center of Disease Prevention and Control and the AMACS HIV seropositive cohort study. The number of PLHIV was estimated using back-calculation models. The interval from seroconversion (SC) to diagnosis was estimated based on a recently published method while from diagnosis to treatment initiation based on the AMACS.

Results: 14147 PLHIV were in Greece at the end of 2013; of these, 78.4% were diagnosed; of the diagnosed, 86% were linked to care; 78.5% of those linked initiated ART; 86.4% of the ever treated group were retained on care; and of these, 87.1% were virally suppressed (Table). Overall, 42.6% of PLHIV were virally suppressed. The median time from HIV SC to diagnosis was 3.89 years (IQR: 2.38-6.23) showing declining trends from 1996 to around 2010 and small increases thereafter. The percentage of diagnosed was lower among MSW (Men/women who have sex with Women/men) compared to that in MSM (Men sex with Men) or PWID (People Who Inject Drugs), and MSW had also the longest time interval from SC to diagnosis. Most MSM were linked to care, while a substantial proportion of PWID were not. When linked to care, 2/3 of PWID initiated ART. However, when PWID started ART, they remained on care in similar proportions to MSM. Unlike PWID, a high proportion of the MSM and MSW who remained on care achieved viral suppression.

Conclusion: At the end of 2013, there were weaknesses in the HIV CoC in Greece, which also differed across risk groups. Targeted interventions are necessary focusing on early diagnosis and timely linkage. A by risk group 6-stage CoC accompanied by quality indicators provide useful public health data and should be implemented when possible.

Table. HIV Cascade of Care in Greece, overall and by risk group.

Group	All N (%)	MSM N (%)	PWID N (%)	MSW N (%)
PLHIV	14147	5832	1523	3165
Diagnosed	11096 (78.4)	5133 (88.0)	1325 (87.0)	2454 (77.5)
Linked to care	9544 (86.0)	4988 (97.2)	1070 (80.8)	2291 (93.4)
Ever treated	7488 (78.5)	4147 (83.1)	699 (65.3)	1991 (86.9)
Retained on care	6466 (86.4)	3692 (89.0)	611 (87.4)	1623 (81.5)
Virally suppressed	5632 (87.1)	3241 (87.8)	438 (71.7)	1441 (88.8)
Virally suppressed (of PLHIV, %)	42.6	59.1	31.3	48.9
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Seroconversion to diagnosis time (years)	3.89 (2.38-6.23)	3.46 (1.80-5.21)	4.20 (2.62-6.68)	4.67 (3.19-7.30)
Diagnosis to ART initiation time (months)	6.29 (1.21-38.72)	8.62 (1.40-43.01)	9.67 (2.72-32.55)	2.59 (0.91-25.11)

1097 IMPACT OF SYSTEMS NAVIGATION AND COUNSELING ON ART, SUT AND DEATH IN PWID: HPTN 074

William C. Miller[1], Irving Hoffman[2], Brett Hanscom[3], Tran V. Ha[2], Kostyantyn Dumchev[4], Zubairi Djoerban[5], Scott M. Rose[6], Kathryn E. Lancaster[1], Vivian Go[2], Sarah Reifeis[2], Estelle Piwowar-Manning[7], Carl A. Latkin[7], David Metzger[8], David Burns[9]
[1]The Ohio State University, Columbus, OH, USA, [2]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [4]Ukrainian Institute on Public Health Policy, Kyiv, Ukraine, [5]University of Indonesia, Jakarta, Indonesia, [6]FHI 360, Durham, NC, USA, [7]Johns Hopkins Hospital, Baltimore, MD, USA, [8]University of Pennsylvania, Philadelphia, PA, USA, [9]NIAID, Bethesda, MD, USA

Background: People who inject drugs (PWID) experience high HIV incidence, poor access to HIV care, and high mortality in worldwide. Interventions to engage HIV-infected PWID in care and reduce transmission are needed. We report the impact of an integrated systems navigation and psychosocial counseling intervention on HIV and substance use outcomes.

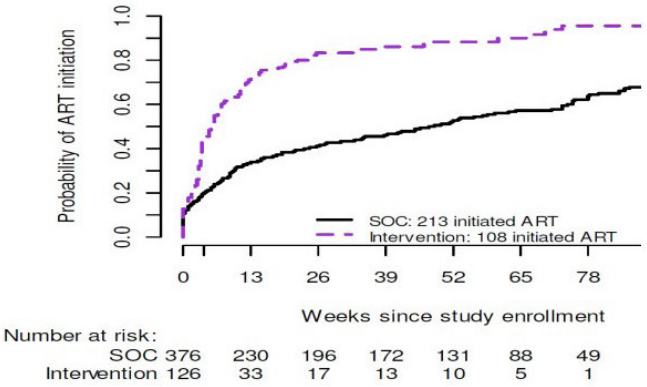
Methods: HPTN 074 is a randomized, controlled vanguard study among PWID conducted in Ukraine, Indonesia, and Vietnam. HIV-infected index participant eligibility included age 18-60 years; active injection drug use; viral load ≥1,000 copies/mL, CD4 >50cells/mm^3, and ability to identify and enroll at least 1 HIV-uninfected injection partner. Up to 5 HIV-uninfected active injection partners were enrolled per index. Index PWID were randomly assigned to standard of care (SOC) or a systems navigation and psychosocial counseling intervention (SNPC). Session number and topics varied based on indexes' needs. Antiretroviral therapy (ART) and substance use treatment (SUT) referrals were made to existing local services. Outcome measures included ART uptake (indexes only), SUT uptake, mortality, and HIV incidence (partners only).

Results: Overall, 502 indexes and 806 partners were enrolled over 15 months and followed for 12-24 months. Among indexes, 85% were men; most women enrolled in Ukraine. Median age was 35 years. Retention was high at week 52 (86% index; 75% partners). At week 26, SNPC indexes were twice as likely to report ART use as compared to SOC (77% vs 38%, risk ratio (RR)=2.0, [95% CI: 1.7, 2.5]; Figure 1). The effect persisted at week 52 (77% vs 49%; RR=1.6 [CI: 1.3, 1.8]). Among SNPC indexes, SUT uptake was increased (hazard ratio (HR)=2.7 [CI: 1.8, 4.1]) and mortality was reduced by half (mortality rate=5.6/100 person-years (PY) vs 12.1/100 PY, HR=0.47 (CI: 0.22, 0.90). The survival benefit was also significant among SNPC partners (HR=0.17 (CI: 0.01, 0.84). Incident HIV

infections among partners occurred only in the SOC arm (SNPC=0 cases/215.6 PY; SOC=7 cases/683.6 PY).

Conclusion: Facilitating ART and SUT referrals through systems navigation, combined with flexible counseling, doubled ART and SUT uptake. Mortality among HIV-infected PWID and their HIV-uninfected partners was reduced. HIV incidence among uninfected partners of indexes receiving the intervention may have been reduced, but the overall number of incident infections was low.

Figure 1: Cumulative probability of ART initiation among indexes (n=502)



1098 TRENDS IN UNSUPPRESSED HIV RNA AFTER LINKAGE TO CARE AMONG KEY POPULATIONS

Fidel A. Desir[1], Catherine R. Lesko[1], Richard D. Moore[1], Michael A. Horberg[2], Peter F. Rebeiro[3], Michael John Gill[4], Mari Kitahata[5], Michael J. Silverberg[6], Julie H. Levison[7], Marina Klein[8], Angel Mayor[9], Amy C. Justice[10], Keri N. Althoff[1]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [3]Vanderbilt University, Nashville, TN, USA, [4]University of Calgary, Calgary, AB, Canada, [5]University of Washington, Seattle, WA, USA, [6]Kaiser Permanente Northern California, Oakland, CA, USA, [7]Harvard University, Cambridge, MA, USA, [8]McGill University Health Centre Research Institute, Montreal, QC, Canada, [9]Universidad Central del Caribe, Bayamon, Puerto Rico, [10]VA Connecticut Healthcare System, West Haven, CT, USA

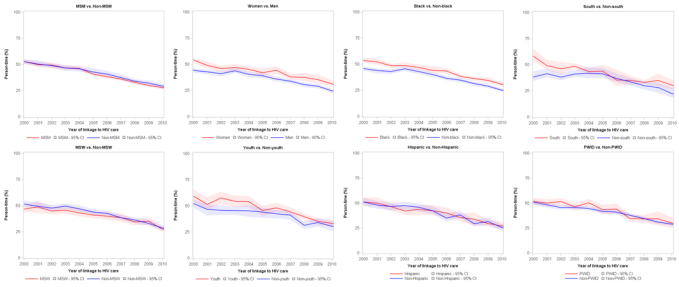
Background: Maintaining consistent engagement in care, antiretroviral therapy (ART) use, and viral suppression (VS) after linkage to HIV care among persons with HIV (PWH) is a cornerstone of HIV transmission prevention. The US National HIV/AIDS Strategy set forth goals to improve HIV care in PWH from specific key populations, including men who have sex with men (MSM). Our objective was to examine trends in unsuppressed HIV RNA among PWH from key populations newly linked to care.

Methods: We studied adult PWH from 8 key populations who successfully linked to care (i.e., ≥2 HIV care visits in ≤12 months) for the first time between 2000-10 in 11 US clinical cohorts in the NA-ACCORD: MSM, men who have sex with women (MSW; men with known transmission risk who did not report male-to-male sexual contact), women, young PWH (ages 18-24), blacks, Hispanics, PWH living in the South (PLS), and persons who inject drugs (PWID). PWH were followed from HIV care linkage until 5 years after linkage, 31 December 2014, or death, whichever occurred first. We added and subtracted cumulative incidence curves for ART initiation, disengagement from care (i.e., not having ≥1 HIV care visit, CD4 count, or HIV RNA measure in ≤12 months), re-engagement in HIV care, VS (HIV RNA ≤200 c/mL), and loss of VS. We then integrated the area between the curves to estimate the mean person-time spent in care but not on ART or virally suppressed (i.e., unsuppressed HIV RNA) in the first 5 years after linkage to care in each key population and its corresponding counter-population (e.g., MSM vs. non-MSM), by year of linkage to care. As appropriate for each key population, analyses were adjusted for age, sex, race, HIV transmission risk, site, CD4 count, and HIV RNA at linkage.

Results: A total of 28,839 PWH (54% MSM, 20% MSW, 22% women, 44% black, 13% Hispanic, 12% PWID, 47% PLS, and 9% youth) were included. The average percentage of person-time spent with unsuppressed HIV RNA decreased with increasing year of linkage in all groups (Figure). Women, blacks, PLS, and youth generally spent more time with unsuppressed HIV RNA than their respective counter-group. This disparity remained statistically significant with increasing year of linkage among women and blacks.

Conclusion: To reduce the time spent with unsuppressed HIV RNA after linkage to care, interventions that jointly improve consistent engagement in care, ART use, and VS among PWH receiving care are needed, particularly for women and blacks.

Figure. Average percentage of person-time spent with unsuppressed HIV RNA in the first 5 years after linkage to care, NA-ACCORD, 2000-2010.



Abbreviations: MSM, male-to-male sexual contact; MSW, men who have sex with men; PWID, persons who inject drugs; CI, confidence interval
95% CIs were calculated using the 2.5th and 97.5th percentiles of 100 non-parametric bootstrap estimates based on unrestricted random samples from the data.

1099 OUTCOMES OF PATIENTS LOST TO FOLLOW-UP IN AFRICAN ART PROGRAMS: MULTI-COHORT STUDY

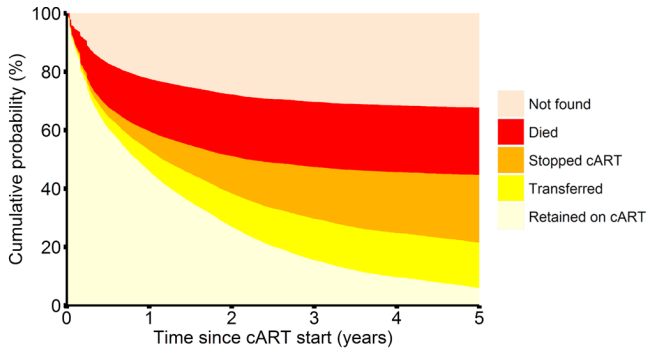
Frédérique Chammartin[1], Kathrin Zürcher[1], Hannock Tweya[2], Paula Braitstein[3], Ralf Weigel[4], Kathryn Chu[5], Elvin Geng[6], Agnes Kiragga[7], Charles Kouanfack[8], Cristina Ardura-Garcia[4], Takuma Kato[9], Hilary Gunguwo[10], James R. Hargreaves[11], **Matthias Egger**[1]
[1]University of Bern, Bern, Switzerland, [2]Lighthouse Trust Clinic, Lilongwe, Malawi, [3]University of Toronto, Toronto, ON, Canada, [4]Liverpool School of Tropical Medicine, Liverpool, UK, [5]MSF, Johannesburg, South Africa, [6]University of California San Francisco, San Francisco, CA, USA, [7]Makerere University, Kampala, Uganda, [8]Central Hospital of Yaoundé, Yaounde, Cameroon, [9]National Center for Global Health and Medicine, Tokyo, Japan, [10]Mpilo Central Hospital, Bulawayo, Zimbabwe, [11]London School of Hygiene & Tropical Medicine, London, UK

Background: Following the massive scale up over the past 10 years of combination antiretroviral therapy (cART) in sub-Saharan Africa, retention in care has emerged as an important threat to reaching the UNAIDS 90-90-90 targets to end the HIV epidemic. We examined outcomes of patients who started cART but were subsequently lost to follow-up (LTFU) in African ART programs.

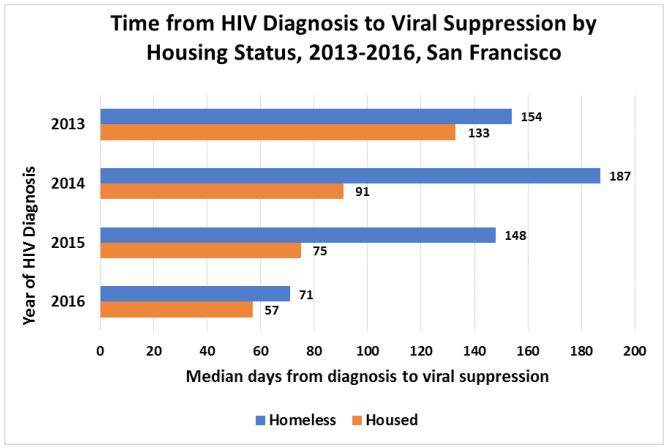
Methods: Collaborative multi-cohort analysis. Longitudinal studies of patients who started ART for their own health in programs in sub- Saharan Africa, were LTFU and actively traced to establish their vital status were eligible. We searched PubMed, EMBASE and LILACS to identify eligible studies and asked authors to participate. We analyzed outcomes 'died', 'stopped cART', 'transferred to other clinic' and 'not found' in a competing risk framework using non-parametric cumulative incidence functions. We used a proportional hazards model for the sub-distribution of competing risks (Fine & Gray 1999) to assess associations of patient characteristics with outcomes.

Results: Ten studies contributed data on 8,529 patients who started cART in one of seven countries (Cameroon, Kenya, Malawi, Mozambique, Uganda, Zambia, Zimbabwe). Most patients were adults (8,329; 97.7%) and from one of three treatment programs in Malawi (5472; 64.2%). The median CD4 count at the start of cART was 120 cells/µl (interquartile range [IQR] 46-212), the median year of starting cART was 2007 (IQR 2006-2009). Five years after ART initiation, an estimated 23.1% (95% CI 22.1-24.0%) had died, 23.1% (22.2-24.1%) were alive but had stopped cART, 15.5% (14.7-16.3%) had transferred to another clinic and 32.3% (31.3-33.3%) could not be found (Figure). Mortality was associated with male sex and lower baseline CD4 count, stopping cART with higher CD4 count and transfer with female sex and less advanced clinical stage. Death, stopping cART and unsuccessful tracing were all associated with shorter duration of cART. Unsuccessful tracing was also associated with younger age.

Conclusion: Mortality is high among patients LTFU. It is essential to account for outcomes of patients LTFU for unbiased assessments of program outcomes and UNAIDS targets in sub-Sahara Africa. Early tracing of patients LTFU should be a priority.



Not found	22.4	27.8	30.3	31.6	32.3
Died	17.9	21.1	22.3	22.8	23.1
Stopped cART	6.5	12.8	17.7	20.8	23.1
Transferred	7.2	11.4	14.2	15.1	15.5
Retained on cART	46.0	26.9	15.5	9.6	6.0



1100 IMPROVEMENT IN HIV CARE INDICATORS AMONG THE HOMELESS IN SAN FRANCISCO

Susan Scheer, Ling Hsu, Darpun Sachdev, Oliver Bacon, Stephanie E. Cohen, Albert Y. Liu, Jennie C. Chin, Susan P. Buchbinder
San Francisco Department of Public Health, San Francisco, CA, USA

Background: Despite significant declines in new HIV diagnoses and improvement in HIV-related care indicators in San Francisco (SF), health disparities persist particularly among homeless persons living with HIV (PLWH). City-wide linkage and case management programs seek to improve outcomes across the continuum of HIV care. We measured HIV care indicators comparing those who were homeless to those housed in SF.

Methods: The SF HIV surveillance registry was used to determine linkage to care and viral suppression among PLWH by housing status. Homelessness was defined as a medical chart notation of homeless or living in a homeless shelter. Temporal trends from diagnosis to viral suppression by housing status for cases diagnosed in 2013-2016 were measured. Care was defined as having a CD4+ cell count or HIV viral load test. Viral suppression (VS) was defined as HIV RNA<200 c/mL.

Results: In 2015, 29 (10%) of 296 newly HIV diagnosed cases were homeless. Linkage to care within one month and VS within 12 months of diagnosis were lower among homeless compared to housed persons; 66% vs 79% (p=.10) and 59% vs 79% (p=.02), respectively. Among 12,769 PLWH in 2015 with last known residence in SF, 301 (2%) were known to be homeless. Compared to all persons diagnosed in 2006-2016, homeless persons were more likely to be cis women (14% vs 7%, p<.0001), trans women (10% vs 3%, p<.0001), African American (27% vs 14%, p<.0001) or a person who injects drugs (58% vs 20%, p<.0001); 35% were <30 years old. In 2015, homeless PLWH were less likely than the housed to have had ≥1 care visit (52% vs 81%, p<.0001) or to have VS (31% vs 74%, p<.0001). In 2015, 30 homeless PLWH who were not-in-care enrolled in LINCS (a short-term intensive case management program); 27 (90%) were re-linked to care within 3 months and 77% were virally suppressed within 12 months. In 2013-2016, city-wide rapid linkage to care was scaled up; median days from diagnosis to viral suppression were greater for homeless than housed cases each year (Figure) but decreased significantly over time (p=.04).

Conclusion: Although a small proportion of all SF PLWH, homeless persons had poorest linkage to care and VS. Time from diagnosis to VS has significantly improved over time for the homeless. Scale–up of city-wide rapid linkage to care and intensive case management programs are beginning to show progress in decreasing disparities among homeless PLWH, our most vulnerable population.

1101LB IMPACT OF SERVICE INTEGRATION ON HIV TESTING UPTAKE AMONG KEY POPULATIONS IN INDIA

Sunil S. Solomon[1], Suniti Solomon[2], Allison M. McFall[1], Aylur K. Srikrishnan[2], Santhanam Anand[2], Pachamuthu Balakrishnan[2], Elizabeth Ogburn[1], Lawrence Moulton[1], Muniratnam S. Kumar[2], David D. Celentano[1], Gregory M. Lucas[1], **Shruti H. Mehta**[1]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]YR Gaitonde Center for AIDS Research and Education, Chennai, India

Background: Stigma and fragmented services impede HIV care access among people who inject drugs (PWID) and men who have sex with men (MSM). We evaluated the impact of integrated care centers (ICCs) in a cluster randomized trial in India. ICCs provided rapid HIV testing, linkage to care and treatment support for HIV and risk reduction services (e.g., opioid therapy, syringe exchange, condoms and sexually transmitted infection treatment).

Methods: We randomized 22 cities (12 PWID, 10 MSM) to ICC or usual care (UC) at a 1:1 ratio. ICC services are supported by the Indian AIDS program and were available in UC sites, but not in integrated venues. We assessed outcomes with cross-sectional, respondent-driven sampling (RDS) surveys in each city, before (2012-13) and 2 years after ICC implementation (2016-17). Our primary outcome was self-reported recent (prior 12 months) HIV testing in ICC vs. UC cities at evaluation, adjusted for baseline testing and stratum. Because we used RDS, our trial evaluated the ability of ICCs to affect outcomes at the community level, irrespective of participants' actual ICC exposure. We also collected biometric data to compare outcomes in RDS participants at ICC sites who did and did not visit the ICC. Population ICC exposure was calculated as the proportion in the evaluation RDS who visited the ICC based on biometric data.

Results: During the intervention phase the 11 ICCs tested a median (range) of 1309 (829 - 2191) clients for HIV. 21,714 participated in the evaluation RDS. Compared with UC cities, ICC cities had 31% higher prevalence of recent HIV testing at evaluation (prevalence ratio [PR]: 1.31; 95% CI: 0.95, 1.81; Figure, Panel A). Moreover, those in ICC cities who had visited the ICC were significantly more likely to report recent HIV testing than those in UC cities (PR: 2.66; 95% CI: 2.19, 3.24). Among the ICC cities, ICC population exposure ranged from 7 to 55% and higher exposure was significantly associated with greater increase (from baseline to evaluation) in recent HIV testing (Figure, Panel B; p=0.002).

Conclusion: While ICCs provided HIV testing to large numbers of PWID and MSM, they were not associated with a statistically significant increase in recent testing at the community level. Pre-specified analyses showed that exposure to ICCs within the target groups was limited within these populous cities and that the degree of population exposure was strongly correlated with testing rates, suggesting that increased ICC coverage could yield community-level impact.

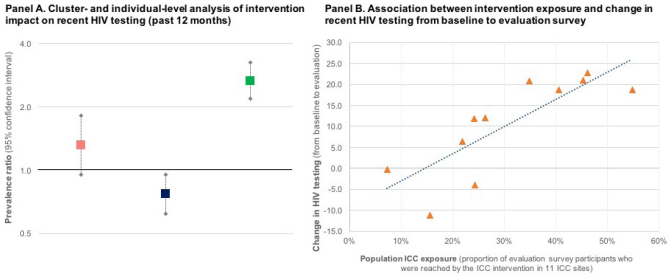


Figure. Effect of integrated HIV prevention and treatment services on HIV testing uptake among MSM and PWID in India: A cluster-randomized trial

1102 SHORT-TERM EFFECTS OF ALTERNATIVE MEDICATION REFILL STRATEGIES IN SOUTH AFRICA

Matthew P. Fox[1], Sophie Pascoe[2], Amy Huber[2], Joshua Murphy[2], Mokgadi Phokojoe[3], Marelize Gorgens[4], **Sydney Rosen**[1], David Wilson[4], Yogan Pillay[3], Nicole Fraser[4]

[1]Boston University, Boston, MA, USA, [2]Health Economics and Epidemiology Research Office, Johannesburg, South Africa, [3]South African National Department of Health, Pretoria, South Africa, [4]World Bank, Washington, DC, USA

Background: Tailoring service delivery to meet the needs of different groups of patients ("differentiated care") has been proposed to improve HIV care and treatment outcomes and reduce costs. We evaluated alternative medication pickup models in the first phase of implementation of South Africa's National Adherence Guidelines (AGL) for Chronic Diseases.

Methods: The AGL has two strategies for streamlining medication pickup: decentralized medication delivery (DMD) and adherence clubs (AC). We conducted a cluster-randomized evaluation in 12 intervention and 12 control health facilities in 4 provinces. We sampled patients who received the intervention at intervention sites or would have been eligible at control sites. We used clinic records to estimate the proportion of patients who picked up medication within four months of enrolling in DMD or an AC. We estimated risk differences (RD) with cluster adjustment using generalized estimating equations. We controlled for baseline differences using difference-in-differences (DiD) by comparing to all patients eligible for AC or DMD prior to AGL implementation (Jan 1, 2015).

Results: For ACs, we included 206 intervention and 212 control subjects. Over half were under age 40 (58%), just above 70% were female, and median ART initiation CD4 count was 268 cells. By randomized group, ACs were associate with a 4.4% (95% CI -0.6% to 6.4%) percentage point increase in initiation. Using the DiD approach, ACs were associated with a 6.7% (95% CI: 3.4% to 10.4%) point increase adjusting for baseline pickup rates (Table) that remained after adjusting for clusters and baseline covariates (RD 7.5%; 95% CI: -1.3% to 16.2%). For DMD, we included 125 intervention and 315 control patients. For DMD we saw no benefit for medication pickup but pickup data were incomplete for DMDs (47% of intervention cohort were missing pickup data). Qualitative data suggest that DMD is popular among health care providers and patients.

Conclusion: Adherence clubs showed a small but significant difference in the proportion of patients who completed medication pickups in their first 4 months of enrollment. If the AC effects translate into higher retention and viral suppression, they could be employed to improve overall ART outcomes. For decentralized medication delivery, data systems have not kept up with practices, making it difficult to determine if there are any benefits. Further experience with DMD and improvements in data flow are needed.

Differences-in-differences analysis for 4-month mediation pick up for those eligible for Adherence Clubs in the period prior to the interventions and during the intervention period

Differences-in-differences					
Medication pick up	**Intervention**	**%**	**Control**	**%**	**Difference**
Pre-intervention period	8223/8713	94%	7039/7241	97%	-2.4% (-3.0% to -1.7%)
Intervention-period	188/206	91%	184/212	87%	4.4% (-0.6% to 6.4%)
Difference in differences					**6.7% (3.4% to 10.4%)**
Difference in differences (Cluster adjusted)*					**6.7% (-2.5% to 16.0%)**
Difference in differences (Cluster and covariate adjusted)*					**7.5% (-1.3% to 16.2%)**

* Analyses are adjusted for clustering by site using a generalized estimating equation with site level clustering and an unstructured correlation matrix

1103 EFFECT OF FAST TRACK INITIATION COUNSELLING ON ART INITIATION IN SOUTH AFRICA

Sophie Pascoe[1], Matthew P. Fox[2], Amy Huber[1], Joshua Murphy[1], Mokgadi Phokojoe[3], Marelize Gorgens[4], **Sydney Rosen**[2], David Wilson[4], Yogan Pillay[3], Nicole Fraser[4]

[1]Health Economics and Epidemiology Research Office, Johannesburg, South Africa, [2]Boston University, Boston, MA, USA, [3]South African National Department of Health, Pretoria, South Africa, [4]World Bank, Washington, DC, USA

Background: In response to suboptimal adherence and retention outcomes, South Africa's National Department of Health introduced National Adherence Guidelines (AGL) for Chronic Diseases. We conducted an evaluation of the AGL and report here the short-term effects of one AGL strategy, Fast Track Treatment Initiation Counselling (FTIC). Under FTIC, patients receive additional counselling but can initiate ART over two visits within one week of eligibility.

Methods: A cluster-randomized evaluation was conducted in 4 provinces at 12 intervention clinics which implemented FTIC and 12 control clinics which delayed implementation of FTIC. Follow up was by passive surveillance using clinical records and electronic databases between 20 June 2016 and 12 May 2017. The primary outcome was ART initiation within 30 days of eligibility for FTIC. We estimated risk differences (RD) and 95% confidence intervals (CI) with adjustment for clustering using generalized estimating equations. We further controlled for baseline differences using a difference-in-differences analysis by comparing to all patients at intervention and control sites eligible for FTIC prior to the intervention being rolled out (Jan 1, 2015 through Dec 31, 2015).

Results: We enrolled 362 FTIC patients in the intervention arm and 368 eligible for FTIC in the control arm (65%< age 40, 61% female, median CD4 224). In crude analyses, FTIC was associated with an increase of less than 1 percentage point in the proportion of patients who initiated ART within 30 days (83% vs 82%, risk difference (RD) 0.5%; 95% CI: -5.0% to 6.0%) (Table). However, differences in 30-day initiation rates existed between arms prior to the intervention period (RD -3.9%; 95% CI: -5.0 to -2.8%). After adjusting for baseline differences, we found a 4% increase in initiation associated with the intervention (RD 4.4%; 95% CI: 0.03% to 8.8%). The difference increased to 6% after adjusting for the cluster randomized design and for baseline covariates (RD 6.3%; 95% CI: -0.6% to 13.3%).

Conclusion: We saw a modest short-term benefit to fast track initiation counselling. In view of the need to add millions of new patients to South Africa's ART program under "treat all," any changes that increase timely uptake of ART can make a valuable contribution to achieving national and global targets.

Effect of Fast Track Initiation Counselling on ART Initiation in South Africa

Differences-in-differences analysis for short-term outcome (ART initiation within 30 days) for those eligible for Fast Track Initiation Counselling cohort in the period prior to the interventions and during the intervention period

* Analyses are adjusted for clustering by site using a generalized estimating equation with site level clustering and an unstructured correlation matrix

Differences-in-differences

3-month ART initiation	**Intervention**	**%**	**Control**	**%**	**Difference**
Intervention-period	298/360	83%	303/368	82%	0.5% (-5.0% to 6.0%)
Pre-intervention period	4719/5293	89%	4611/4956	93%	-3.9% (-5.0% to -2.8%)
Difference in differences					4.4% (0.03% to 8.8%)
Difference in differences (covariate adjusted)*					6.3% (3.0% to 10.0%)
Difference in differences (covariate adjusted and cluster adjusted)*					6.3% (-0.6% to 13.3%)

1104 ART ELIGIBILITY EXPANSION AND TIMELY ART INITIATION: 22-COUNTRY META-ANALYSIS

Olga Tymejczyk[1], Ellen Brazier[1], Constantin T. Yiannoutsos[2], Kara K. Wools-Kaloustian[2], Keri N. Althoff[3], Brenda Crabtree-Ramírez[4], Kinh V. Nguyen[5], Elizabeth Zaniewski[6], François Dabis[7], Jean d'Amour Sinayobye[8], Nanina Anderegg[6], Nathan Ford[9], Radhika Wikramanayake[1], **Denis Nash**[1]

[1]City University of New York, New York, NY, USA, [2]Indiana University, Indianapolis, IN, USA, [3]Johns Hopkins University, Baltimore, MD, USA, [4]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [5]National Hospital for Tropical Diseases, Hanoi, Vietnam, [6]Institute of Social and Preventive Medicine, Bern, Switzerland, [7]University of Bordeaux, Bordeaux, France, [8]Rwanda Military Hospital, Kigali, Rwanda, [9]WHO, Geneva, Switzerland

Background: Over the past decade the World Health Organization has expanded antiretroviral therapy (ART) initiation criteria. The influence of eligibility expansions on the timeliness of ART initiation has not been assessed.

Methods: We examined the influence of eligibility expansions on cumulative incidence of ART initiation (CI ART) at the original site within 6 months of

enrolment in HIV care, using data from 239,311 adult ART-naïve patients at 151 International Epidemiology Databases to Evaluate AIDS (IeDEA) consortium sites in 22 countries where national treatment guidelines changed between 2007-14. We assessed CI ART before and after major eligibility expansions for asymptomatic adults (i.e., to treat persons with CD4≤350 cells/μL and CD4≤500 cells/μL). CI ART was estimated via competing risks regression, with death and pre-ART loss-to-clinic treated as competing events. Random effects meta-regression models were used to estimate absolute changes in CI ART at each site between those enrolling in HIV care prior to ART eligibility expansion and those afterwards.

Results: The crude pooled estimate of change in CI ART within 6 months of care enrolment was +4.3 percentage points (pp) (95% CI: +2.6,+6.0) after eligibility expansion to CD4≤350, from a baseline median CI-ART of 53.7%, and +16.0 pp (95% CI: +14.4,+17.6) after eligibility expansion to CD4≤500, from a baseline median CI-ART of 59.2%. For eligibility expansion to CD4≤350, changes in CI ART were largest at sites where patients had higher baseline median enrolment CD4 counts and at sites with lower baseline levels of CI ART. For eligibility expansion to CD4≤500, changes in CI ART were largest at sites with lower baseline levels of CI ART, and among women and patients <25 years old. For both policy changes, the largest effects were observed among patients newly eligible for treatment (+18.5 pp after expansion to CD4≤350 and +43.3 pp after expansion to CD4≤500), with no change or small improvements among those eligible under prior guidelines.

Conclusion: Timely ART initiation among adults substantially improved after ART eligibility expansion, especially among younger patients and at sites with lower initial levels of CI ART. ART initiation among newly eligible patients with less advanced disease did not appear to negatively affect ART initiation among previously eligible patients with more advanced disease. These findings underscore the utility of ART eligibility expansion as an essential strategy in support of global UNAIDS 90-90-90 targets.

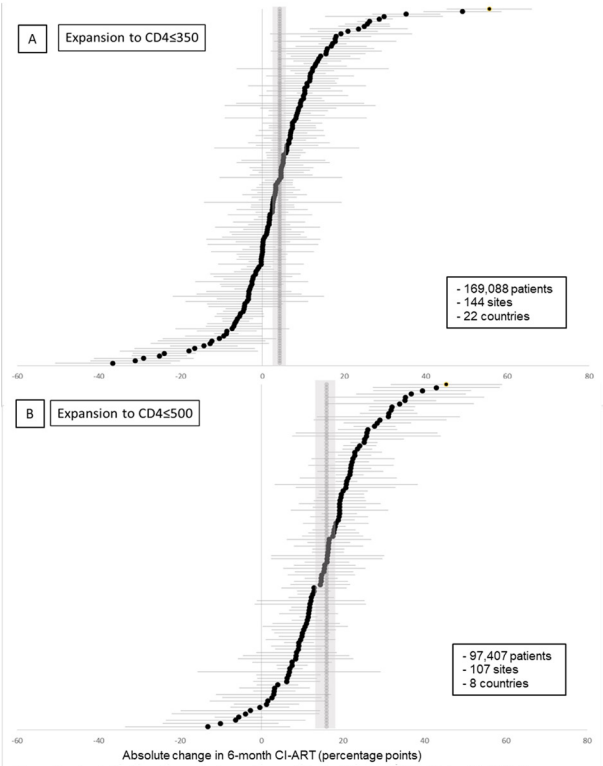


Figure. Site-level absolute changes in 6-month cumulative incidence of ART initiation (CI-ART) after guideline expansions to (A) CD4≤350 and (B) CD4≤500; estimated confidence intervals in gray.

1105 A STREAMLINED ART INITIATION ALGORITHM OF CARE REDUCES TIME TO ART

Izukanji Sikazwe[1], Samuel Bosomprah[2], Jake Pry[2], Mpande Mukumbwa-Mwenechanya[2], Anjali Sharma[2], Paul Somwe[2], Nancy Padian[3], Monika Roy[4], Carolyn Bolton Moore[2], Charles B. Holmes[2], Elvin Geng[4]

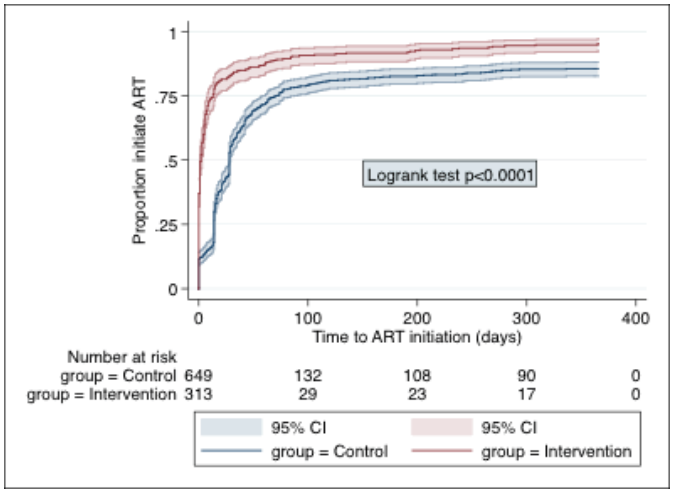
[1]Center for Infectious Disease Research in Zambia, Lusaka, Zambia, [2]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, [3]University of California Berkeley, Berkeley, CA, USA, [4]University of California San Francisco, San Francisco, CA, USA

Background: Multi-step ART initiation algorithms result in loss of patients between eligibility and treatment, thus eroding gains towards the 90-90-90 targets. Although individual randomized trials show improved outcomes with accelerated ART initiation, the success of accelerated ART practices in real world settings is less understood. We evaluated a revised ART initiation approach based on same-day readiness assessment and point of care CD4 assessment, among public facilities in Zambia as compared to standard of care (SOC) procedures including protracted pre-treatment counseling sessions.

Methods: The rapid treatment approach was implemented between March and July 2016 in two rural and two urban public health facilities and compared to 5 comparator sites practicing standard of care (SOC) among ART naïve, treatment eligible patients and followed for 12 months. Demographic and clinical data were abstracted from patient charts. We estimated the average treatment effect on time-to-ART initiation using survival-time inverse-probability-weighted regression adjustment models. The mean survival time was modeled as WeibulL, controlling for sex and WHO stage and treatment assignment as logit with covariates sex, WHO stage, and clinic site.

Results: A total of 962 patients were available for analysis, with 313 exposed to intervention and 649 to SOC groups. Except for sex and WHO stage, there was no difference in age, marital status, level of education or income between the two groups. The median CD4 count was 249 (IQR=133, 394) and the median age was 35 years (IQR=29, 42). The median time-to-ART initiation was 2 days (IQR: 0, 13) in the intervention group compared to 28 days (IQR: 14, 70) in the SOC group, with more frequent same day ART initiation in the intervention group (Figure 1). The average time to ART initiation was 24 days (95%CI: [16, 32]; p<0.0001) less in the intervention (or START) group compared to 40 days (95%CI: [34, 45] in SOC group. This difference was maintained up to one year of follow up.

Conclusion: Rapid ART initiation as part of routine care in public sector facilities can increase both the rate of ART initiation as well as overall completeness of uptake among treatment eligible patients. Ongoing expansion of treatment guidelines to include all persons living with HIV may be able to achieve greatest gains when coupled with rapid ART initiation practices, which should include CD4 determination to identify patients with advanced disease and at risk of increased morbidity and mortality.



1106 SAME-DAY ART INITIATION IN THE SLATE TRIAL IN SOUTH AFRICA: PRELIMINARY RESULTS

Mhairi Maskew[1], **Alana T. Brennan**[2], Matthew P. Fox[2], Willem D. Venter[3], Lungisile Vezi[1], Bruce Larson[2], Isaac Tsikhutsu[4], Margaret Bii[4], Sydney Rosen[2]

[1]Health Economics and Epidemiology Research Office, Johannesburg, South Africa, [2]Boston University, Boston, MA, USA, [3]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [4]KEMRI/Walter Reed Proj, Kericho, Kenya

Background: The World Health Organization recommends "same-day" initiation of ART for patients who are eligible and ready and initiation within 7 days of diagnosis for all patients. Identifying efficient operational procedures for

determining same-day eligibility and readiness is now a priority. The Simplified Algorithm for Treatment Eligibility (SLATE) trial is testing a clinical algorithm that allows nurses to determine eligibility for immediate ARV dispensing at the same clinic visit. We report early results from South Africa.

Methods: SLATE is an individually randomized trial at 3 public outpatient clinics in informal settlements in Johannesburg. Ambulatory patients presenting for any HIV care, including an HIV test, but not yet on ART were enrolled, consented, and randomized to the SLATE algorithm arm or standard care. The SLATE algorithm used a symptom self-report, medical history questionnaire, brief physical examination, and readiness assessment to distinguish between patients eligible for immediate ARV dispensing and those who should have further care, tests, or counseling before starting treatment. Follow up was by passive record review. We report the primary outcome of ART initiation ≤28 days of study enrollment.

Results: From Mar 7-Jul 28, 2017, we enrolled 602 adult, HIV+, non-pregnant patients not yet on ART (median [IQR] age 34 [29-40] and CD4 count 288 [140-487]; 63% female). In the SLATE arm, 149 (50%) were found to be eligible for immediate initiation and were dispensed ARVs at the same visit. The other 50% met one or more algorithm criteria for referral for additional services before initiation, of whom 2/3 (100/149) had TB symptoms. Table 1 reports time to initiation. In the SLATE arm, 83% of patients initiated ≤28 days, compared to 71% in the standard arm (risk difference (RD) [95% CI] 12% [5-19%]; relative risk (RR) 1.16 [1.06-1.28]). Within 7 days, 69% of SLATE arm patients and 39% of standard arm patients had initiated (RD 30% [22-38%], RR 1.75 [1.49-2.07]).

Conclusion: The SLATE algorithm, comprising simplified steps for ART initiation, increased uptake of ART within 28 days by 16% and 7 days by 75%. Nurses were able to implement it in routine care settings without additional equipment or clinical supervision. Longer follow-up is needed to draw conclusions about overall effectiveness, but early results suggest that simpler treatment initiation procedures are feasible and can increase and accelerate ART uptake and reduce the visit burden on patients and facilities.

Table 1: Time to ART initiation by study arm

Outcome	Total (n=602)	Control arm (n=304)	Intervention arm (n=298)	Crude risk difference (95%CI)*	Crude relative risk (95% CI)*
Record traced, outcome ascertained	546 (91%)	273 (90%)	273 (92%)	-	-
Record missing, outcome not ascertained	56 (9%)	31 (10%)	25 (8%)	-	-
Of those with record traced:					
Did not initiate ART within 28 days of enrolment	126 (23%)	79 (29%)	47 (17%)	12% (5-19%)	0.59 (0.43-0.82)
Initiated ART within 28 days of enrollment	420 (77%)	194 (71%)	226 (83%)	12% (5-19%)	1.16 (1.06-1.28)
Initiated within:					
14 days of enrolment	362 (67%)	162 (60%)	200 (74%)	14% (6-22%)	1.23 (1.09-1.39)
7 days of enrolment	294 (54%)	107 (39%)	187 (69%)	30% (22-38%)	1.75 (1.49-2.07)
Day of enrollment	184 (34%)	30 (11%)	154 (57%)	46% (39-53%)	5.13 (3.61-7.31)

* Reference group: control arm

1107 STARTING ART IN HIV+ DRUG USERS WHILE HOSPITALIZED PREDICTS HIV TREATMENT ENGAGEMENT

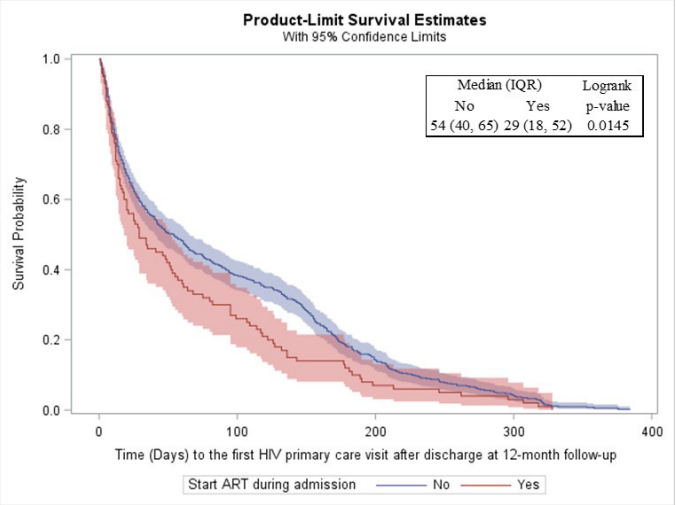
Petra Jacobs[1], Daniel Feaster[2], Yue Pan[2], Lauren Gooden[3], Carlos del Rio[4], Eric Daar[5], Gregory M. Lucas[6], Mamta K. Jain[7], Eliza Marsh[8], Lisa Metsch[3]
[1]National Institute on Drug Abuse, Rockville, MD, USA, [2]University of Miami, Miami, FL, USA, [3]Columbia University, New York, NY, USA, [4]Emory University, Atlanta, GA, USA, [5]University of California Los Angeles, Los Angeles, CA, USA, [6]Johns Hopkins Hospital, Baltimore, MD, USA, [7]University of Texas Southwestern, Dallas, TX, USA, [8]Trinity College, Hartford, CT, USA

Background: Project HOPE (CTN0049) was a randomized controlled trial that tested the effect of 6 months of Patient Navigation alone or with Contingency Management vs. treatment as usual on viral suppression rates (<200 copies/mL) at 6 and 12 months post-randomization among substance using HIV+ patients recruited from the hospital. Antiretroviral therapy (ART) was initiated at providers' discretion. This secondary analysis examined factors related to initiating ART in the hospital and its association with engagement in care and viral suppression.

Methods: Project HOPE recruited 801 HIV+ substance users in 11 hospitals across US. We examined differences in socio-demographics, HIV treatment history and other service use, site, substance use and social determinants of health by those prescribed and not prescribed ART while hospitalized (chi-square and t-tests). We explored the relationship of predictors with a p-value <.01 on likelihood of subsequent engagement in HIV care and viral suppression, controlling for study group.

Results: Of 801 patients, 124 (15%) were prescribed ART in the hospital; this did not differ by study arm (p=.525). Opioid use (OR=2.06, 95%CI [1.35,3.13]) and having participated in substance use treatment (OR=1.87, 95%CI [1.17,2.98]) were associated with greater likelihood of receiving ART in the hospital, and opioid use with higher likelihood of substance treatment (OR=3.75, 95%CI [2.50,5.62]). Controlling for rates of in hospital ART prescription, substance treatment and opioid use, which differed by site (all p<.001), sites in the South (compared to North) were less likely to prescribe ART in the hospital (OR=0.48, 95%CI [0.25,0.93]). At the 12-month follow-up, median days before first HIV primary care visit was 29 in those who started ART in the hospital and 54 in those who did not (p=0.015) (Figure). Controlling for these factors and study group, there was no association between starting ART in the hospital and viral suppression at 6- or 12-months (OR=1.51, 95%CI [0.98,2,34]) and (OR=.83, 95% CI [.53, 1.31]), respectively.

Conclusion: Starting ART during hospitalization was associated with shorter time to engagement in HIV care. Although not significant, there was a trend towards those prescribed ART in the hospital being more likely to be virally suppressed at 6 months than those who were not. Further research should assess the impact that rapid initiation of ART in hospitalized substance users may have on treatment engagement and virologic outcomes.



1108 GETTING A JUMP ON HIV: EXPEDITED ARV TREATMENT AT NYC SEXUAL HEALTH CLINICS, 2017

Susan Blank, Christine M. Borges, Michael A. Castro, Kelly Jamison, John Winters, Tarek Mikati, Julie Myers, Demetre C. Daskalakis
New York City Department of Health and Mental Hygiene, Long Island City, NY, USA

Background: Early HIV viral load suppression (VLS) is associated with decreased mortality and HIV transmission. The New York City Department of Health & Mental Hygiene Sexual Health Clinics (SHC) identify 10% of new HIV cases and 20% of acute HIV infections (AHI) citywide. The NYC SHC recently introduced Jumpstart (JS): on-site HIV antiretroviral (ARV) treatment with navigation. JS was designed to expedite HIV treatment initiation, support VLS, and improve adherence. We report on implementation and preliminary outcomes of the JS efforts available at 6 of 8 SHC.

Methods: NYC SHC patients are routinely tested for HIV via rapid antibody test; individuals at highest risk are screened for AHI via pooled Nucleic Acid Testing. Patients eligible for JS were > 18 years, lived in-state and reported no prior ARV treatment. Initiation visits included 30-day supply of ARVs, navigation, medical monitoring and linkage to HIV primary care. Using medical record data, we described JS initiates 11/23/16-7/31/17, their pretreatment drug resistance (PDR) patterns, CD4, viral load, care linkage, and VLS of those requiring additional ARV from SHC.

Results: 149 patients initiated ARVs. 108 patients were newly diagnosed at SHC offering JS; of these, 78 (72%) initiated ARVs (38/78 (49%) at diagnosis; 68/78 (87%) within 7 days). 71 additional patients initiated ARVs (20 newly diagnosed patients were transferred from SHC that did not yet have JS; 51 were previously

diagnosed). Of the 149 ARV initiates, 126 (85%) were men reporting sex with men, 100 (67%) were Hispanic or black; 70 (47%) were foreign born. Median age was 29 years; 15 (10%) had AHI; 25 (17%) had CD4<200; 46 (31%) had baseline VL ≥100,000. 24 of 127 with baseline genotyping had evidence of PDR, most commonly to non-nucleoside ARVs. One patient required a change in therapy due to PDR. 30-day linkage to care was 84% (82/98) among new positives and 63% (32/51) among previous positives. Of 149 ARV initiates, 64 (43%) required a second month of ARV from SHC. The majority of these patients (41/64; 64%) had attended an appointment at a linkage facility. Among those with VL testing at SHC follow-up, 87% (45/52) had achieved VLS by day 45.

Conclusion: Incorporation of same-day HIV navigation and ARV initiation is feasible in the setting of a public health clinic system, with high patient acceptability. Scale up to all 8 SHC clinics is expected in 2018. Future evaluation will assess impact of these efforts on time to VLS.

1109 A RAPID ENTRY PROGRAM IN THE SOUTH: IMPROVING ACCESS TO CARE AND VIRAL SUPPRESSION

Jonathan Colasanti[1], Jeri Sumitani[2], Cyra Christina Mehta[1], Yiran Zhang[3], Minh Ly Nguyen[3], Wendy S. Armstrong[1], Carlos del Rio[1]

[1]Emory Center for AIDS Research, Atlanta, GA, USA, [2]Grady Health System, Atlanta, GA, USA, [3]Emory University, Atlanta, GA, USA

Background: Time between presentation to HIV care and viral suppression has been too long. Rapid entry programs (REP) have demonstrated efficacy for select populations in San Francisco, South Africa and Haiti but no REPs have been reported from the Southern U.S. We assessed the feasibility and effectiveness of a REP in a large Ryan White (RW) funded clinic in Atlanta, Georgia. The clinic serves a predominantly minority and economically disadvantaged population. The REP goal was to enroll patients into clinic, complete a social needs assessment, provider visit, labs and give the option to start ART within 72 hrs.

Methods: A cohort of consecutive patients was enrolled in the REP protocol from May 16, 2016 to July 31, 2016. To assess the effectiveness of the REP, the intervention group was compared to new enrollees to clinic from the months preceding the REP (January 1, 2016 - May 15, 2016). Inclusion criteria were HIV+, new to the clinic (not necessarily new diagnosis) and viremic at intake. Six-month follow-up data were analyzed for each group. Time to viral suppression (VS) was the primary outcome. Time to provider visits and time to ART start, were secondary outcomes. A survival analysis compared time to viral suppression for the groups. Linear regression models were run for the secondary outcomes.

Results: The sample size was 118 pre-REP and 91 post-REP. Pre-REP demographics include age 33 (IQR 24, 44), 81% male, 86% Black, 60% MSM, 58% uninsured, $8,808 (IQR 0, $18,668) annual income, 67% unstably housed, 9% incarcerated in last 6 months, 42% active substance use, CD4 141 cells/uL (IQR 33, 301) and 59% ART naïve. The post-REP group differed only in age being slightly older at 38 yo (IQR 27, 48) (p=0.039). The median time to VS decreased from 63 days (IQR 36, 112) to 45 days (30, 72) post-REP (p=0.0038). Regression analyses evaluating time to 1st scheduled visits, time to attended visit and time to ART start are shown in the table. Time to VS, first provider visits and ART start remained significant when adjusted for age, sex, race, ART nativity, INSTI use and baseline $\log_{10}$ VL.

Conclusion: This is the largest rapid entry cohort described in the U.S. Time to viral suppression, in an economically and socially disenfranchised population in the South, was significantly improved through implementation of a REP. This was likely due to shortening the time to initial provider visit and ART prescription. REP programs are feasible in the area of the US with greatest numbers of new infections.

Table. Secondary Outcomes in a pre- post- analysis of a rapid entry program at a Ryan White funded HIV clinic in the Southern U.S

Days from date presenting to clinic to:	Pre-REP (Jan 1, 2016 – May 15, 2016) N=118	Post-REP (May 16, 2016 – July 31, 2016) N=91	P-value
Days from clinic presentation to:	Median (IQR)	Median (IQR)	
1st scheduled provider visit	15 (7, 20)	2 (1, 7)	<0.0001*
1st attended provider visit	17 (7, 26)	5 (2, 8)	<0.0001*
ART start	21 (13, 31)	7 (3, 17)	<0.0001*
Other outcomes of interest			
Attended 1st scheduled visit	73%	81%	0.153
Ever achieved VS (HIV RNA < 200 c/mL)	75%	68%	0.305
Change in CD4 count	+ 62(14, 152)	+76(25, 146)	0.805

*p value from linear regression analyses was adjusted for age, sex, race, ART naive, INSTI use and baseline log10 VL

1110 EARLY RETENTION DOES NOT MEDIATE/MODERATE EFFECT OF SEX/SEXUAL BEHAVIOR ON SURVIVAL

Lara Coelho[1], Peter F. Rebeiro[2], Jessica L. Castilho[2], Yanink Caro-Vega[3], Fernando A. Mejia[4], Carina Cesar[5], Claudia P. Cortes[6], Denis Padgett[7], Catherine McGowan[2], Valdilea Veloso[1], Timothy R. Sterling[2], Beatriz Grinsztejn[1], Bryan E. Shepherd[2], Paula M. Luz[1]

[1]Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro. Brazil, [2]Vanderbilt University, Nashville, TN, USA, [3]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [4]University Peruana Cayetano Heredia, Lima, Peru, [5]Fundación Huésped, Buenos Aires, Argentina, [6]Fundación Arriarán, Santiago, Chile, [7]Instituto Hondureño de Seguridad Social, Tegucigalpa, Honduras

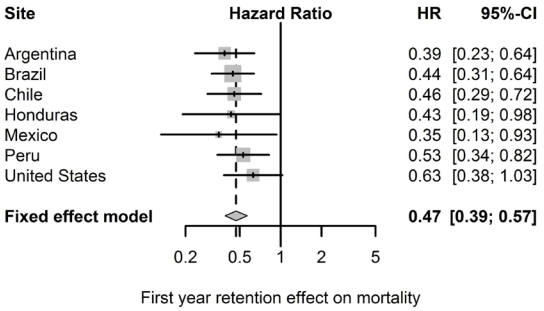
Background: Early retention in care (RIC), sex, and sexual mode of HIV acquisition have each been associated with mortality risk among persons living with HIV (PLWH). We therefore assessed whether early RIC mediates or modifies the effect of sex and sexual mode of HIV acquisition on mortality among PLWH on antiretroviral therapy (ART) in the Americas.

Methods: ART-naïve, adult PLWH (≥18 years old) enrolling at Caribbean, Central and South America network for HIV epidemiology (CCASAnet) and Vanderbilt Comprehensive Care Clinic sites 2000-2015, starting ART, and with ≥1 visit after ART-start were included. Early RIC was defined as ≥2 HIV care visits/labs ≥90 days apart in the first year after ART-start. Sex and sexual mode of HIV acquisition were categorized as women, heterosexual men, and men who have sex with men (MSM). Individuals were followed from one year after ART-start to date of death, last clinic visit or study closure. Cox regression models assessed the association between early RIC, sex and sexual mode of HIV acquisition, and mortality beyond the first year of ART; interactions between RIC and sex and sexual mode of HIV acquisition were tested. Associations were estimated for each site separately and pooled.

Results: Among 11,721 PLWH with ≥1 visit after starting ART, 647 subsequently died (rate=10.9/1000 person-years) and 1985 were lost to follow-up (rate=33.6/1000 persons-years). Early RIC substantially decreased mortality during subsequent years at all sites (Figure), adjusting for age, sex and sexual mode of HIV acquisition, ART-start year, and pre-ART nadir CD4, AIDS, and HIV-1 RNA. Sex and sexual mode of HIV acquisition were also associated with mortality beyond the first year of ART, with MSM having lower risk (pooled adjusted aHR=0.75; 95%CI: 0.61-0.92) and heterosexual men having similar risk (aHR=0.92; 95%CI: 0.74-1.13) to women. Point estimates for sex and sexual mode of HIV acquisition were similar whether or not retention was included. Moreover, there was no evidence of an interaction between sex and sexual mode of HIV acquisition and early RIC (p>0.05).

Conclusion: In the Americas, early RIC significantly decreased mortality risk after one year on ART. Additionally, MSM had a lower mortality risk than women. We found no evidence of RIC mediating or modifying the association between sex and sexual mode of HIV acquisition and mortality in our population.

Figure. Site-specific and pooled associations between early retention and mortality.



1111LB SAME-DAY ART INITIATION ASSOCIATED WITH POORER RETENTION BUT HIGHER VIRAL SUPPRESSION

Dvora Joseph Davey, Claire Serrao, Madaline Feinberg, Marlien Prins, Ernest Darkoh
BroadReach Corporation, Cape Town, South Africa

Background: South Africa rolled out universal HIV testing and treatment in September 2016 including ART initiation on the same-day as HIV diagnosis. Apart from the anticipated improvement in ART uptake, it is essential to understand the impact of same-day ART initiation on loss to follow-up (LTFU), as well as on viral suppression (VS) and mortality.

Methods: We analysed national data from five high HIV prevalence Provinces in South Africa to evaluate the impact of same day ART initiation on treatment outcomes including LTFU, VS (<400 copies/mL) and mortality in adults on ART for >90-days who initiated on ART between September 2016 and August 2017 who had a diagnosis date on file using multivariable regression models controlling for a priori confounders (e.g. age, gender, baseline CD4, District, time on ART) censoring patients who transferred or moved.

Results: In total 20,847 patients >15-years old initiated ART and were on ART for >90-days. Overall, 2013 patients initiated ART on the same day as diagnosis (11.6%) of which 725 (36%) were pregnant at ART start. Median baseline CD4 cell count was higher in same-day ART patients (386, IQR=228-560), vs. other patients (323, IQR=163-529; z=-13.8; p<0.001). LTFU was higher in the same-day ART patients (22% vs. 15%; p<0.001). Adjusting for age, time on ART, baseline CD4, District and gender, odds of LTFU at >6-months on ART were 1.5-times higher in patients with same-day ART (aOR=1.45; 95%CI=1.18-1.78). Stratifying by pregnancy status, odds of LTFU were 1.9-times higher in pregnant women (aOR=1.86; 95% CI=1.23-2.80) and 1.4-times higher in non-pregnant adults (aOR=1.41; 95%CI=1.06-1.86) vs. non-same day initiators. However, mortality was lower in the same-day ART group (n=7 [0.5%] vs. n=182 [1.2%]; aOR=0.46;95%CI=0.26-0.82). In patients with a viral load done (n=17,704; 85%), VS was higher in the same-day ART group (87% vs. 85% of patients with a viral load done, p=0.02). Adjusting for the same factors, same-day ART initiators had greater odds of achieving VS (aOR=1.16; 95% CI=1.02-1.33).

Conclusion: This is one of the first studies to demonstrate treatment outcomes in a large cohort of patients who initiated ART the same day as diagnosis. Same-day ART initiation was associated with poorer retention, but was associated with lower mortality and viremia compared with non-same-day patients. Additional research on targeted interventions to improve counselling and ART readiness in patients who initiate ART on the same-day as their diagnosis are needed.

Table. Treatment outcomes in patients initiated on same-day ART vs. non-same-day ART in South Africa (September 2016 – December 2017)

	Total	Same-day as diagnosis initiation	%	>1 day after diagnosis for ART initiation	%	aOR (95% CI) *
New ART initiations in patients ≥15 years old & >90-days on ART	20,847	2013	9.7%	18834	90.3%	
Total LTFU (>90 days without visit) **	3035	404	22.0%	2631	15.0%	1.25 (1.05, 1.51)
LTFU in patients on ART for 6+ months**	2383	304	20.6%	2079	13.7%	1.45 (1.18, 1.78)
Mortality ***	189	7	0.5%	182	1.2%	0.46 (0.26, 0.82)
VS (<400 copies) in patients with a viral load done	17,704	1743	86.6%	15961	84.7%	1.16 (1.02, 1.33)

*adjusted for age, gender, baseline CD4, District
** censored patients who died or transferred /moved away
*** censored patients who were LTFU or transferred/moved away

1112 HIGH HIV-RELATED TUBERCULOSIS RISK IN COUNTIES WITH LOW HIV PREVALENCE– KENYA, 2015

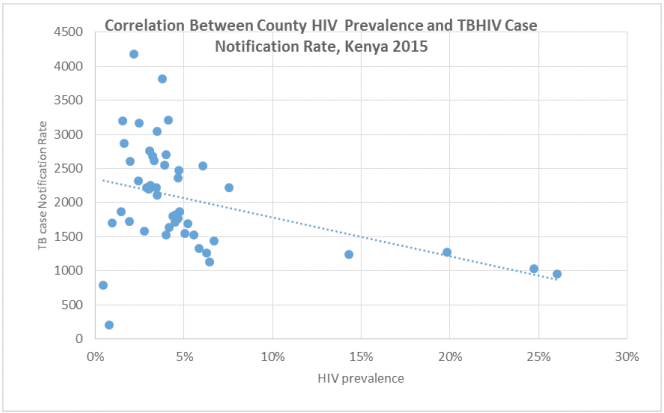
Herman O. Weyenga[1], Abraham Katana[1], Thomas Achia[1], Brian Baker[1], Lucy Ng'ang'a[1], Evelyne Ngugi[1], Tai Ho Chen[1], Maureen Kamene[2], Emily C. Zielinski-Gutierrez[1], Enos Masini[2], **Dunstan Achwoka**[1], George K. Kadondi[2], Christine Wambugu[2], Kenneth Masamaro[1], Kevin M. De Cock[1]
[1]US CDC Nairobi, Nairobi, Kenya, [2]Ministry of Health, Nairobi, Kenya

Background: Infection with human immune deficiency virus (HIV) is an independent risk factor for tuberculosis (TB). Antiretroviral therapy (ART) reduces TB risk and mortality at both patient and population levels. Kenya has geographically differentiated HIV and TB epidemics and control efforts have to-date been focused on the counties with the highest HIV prevalence. However, the risk of people living with HIV (PLHIV) developing and dying from TB in different Kenyan counties might better inform TB/HIV prevention efforts.

Methods: We conducted a retrospective analysis of 2015 data from the national TB surveillance database (TIBU) and Ministry of Health HIV estimates. Variables included county smear positive, TBHIV and total TB case notification (CN), population estimates, estimated HIV prevalence, number of PLHIV (including children), ART coverage and poverty index. Eleven counties with HIV prevalence >5.6% (national estimate) were defined as high HIV prevalence and the rest as low HIV prevalence. Using MS excel and STATA statistical software, county CN rate for TBHIV and deaths were computed. Poisson regression models with and without spatially-structured and unstructured random effects were fitted controlling for potential confounders. Deviance information criterion was used to identify the best fitting model. Correlation analysis was done to determine the association between TB risk and death among PLHIV and HIV prevalence. Results were presented as counts, CN rate, relative risk and Pearson correlation coefficient.

Results: Overall, of 82,406 reported TB cases and 1,517,707 estimated PLHIV in all 47 counties 26,615 were co-infected. Case fatality rates among HIV-positive and HIV-negative TB cases were 10.4% and 3.4%, respectively. Fifty-three percent of deaths among persons with TB/HIV were in high HIV prevalence counties. The median TBHIV CN rate was 1,866 (IQR, 1,538-2,606) per 100000 PLHIV. TB risk among PLHIV correlated negatively with HIV prevalence (Spearman's r=-0.40, p=0.005). Low HIV prevalence counties had higher TB risk among PLHIV when compared to counties with high HIV prevalence, RR=1.56, 95% CI (1.26–1.97). The TBHIV case fatality rate was not associated with HIV burden, smear positive TB rate, ART coverage or poverty index.

Conclusion: PLHIV in low HIV prevalence counties have a higher relative risk of TB than PLHIV in high HIV prevalence counties in Kenya. Resource allocation for comprehensive HIVTB prevention in low burden counties is recommended.



1113 BURSTING MYTHS: PROGRAMMATIC SCALEUP OF ISONIAZID PREVENTIVE THERAPY, KENYA 2014-2016

Evelyn M. Karanja[1], Herman O. Weyenga[2], Abraham Katana[2], Martin Sirengo[1], Enos Masini[3], Lucy Ng'ang'a[2], Evelyne Ngugi[2], Shobha Vakil[1], Caroline Olwande[1], Agnes Langat[2], Christine Wambugu[3], Brian Baker[4], **Kevin M. De Cock**[2]
[1]National AIDS and STD Control Programme, Nairobi, Kenya, [2]US CDC Nairobi, Nairobi, Kenya, [3]Ministry of Health, Nairobi, Kenya, [4]US CDC Kisumu, Kisumu, Kenya

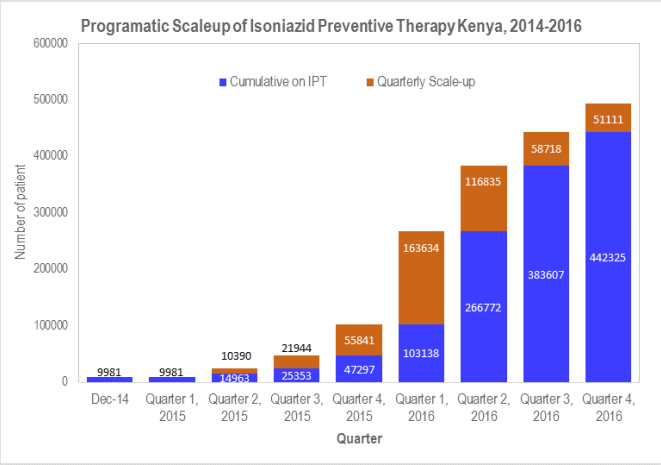
Background: Infecting a third of the global population, M tuberculosis has a large pool of individuals from whom millions of active tuberculosis(TB) cases emerge annually. HIV infection is associated with a tenfold life-time risk of

TB. Isoniazid preventive therapy(IPT) decreases TB risk by 65% and up to 80% when combined with antiretroviral therapy. Despite this benefit, countries have been slow in implementing this intervention. This study describes processes, outcomes and lessons learnt in IPT scale up in Kenya

Methods: We conducted a desk-review of guidelines, standard operating procedures(SOPs), Ministry of Health (MOH) and PEPFAR work plans, meeting notes, reports, and analyzed MOH IPT uptake and treatment outcome data from January 2014 to December 2016 in MS Excel®. Treatment outcomes were defined as: Treatment completed- completion of 6 month IPT; Dead- died while on IPT; Default- lost to followup; not evaluated- no outcome and; discontinued- stopped IPT. Results were presented as counts, percentages, and graph.

Results: From 2009 to 2013, revision of national guidelines allowed wider IPT implementation, TB screening was institutionalized and Xpert MTB/RIF testing rolled out. Pilot projects were implemented, documented and used to inform scale-up. IPT was included in HIV and TB program performance contracts. A joint MOH, US government and implementing partner technical working group was formed, SOPs and materials for training of counties and site level staff developed and IPT launched nationally in 2015. Joint procurement planning was done, drugs purchased by the TB program and distributed by the HIV program. IPT was integrated into the standard package of HIV care and prioritized in HIV treatment acceleration initiatives. PEPFAR implementing partners (IP) were assigned targets and engaged in quarterly progress review meetings. IPT uptake among 1050000 PLHIVs increased almost 50-fold from 9,981 at end-2014 to 493436 in December 2016 and to 80% national coverage by August 2017. Among 28,483 patients initiating IPT in 2015 in 14 Nairobi sites, 90% completed treatment, 0.4% died, 4.9% defaulted, 2.0% were not evaluated and 3.0% were discontinued. Among those discontinued, 0.2% had TB while 0.5% had adverse drug reactions. Challenges included occasional stock out of drugs and reporting tools.

Conclusion: IPT can be scaled up with high completion rates. Strong MOH leadership, integration of IPT in routine HIV care, IP involvement, and accountability are critical to program success.



1114 THE EFFECTS OF HIV TREATMENT ON UPTAKE OF TB AND NCD TREATMENT BY HOUSEHOLD MEMBERS

Suzue Saito[1], Andrea Howard[1], Magdalena Cerda[2], Frank Tanser[3], Deenan Pillay[3], Wafaa M. El-Sadr[1], Till Bärnighausen[4]

[1]Columbia University, New York, NY, USA, [2]University of California Davis, Davis, CA, USA, [3]Africa Health Research Institute, Mtubatuba, South Africa, [4]Harvard University, Cambridge, MA, USA

Background: The global response to the HIV epidemic has achieved remarkable increase in access to antiretroviral therapy (ART) through largely vertical programs. Whether the HIV treatment programs have strengthened the broader health system to achieve better outcomes for tuberculosis (TB) and non-communicable diseases (NCDs) is unclear. We conducted a quasi-experimental study in rural Kwazulu-Natal (KZN), South Africa to determine whether exposure to health benefits from ART utilization by a person living with HIV (PLHIV) in the household affects uptake of TB, hypertension (HTN) and diabetes (DM) treatment by other household members with these conditions.

Methods: The study was conducted in the comprehensive population cohort run by the Africa Health Research Institute (AHRI) in KZN. We linked PLHIV engaged in HIV care to their cohabiting household members aged ≥15 years using a unique identifier for homesteads. We implemented regression discontinuity quasi-experiments fitting Weibull and Cox survival models to establish the causal effect of ART utilization on uptake of TB, HTN, and DM treatment among household members. We ran unadjusted models and models adjusting for age and sex, restricting the analysis to a narrow CD4+ cell count range around the regression discontinuity threshold.

Results: There were 4867 PLHIV enrolled in care living with 17,253 household members ≥15 years in 4212 unique homesteads between 2008-2014. Most PLHIV in care were women (77%) with mean age of 33 years. Cohabiting household members were 55% female with mean age of 31 years and a median household ART utilization exposure of 1.7 years (IQR: 0.6-3.2). During the study period, 3.0% (95.6% of those with TB), 11.4% (86.0% of those with HTN) and 3.1% (83% of those with DM) of cohabiting household members reported that they were currently being treated for TB, HTN, or DM, respectively. Household ART utilization increased treatment for diabetes (RR 1.90: 95% CI 1.07-3.40) but not for TB (RR 1.12: 95% CI 0.71-2.03) or hypertension (RR 1.31: 95% CI 0.97-1.77) (Table 1).

Conclusion: Household exposure to public-sector HIV treatment programs substantially increased uptake of DM treatment but not for HTN and TB treatment among household members. Future research needs to establish the mechanisms leading to these effects and how HIV treatment programs can be even better leveraged to improve access to other needed chronic care in Africa.

Table 1: Effects of ART on uptake of diabetes, hypertension and TB treatment by cohabitating household members*

Exposed	Unexposed	RR** (Weibull)	95% CI	P	RR (Cox)	95% CI	P
1.1 Diabetes treatment							
Treatment per 100 person years				*Unadjusted*			
		1.79	**0.996, 1.001**	**0.05**	**1.79**	**0.999, 3.205**	**0.05**
2.7	1.6			*Adjusting for age and sex*			
		1.90	**1.066, 3.401**	**0.03**	**1.90**	**1.065, 3.396**	**0.03**
1.2 Hypertension treatment							
Exposed	**Unexposed**	**RR (Weibull)**	**95% CI**	**P**	**RR (Cox)**	**95% CI**	**P**
Treatment per 100 person years				*Unadjusted*			
		1.19	0.881, 1.613	0.26	1.19	0.881, 1.614	0.25
14.3	13.5			*Adjusting for age and sex*			
		1.31	0.968, 1.763	0.08	1.31	0.970, 1.766	0.08
1.3 TB treatment							
Exposed	**Unexposed**	**RR (Weibull)**	**95% CI**	**P**	**RR (Cox)**	**95% CI**	**P**
Treatment per 100 person years				*Unadjusted*			
		1.18	0.699, 2.016	0.53	1.19	0.700, 2.011	0.53
2.8	2.3			*Adjusting for age and sex*			
		1.20	0.707, 2.026	0.50	1.20	0.709, 2.034	0.50

* Restricted to CD4+ cell count range of 50-350 cells/μL
** Rate ratios

1115 HYPERTENSION SCREENING AND MANAGEMENT IN TWO PEPFAR-FUNDED CLINICS IN MALAWI

Sam Phiri[1], Hannock Tweya[2], Alice Maida[3], Sundeep Gupta[4], Colin Speight[2], Denise Giles[4], Oliver J. Gadabu[5], Fleetwood Loustalot[4], **Pragna Patel**[4]

[1]Lighthouse Trust Clinic, Lilongwe, Malawi, [2]Lighthouse Trust, Lilongwe, Malawi, [3]CDC Malawi, Lilongwe, Malawi, [4]CDC, Atlanta, GA, USA, [5]Baobab Health Trust, Lilongwe, Malawi

Background: As HIV-infected persons live longer, common comorbidities shift from opportunistic infections to chronic conditions. The PEPFAR-supported clinic network in Malawi provides a unique opportunity to leverage the established clinic structure to incorporate screening and management of noncommunicable diseases (NCDs) such as hypertension (HTN) and provide enhanced HIV care. In addition, integrated services can facilitate testing among adult men, a hard-to-reach population for PEPFAR.

Methods: We integrated a HTN screening and management program using standardized HTN treatment protocols and cohort monitoring with HIV service delivery at two PEPFAR- supported clinics in Lilongwe, Malawi. Persons with at least three elevated blood pressures (SBP >140 or DBP>90) on each of two separate visits were diagnosed with HTN. The first elevated value was be rechecked during the same visit. Patients with HTN who had stable HIV were treated using a stepwise approach based on the Malawi Standard Treatment Guidelines with adaptation for HIV patients. We enhanced an electronic medical record system by developing a HTN module to monitor this subpopulation for outcomes of interest. Antiretroviral (ART) adherence was measured using pill counts.

Results: From 2/15 to 7/16, 29,359 adults >20 years old [median age 38 (interquartile range: 32-45) and 61% female] were screened for HTN at two

clinics. Of those screened, 3,448 (11%) were diagnosed with HTN, of whom 85% were given lifestyle modification advice or started on treatment. Severe disease (BP >180/110) requiring immediate treatment with ≥ 2 drugs was noted in 38%. Of all patients on antihypertensive treatment for 6 months, 26% had achieved controlled BP (Table). Of the 3,448 persons diagnosed with HTN, 53% were male, of whom 46% were 40-49 years of age; 200 men aged 40-49 received treatment for six months and 25% achieved BP control. ART adherence for hypertensive patients receiving HTN medications was similar with patients not on HTN medications (80% vs. 79%, respectively). The annual cost of treatment of the entire cohort with HTN was approximately $14,000 or $4/patient.

Conclusion: HTN screening and management can be successfully integrated into PEPFAR-funded HIV service delivery sites at low cost and with moderate blood pressure control rates. These findings support integration of NCD and HIV services to enhance HIV care as well as to target middle-aged men.

Table. Post Implementation Program Evaluation Data for two Lighthouse Trust pilot sites in Lilongwe, Malawi, February 2015 to June 2016.

Characteristic	Total
Screening parameters	
Number of persons screened*†	29,359
Median age (IQR)	38 (32-45)
Male gender (%)	11,794 (39)
Diagnosis parameters	
Number newly diagnosed with hypertension (%)‡	3,448 (11)
Mild (SBP 140-159 or DBP 90-99)	1,619 (47)
Moderate (SBP 160-179 or DBP 100-109)	514 (15)
Severe (SBP ≥ 180 or DBP ≥ 110)	1,315 (38)
Treatment parameters	
Number of hypertensive patients started on treatment or given lifestyle advice (%)	2,915 (85)
Number of all hypertensive patients on pharmacologic treatment for hypertension (%)‖	1,681 (49)
Control parameters	
Of those on treatment for 3 months, number with normal blood pressure at last visit (%)	240 (22)
Of those on treatment for 6 months, number with normal blood pressure at last visit (%)	229 (26)
Adherence parameters	
Number of hypertensive patients on treatment with at least 95% antiretroviral adherence	1,165 (80)
Number of patient without hypertension with at least 95% antiretroviral adherence	20,073 (79)

*Phased approach was used at the Martin Preuss Clinic; therefore, the program was considered fully operational in June 2015 and the evaluation period extends to 12 months from this date to June 2016.
†All patients were screened with an automated sphygmomanometer
‡Definition new diagnosis of hypertension based on Malawi Standard Treatment Guidelines (4th edition): SBP≥140 mm hg or DBP≥ 90mm hg measured on two consecutive visits or severe HTN (SBP≥180 mm hg or DBP≥ 110mm hg) on a single visit; SBP = systolic blood pressure; DBP= diastolic blood pressure
‖Provision for treatment: all persons with moderate or severe hypertension were eligible for treatment. Of those with mild hypertension, those with mild hypertension, lifestyle modifications unless they have one CVD risk factor (current smoker, DM, history of CVD, history of CVD in first-degree relative).

1116 HISTORICAL & CURRENT ANAL CYTOLOGY, HRHPV-DNA AND -MRNA-E6/E7 TESTS PREDICT ANAL HSIL

Dorothy J. Wiley[1], Hilary K. Hsu[1], Martha Ganser[1], Jenny Brook[1], David Elashoff[1], Matthew G. Moran[1], David H. Morris[2], Ronald T. Mitsuyasu[1], Stephen Young[3], Nancy Joste[3], Teresa Darragh[4], Hilary Robbins[5], Gypsyamber D'Souza[5], Otoniel Martínez-Maza[1], Roger Detels[1]
[1]University of California Los Angeles, Los Angeles, CA, USA, [2]Desert AIDS Project, Palm Springs, CA, USA, [3]Tricore Reference Laboratories, Albuquerque, NM, USA, [4]University of California San Francisco, San Francisco, CA, USA, [5]Johns Hopkins University, Baltimore, MD, USA

Background: Accuracy for anal cytology (Pap) & high-risk HPV (hrHPV) tests to predict anal histological high-grade squamous intraepithelial lesions (hHSIL) is unclear.

Methods: Historical anal Pap test findings, concurrently sampled Pap & two high-threshold HPV tests, High-Resolution Anoscopy (HRA) & biopsy results were gathered from 201 MSM (n=198) & transgender women (n=3). Dacron-swab Paps were evaluated as >Atypical Squamous Cells of Unknown Significance (>ASC-US), unsatisfactory, & no intraepithelial lesions (NIL, referent). Historical Pap findings were gathered from medical records or a large longitudinal study (Multicenter AIDS Cohort Study). Concurrent Pap & histology analyses were performed by one CLIA-certified lab; historical Paps were not. HRA-biopsy findings were classified as hHSIL vs. <="" div="">

Results: On average, subjects were 55 (σ=12) years old, White (73%), smokers (77%); 39% were HIV+ with >500 CD4 cells/mm^3, & 19% with <500. Few receptive anal sex partners were reported the 6-30 months before HRA: 58% reported none; 28%, 19%, & 4% reported 1, 2, or >3, respectively. The fully-adjusted models suggested, separately, that >2 Paps >ASC-US (OR=5.7) or a current >ASC-US Pap (OR=2.3) increased odds of hHSIL. A positive hrHPV-DNA (OR=4.7) or –mRNA-E6/E7 (OR=9.0) test increased odds of hHSIL as well. Fully-adjusted models showed diagnostic accuracy for historical & current Paps together, current Pap test alone, & hrHPV-DNA differed little & only hrHPV-mRNA-E6/E7 test more accurately predicted hHSIL: 0.76 (ref), vs. 0.74 (p=0.16), 0.78, (p=0.6), & 0.83 (p=0.05) respectively. A positive hrHPV-mRNA-E6/E7 test more accurately predicted hHSIL than a single (current) Pap test showing >ASC-US (p=0.003). The hrHPV-mRNA-E6/E7+ test also better predicted hHSIL than a hrHPV-DNA+ test finding (p=0.007).

Conclusion: A single hrHPV-mRNA-E6/E7 test may more accurately predict hHSIL than a single Pap or hrHPV-DNA test finding. While multiple abnormal Pap findings 6-30 months prior to HRA increased odds of detecting hHSIL, the accuracy of historical Pap was no greater than a single Pap measure. More research is needed.

Table: Comparison of Test Performance Characteristics for Current and Historical Cytology and High-Risk HPV DNA and mRNA-E6/E7 Molecular Tests to Predict Histological High-Grade Squamous Intraepithelial Lesions for 201 Subjects Evaluated in a Randomized Clinical Trial: the *ISTA* Study. Adjusted Odds Ratios, Sensitivity, Specificity, Area Under Receiver-Operating Characteristic Curves (AUC).

Cytology	Current Cytology	Number of Historical Cytology Results				Sensitivity / Specificity	AUC (α_1)
		≥ASCUS		NIL			
	≥ASCUS vs NIL	1 vs. 0	≥2 vs. 0	1 vs. 0	≥2 vs. 0		
Current + Historical	1.8 (0.8, 4.2)	1.4 (0.6, 3.1)	5.7 (2.0, 16.6)	1.1 (0.5, 2.4)	1.2 (0.3, 4.9)	52% / 74%	0.76 (0.03)[1]
Current Alone	2.5 (1.3, 4.6)	-	-	-	-	44% / 72%	0.74 (0.03)[2]
Molecular hrHPV Test	Positive vs. Negative						
hrHPV-DNA	4.7 (2.4, 9.2)	-	-	-	-	57% / 67%	0.78 (0.03)[3]
hrHPV-mRNA-E6/E7	9.0 (4.4, 18.6)	-	-	-	-	70% / 66%	0.83 (0.03)[4]

Footnotes: [1] referent. [2] p=0.16. [3] p=0.61. [4] p=0.05. Additional contrasts: hrHPV-mRNA-E6/E7 vs. hrHPV-DNA: p=0.007; hrHPV-mRNA-E6/E7 vs. Current Dacron Cytology: p=0.003.

1117LB COST-EFFECTIVENESS OF URINE TB SCREENING FOR HOSPITALIZED PEOPLE WITH HIV IN AFRICA

Krishna P. Reddy[1], Ankur Gupta-Wright[2], Katherine Fielding[2], Sydney Costantini[1], Amy Zheng[1], Elizabeth L. Corbett[2], Liyang Yu[1], Joep J. van Oosterhout[3], Stephen C. Resch[4], Doug K. Wilson[5], C. Robert Horsburgh[6], Robin Wood[7], Kenneth Freedberg[1], Stephen D. Lawn[2], Rochelle P. Walensky[1]
[1]Massachusetts General Hospital, Boston, MA, USA, [2]London School of Hygiene & Tropical Medicine, London, UK, [3]Dignitas International, Zomba, Malawi, [4]Harvard University, Boston, MA, USA, [5]University of KwaZulu-Natal, Durban, South Africa, [6]Boston University, Boston, MA, USA, [7]Desmond Tutu HIV Foundation, Cape Town, South Africa

Background: The STAMP trial showed urine-based tuberculosis (TB) screening in unselected people with HIV (PWH) hospitalized in Malawi and South Africa (SA) reduced 2m all-cause mortality by 2.8% and increased TB diagnoses by 7.3%. We examined the cost-effectiveness of this screening strategy, projecting outcomes at longer time horizons.

Methods: We used the CEPAC-International model to project clinical and economic outcomes of 2 TB screening strategies among hospitalized PWH: (1) Intervention: testing sputum with Xpert MTB/RIF and urine with Xpert and Determine TB-LAM; (2) Standard of Care: sputum Xpert alone. The modeled cohort matched the trial cohort (median CD4 219/μL [Malawi], 236/μL [SA]). Costs of Xpert/LAM were US$26/$3 in Malawi and $15/$3 in SA. We calibrated model output at 2m to STAMP trial outcomes and then projected longer-term outcomes including life expectancy (LE), costs, and incremental cost-effectiveness ratios (ICERs), discounted at 3%/y. We considered the Intervention cost-effective if its lifetime ICER was less than that of second-line antiretroviral therapy in each country: $740/year of life saved (YLS) in Malawi and $950/YLS in SA. Informed by the trial, in the base case true TB prevalence in Malawi/SA was 18%/28%, proportion of patients providing sputum was 39%/75%, and probability of empiric TB treatment was 4%/10%, all of which were varied in sensitivity analysis. We estimated the 5y clinical and budget impact of implementing the Intervention countrywide in Malawi and SA.

Results: Model-generated absolute reductions in mortality by the Intervention in Malawi/SA were 3.5%/2.2% at 2m, and LE increased by ~0.5y (undiscounted) in both settings. The Intervention's lifetime ICER was $490/YLS in Malawi and $850/YLS in SA (Table). The Intervention's ICER was lower (more attractive) at higher TB prevalence, lower proportion of patients providing sputum, and lower empiric treatment rate. When we modeled a modified intervention, testing urine with only LAM was more cost-effective and possibly cost-saving. Implementing the Intervention countrywide over 5y among hospitalized PWH was associated with ~35,000 and ~171,000 YLS in Malawi and SA, with budget

impact of $30 million in Malawi and $228 million in SA (6.6% and 2.3% increases in total health expenditures in these populations).

Conclusion: Urine-based TB screening for hospitalized PWH would increase life expectancy and is cost-effective in resource-limited settings.

Table. Clinical and economic outcomes and cost-effectiveness of tuberculosis screening strategies among hospitalized people with HIV in Malawi and South Africa.

Malawi	*Projected mortality*			*Lifetime outcomes*			
Strategy	**2 months**	**2 years**	**5 years**	**Life-years (undisc.)**	**Life-years***	**Cost (2017 US$)***	**ICER ($/YLS)***
SOC	24.4%	35.4%	47.3%	11.95	8.25	$3,320	-
Intervention	20.9%	33.0%	45.2%	12.43	8.59	$3,480	490

South Africa	*Projected mortality*			*Lifetime outcomes*			
Strategy	**2 months**	**2 years**	**5 years**	**Life-years (undisc.)**	**Life-years***	**Cost (2017 US$)***	**ICER ($/YLS)***
SOC	17.7%	33.5%	45.3%	12.12	8.42	$8,210	-
Intervention	15.5%	31.1%	43.3%	12.56	8.74	$8,480	850

SOC: Standard of Care. Undisc.: undiscounted. ICER: incremental cost-effectiveness ratio. YLS: year of life saved.
*Discounted 3%/y.
Reflecting the STAMP clinical trial, the Standard of Care strategy consists of only sputum Xpert testing, while the Intervention strategy consists of sputum Xpert, urine Xpert, and urine lipoarabinomannan (LAM) testing. Cost includes all healthcare expenditures. The ICER is the difference (between the Intervention and the SOC) in discounted costs divided by the difference in discounted life-years. The displayed life-years and costs are rounded, but the ICER was calculated using non-rounded life-years and costs. We used a cost-effectiveness threshold equivalent to the ICER of second-line antiretroviral therapy: $740/YLS in Malawi and $950/YLS in South Africa.

1118 HIGH RATES OF VIRAL RESUPPRESSION ON FIRST-LINE ART AFTER INITIAL VIROLOGICAL FAILURE

Lucas E. Hermans[1], Hugo Tempelman[2], Sergio Carmona[3], Monique Nijhuis[1], Diederick Grobbee[1], Douglas D. Richman[4], Michelle A. Moorhouse[5], Willem D. Venter[5], Annemarie Wensing[1]
[1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Ndlovu Care Group, Groblersdal, South Africa, [3]National Health Laboratory Service, Johannesburg, South Africa, [4]VA San Diego Healthcare System, San Diego, CA, USA, [5]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa

Background: ART achieves viral suppression in the majority of HIV infected patients in low and middle-income countries. WHO guidelines recommend annual viral load (VL) monitoring with confirmatory VL testing in case of a VL ≥1000 copies/mL (c/mL), and switch to second-line ART without resistance testing if virological failure (VF) is confirmed. However, challenges exist regarding clinical follow-up of VL results, prompting discussion around the criteria for VF and switch to second-line ART.

Methods: Patients from 19 urban and 38 rural South African HIV treatment sites were studied. Adult patients on first-line ART for ≥20 weeks and with ≥1 VL performed ≥20 weeks after start of ART were included. Proportions of viremia ≥1000 c/mL, confirmed VF (>1 VL ≥1000 c/mL) on first-line ART, likelihood of switch to second-line ART, and resuppression on first-line ART were analyzed.

Results: 69,454 patients were included. 20.7% of patients (14,380/69,454) had ≥1 VL ≥1000 c/mL during 209,638 patient years of first-line ART. After 1 year of ART, 88.3% of patients achieved viral suppression <1000 c/mL. Patients with a VL ≥1000 c/mL were more often male (35.6% vs 31.2%), younger (34.9 vs 36.0 years), and had a lower baseline CD4-count (159 vs 193 cells/uL). Of 9,351 patients with a VL ≥1000 c/mL and ≥1 subsequent VL result during first-line ART, VF was not confirmed in 44.8% (4,186/9,351) of patients, with 90.4% (3,785/4,186) of these patients achieving resuppression <50 c/mL without switch to second-line ART. In patients with confirmed VL ≥1000 c/mL, resuppression without switch occurred in 15.9% (581/3,649), but they remained at increased risk of subsequent VF. Median time between first detection of a VL ≥1000 c/mL and confirmation of VF was 30 weeks [IQR: 17 - 53]. Median time between first detection of VF and switch was 67.7 weeks [35 - 124].

Conclusion: In this large cohort of patients on first-line ART monitored according to WHO guidelines, viral resuppression occurred in just under half of cases after a single VL ≥1000 c/mL, and in a considerable number of cases after VF was confirmed. Confirmation of VF and switch to second-line ART was performed after significant delay, allowing for prolonged episodes of viremia and potential onward HIV transmission. These data confirm the relevance of timely confirmatory VL testing, and suggest that once virological failure is confirmed, diagnostic tools to discriminate between non-adherence and loss of drug activity may prevent unnecessary switches to second-line ART.

1119 IS CLINICAL STABILITY STABLE? MULTI-STATE SURVIVAL ANALYSIS OF HIV PATIENTS IN ZAMBIA

Monika Roy[1], Charles B. Holmes[2], Izukanji Sikazwe[3], Theodora Savory[3], Mwanza wa Mwanza[3], Carolyn Bolton Moore[3], Nancy Czaicki[1], David Glidden[1], Nancy Padian[4], Elvin Geng[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]Johns Hopkins University, Baltimore, MD, USA, [3]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, [4]University of California Berkeley, Berkeley, CA, USA

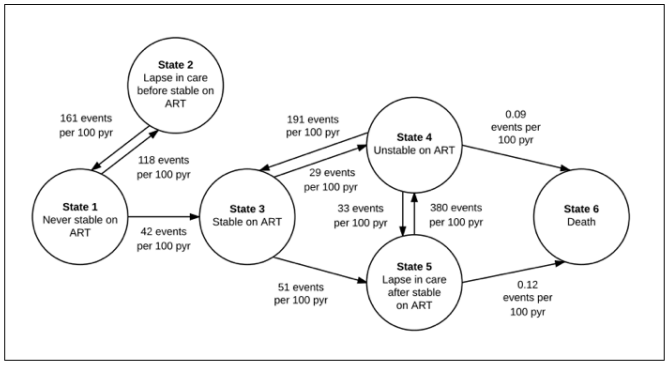
Background: Differentiated service delivery (DSD) models increase the efficiency of HIV services by de-intensifying contact with the health system for clinically stable patients. Although a large proportion of patients may be clinically stable at any given time, the durability of clinical stability under routine care will influence the potential Impact of these models. We used a multi-state survival analysis to describe the rate of becoming stable on treatment after enrollment in care and the dynamics of becoming unstable to assess the durability of clinical stability.

Methods: We evaluated visit data in a cohort of HIV-infected adults who made at least one visit between March 1, 2013 and February 28, 2015 at 56 clinics in Zambia. Clinical, laboratory, and visit data were collected from an existing electronic medical record system. Definition of stability was based on Zambian guidelines and WHO criteria for stability in the absence of viral load. We developed a 6-state model: States 1: never stable on ART; 2: lapse in care before stable on ART; 3: stable on ART; 4: previously stable on ART; 5: lapse in care after stable on ART; 6: death. Cumulative incidence and Incidence rates for transitions between states (from time from enrollment) were calculated overall and by gender, age, and time.

Results: Among 160,487 patients, cumulative incidence of stability on ART was 39.6% (95% CI: 39.3-39.8) 12 months post-enrollment. However, among those who had achieved stability, only 39% were still stable on ART, 54% had already become unstable, and 7.8% had lapsed in care at 12 months. Once stable, the rate of becoming unstable was highest in the first two years post-enrollment (45 and 37 events per 100 person years (pyrs) in Years 1 and 2 respectively) but remained greater than 20 events per 100pyrs thereafter. Rates for lapse in care after being stable on ART were similar regardless of gender, age, or time period, ranging from 45 to 58 events per 100 pyrs. Rate of lapse in care was greater before becoming stable on ART compared to after becoming stable on ART (118 vs 51 events per 100pyrs).

Conclusion: Although most patients became clinically stable shortly after enrollment, many stable patients subsequently became unstable or experienced lapses in care. DSD models targeting stable patients need to account for transient clinical stability among enrollees. Robust systems to detect and react to clinical instability (including viral load testing) will strengthen DSD models.

Figure 1. Transition rates between states in a multi-state survival analysis of clinical stability from time of enrollment in HIV care



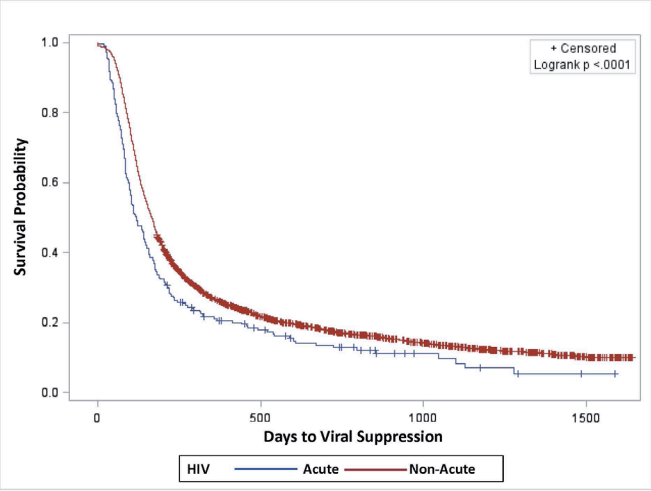
1120 COMPARING TIME TO VIRAL SUPPRESSION AMONG ACUTE AND NON-ACUTE HIV IN NORTH CAROLINA

Nicole Dzialowy Adams[1], Anna Cope[2], Brad Wheeler[1], Victoria L. Mobley[1], John Barnhart[1], Joann D. Kuruc[3], Cynthia L. Gay[3], Lindsey M. Filiatreau[3], Rhonda Ashby[1], Erika Samoff[1]
[1]North Carolina Division of Public Health, Raleigh, NC, USA, [2]CDC, Atlanta, GA, USA, [3]University of North Carolina Chapel Hill, Chapel Hill, NC, USA

Background: North Carolina (NC) has had statewide screening for acute HIV infection (AHI) since 2002. The program involves a coordinated effort between

NC Disease Intervention Specialists (DIS) to locate and interview people diagnosed with AHI within 72 hours of case notification and HIV providers to expedite their care appointments. It takes approximately two weeks for the DIS to locate and interview non-AHI. We sought to determine if this elevated public health response improved retention in HIV care and viral suppression outcomes.
Methods: For all persons newly-diagnosed with HIV during 2013-2016, we defined AHI as negative antibody test and 1) positive HIV RNA or 4th gen HIV Ag/Ab test, 2) negative HIV Ab test within 30 days, or 3) positive HIV RNA and symptoms specific to AHI. Using our NC Engagement in Care Database for HIV Outreach (NC ECHO), laboratory, drug dispense, and claims data were assessed for all HIV-infected persons (AHI and non-AHI) to determine linkage to care (a CD4 or viral load within one month), retention in care (virally suppressed during the year or two care visits at least 90 days apart), and viral suppression (viral load <200 copies/ml). Chi-square analyses were performed on the proportions of linked within one month, retention in care, and viral suppression within 12 months of both AHI and non-AHI. A Kaplan-Meier survival analysis was conducted to determine time to viral suppression for both AHI and non-AHI.
Results: Between 2013 and 2016, a total of 5,357 (252 AHI; 5,105 non-AHI) persons were diagnosed with HIV in NC. Overall, 82% of people diagnosed with AHI were linked to care within one month of their initial HIV diagnosis, compared to 63% of people diagnosed with non-AHI (p<0.001). More people diagnosed during AHI were retained in care (83%) than non-AHI (76%) (p=0.01). The median time for viral suppression for AHI was 118 days (95% CI: 101-144) compared to 166 days (95% CI: 161-171) for non-AHI (log-rank test p<0.0001). Viral suppression was achieved within 12 months in 75% of AHI diagnoses versus 63% of non-AHI diagnoses (p=0.003).
Conclusion: The prioritization of AHI as a public health emergency in NC and the subsequent coordinated effort between the health department and HIV providers to expedite care and treatment initiation may improve linkage to and retention in care, and viral suppression outcomes among AHI.

Figure 1. Time to Viral Suppression for Acute HIV Infections (AHI) and Non-Acute HIV Infections (non-AHI), 2013-2016



1121 CD4 COUNT AND HIV VIRAL SUPPRESSION IMPROVE AFTER HOUSING PROGRAM ENROLLMENT, 2013-16

Yaoyu Zhong[1], Ellen Wiewel[1], Christopher Beattie[1], Xiomara Farquhar[1], Jesse Thomas[2], Sarah L. Braunstein[1], John Rojas[1]
[1]New York City Department of Health and Mental Hygiene, Long Island City, NY, USA, [2]RDE System Support Group, LLC, Little Falls, NJ, USA

Background: The U.S. Housing Opportunities for Persons with AIDS (HOPWA) program provides housing assistance and related supportive services for low-income persons living with HIV (PLWH) and their families. The New York City (NYC) Department of Health and Mental Hygiene oversees 37 HOPWA contracts in NYC across three service categories: housing placement assistance (HPA), supportive permanent housing (SPH), and rental assistance (REN). We evaluated CD4 count and viral load (VL) improvements after NYC HOPWA enrollment compared with matched controls.
Methods: We matched each of the 561 NYC residents newly enrolled in NYC HOPWA during July 2014-December 2015 with two NYC PLWH never enrolled in HOPWA based on the NYC HIV surveillance registry and housing administrative databases, including NYC eCOMPAS for HOPWA. The two groups were matched on as many of these factors as possible: age, gender, race/ethnicity, birth country, other housing program use, HIV transmission risk, area-level poverty, clinical status, and HIV diagnosis year; baseline attributes were balanced between groups after matching. Length of HOPWA enrollment was classified as short-term (<1 year) or long-term (≥1 year). Last CD4 count (grouped as <200, 200-499, ≥500 cells/μL, or missing) and VL were measured 1 year pre- and post-enrollment per laboratory tests electronically reported to the registry. Conditional logistic regression measured if HOPWA enrollees were more likely than matched controls to improve (e.g., from <200 or missing to 200-499) or maintain optimal (≥500) CD4 count. McNemar's test analyzed if the proportion virally suppressed (VS; VL≤200 copies/mL) increased for each group.
Results: Compared to their respective non-HOPWA controls, the 287 long-term HOPWA enrollees were 82% more likely (95% CI: 1.34-2.46), and the 274 short-term HOPWA enrollees 35% were more likely (95% CI: 0.99-1.83), to improve or maintain an optimal CD4 count. VS among long-term HOPWA enrollees increased from 78% pre-enrollment to 86% post-enrollment (p<0.01), while it was constant in their controls; neither short-term HOPWA enrollees nor their controls showed significant improvement in VS. By service category, enrollment length impacted SPH enrollees most: VS increased 14 percentage points for long-term SPH enrollees (p=0.05) but decreased 6 percentage points for short-term enrollees.
Conclusion: Providing HOPWA housing services to PLWH resulted in improved CD4 count and VL within 1 year relative to matched controls, especially with longer enrollment.

Table. Improvement in CD4 count and viral load at 1 year pre- and post-enrollment for HOPWA enrollees and control groups, 2013-2016.

HOPWA group by enrollment length and service category	Total (HOPWA / non-HOPWA)	% who improved or maintained optimal CD4 count levels[1] (HOPWA / non-HOPWA)	Odds ratio (95% confidence interval)	% virally suppressed (HOPWA / non-HOPWA)		Percentage-point increase in proportion virally suppressed (HOPWA / non-HOPWA)	McNemar's test P-value (HOPWA / non-HOPWA)
				1 year pre-enrollment	1 year post-enrollment		
HOPWA overall – Long-term	287 / 574	65% / 52%	1.82 (1.34, 2.46)*	78% / 65%	86% / 65%	8% / 0%	<0.01*/0.92
HOPWA overall – Short-term	274 / 548	57% / 50%	1.35 (0.99, 1.83)	73% / 64%	75% / 66%	2% / 2%	0.70/0.18
Housing placement assistance – long-term	149 / 298	63% / 52%	1.63 (1.08, 2.46)*	76% / 69%	82% / 70%	6% / 1%	0.14/0.81
Housing placement assistance – short-term	237 / 474	57% / 50%	1.35 (0.98, 1.88)	73% / 65%	75% / 67%	2% / 2%	0.68/0.41
Supportive permanent housing – long-term	70 / 140	66% / 58%	1.45 (0.77, 2.73)	70% / 64%	84% / 61%	14% / -3%	0.05/0.57
Supportive permanent housing – short-term	31 / 62	52% / 48%	1.16 (0.46, 2.93)	74% / 53%	68% / 65%	-6% / 12%	0.69/0.11
Rental assistance[2]	74 / 148	69% / 45%	2.99 (1.57, 5.69)*	89% / 58%	97% / 59%	8% / 1%	0.03*/0.79

1. Four CD4 count levels: 1) missing; 2) <200 cells/μL; 3) 200-499 cells/μL; 4) ≥500 cells/μL
2. The analysis did not distinguish consumers in the rental assistance service category by enrollment length, since only 6 persons (8%) in this service category were enrolled <1 year.
*Statistically significant at an alpha level of 0.05.

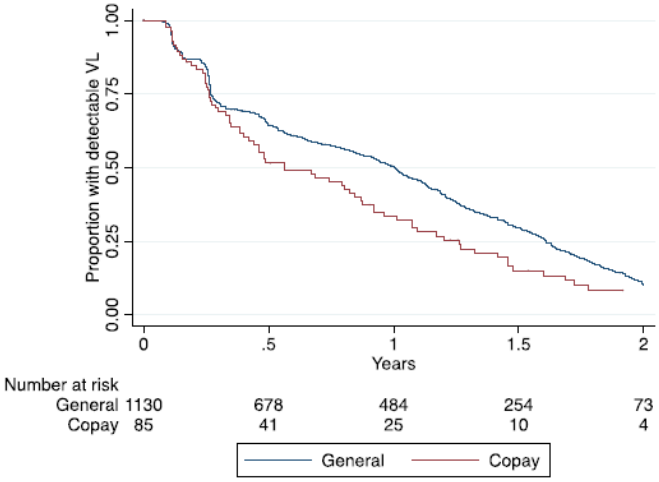
1122 IMPROVED VIROLOGICAL OUTCOMES IN A CO-PAY MODEL SUPPORTING DIFFERENTIATED CARE

Rosalind M. Parkes-Ratanshi[1], Samuel Lewis[2], Maria S. Nabaggala[1], Adelline Twimukye[1], Tom Kakaire[1], Noela Owarwo[1], Barbara Castelnuovo[1], Agnes Kiragga[1], Walter Schlech[3], Mohammed Lamorde[1]
[1]Infectious Disease Institute, Kampala, Uganda, [2]Cambridge University, Cambridge, UK, [3]Dalhousie University, Halifax, NS, Canada

Background: Differentiation of care is an increasingly important mechanism to help increase the number of people living with HIV (PLHIV) accessing anti-retroviral treatment (ART) in resource limited settings. At the Infectious Diseases Institute (IDI) HIV care is offered through a general and integrated specialized clinics (e.g. sexual reproductive health, young adults). In 2013 we introduced a co-pay (US$8-16) convenience clinic providing out of hours services with free ART and tests. We present a retrospective cohort analysis of the clinic.
Methods: All patients enrolling at IDI with at least 2 clinic visits between 1st Aug 2013 and 31st Jan 2016 were included and followed up to 31st Jan 2017. Patients were eligible if they accessed the co-pay clinic for >2 visits during the period, otherwise they were considered general clinic patients. Using univariate and multivariate linear regression, we assessed these factors for association with co-pay clinic attendance: baseline demographics, CD4 count, Viral load [VL], WHO stage, ART regimen and duration. We used survival analysis to evaluate time to virological suppression (in those with initial VL >400copies/ml), death and loss to follow up (LTFUP).
Results: In the study period, 11,848 PLHIV had a clinic attendance; 710 in co-pay. 1555 new PLHIV registered; of these 212 (13.6%) were co-pay and 150 (9.6%) of these enrolled directly into the co-pay clinic. Co-pay PLHIV were more likely to be male (47.1% vs 34.7%; p<0.001 and older (44[IQR 37-51] vs 42[35-48] p<0.001). Of co-pay patients 83.7%vs.52.4% had a greater than primary education and were less likely to be unemployed (13.7%vs.23.9%). There was no difference in baseline CD4, or VL>400 c/ml (p=0.27). Co-pay PLHIV were more likely to be either naïve, on 2nd/ 3rd line ART compared to general clinic PLHIV

(p<0.001). 1215 PLHIV had baseline VL >400 c/ml (85 in co-pay). Co-pay PLHIV had greater odds of virological suppression odds ratio (OR 1.51 [95%CI:1.15-1.98]) after adjusting for baseline age, sex, ART regimen and CD4 -Fig. 1. We found a lower risk of LTFUP from the co-pay compared to general clinic (OR 0.63 (95%CI:0.45-0.89) in the adjusted model. There was a lower risk of death in the co-pay clinic compared to (OR 0.46 [95%CI:0.31-0.71] but this was non-significant in adjusted model.

Conclusion: The co-pay clinic was accessed by harder to reach sub-sets of PLHIV (e.g men, formally employed PLHIV) and uptake of this differentiated care model was associated with favourable clinical outcomes.



1123 CLINIC-LEVEL FACTORS ASSOCIATED WITH TIME TO VIRAL SUPPRESSION IN WASHINGTON DC

Anne K. Monroe[1], Nabil Rayeed[2], Maria Jaurretche[1], Lindsey Powers Happ[1], Kevin Trac[1], Arpi Terzian[1], Alan Greenberg[1], Amanda D. Castel[1]

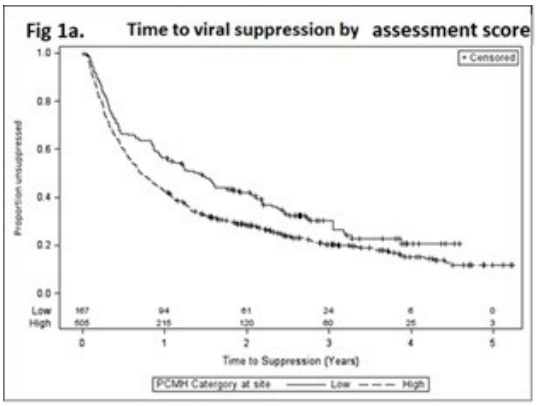
[1]The George Washington University, Washington, DC, USA, [2]Cerner Corp, Kansas City, MO, USA

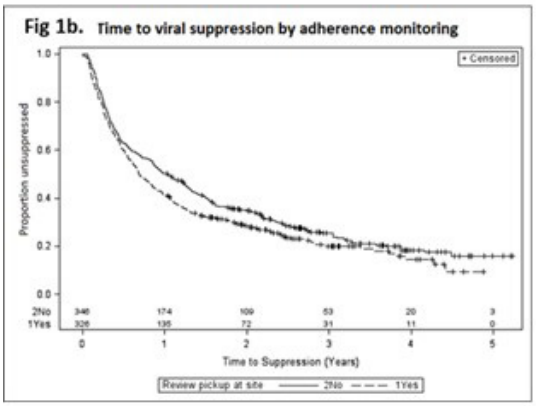
Background: Multiple individual-level factors are associated with prolonged time to antiretroviral therapy (ART) initiation and viral suppression (VS), e.g., younger age and higher CD4 cell count. Less is known about the impact of clinic-level factors, i.e., characteristics of the clinic where care is received. The DC Cohort, an observational cohort with 14 clinics enrolling people with HIV (PWH) in Washington, DC, offers a unique opportunity to examine multiple clinics in one city. We examined the association between clinic-level factors and time to ART initiation/VS.

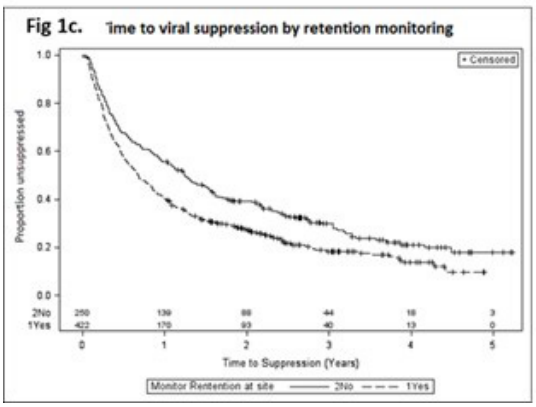
Methods: We included data from 2011-2016 from PWH who were not on ART and not virally suppressed at enrollment, had ≥ 12 months of follow-up, and had baseline and follow-up HIV RNA values. Outcomes were ART initiation and VS (HIV RNA < 200 copies/mL) anytime post-enrollment. We conducted a clinic survey and calculated an assessment score (range 0-9; high score 7-9) based on clinic hours, outside referrals, visit wait time, reengagement after missed visits, text messages, and availability of group visits, urgent care, and subspecialty medical services. Additional variables were: 1) "retention monitoring," i.e., review of clinic databases and electronic health records and 2) "ART monitoring" i.e., routine review of medication pick up. We performed univariate and multivariate Cox proportional hazards analyses to identify factors associated with time to ART initiation/VS.

Results: The median age of the 672 participants was 42 years, 82% were black, 74.3% were male, and 42.3% were men having sex with men. Almost half attended a clinic with a high assessment score, 62.8% attended a clinic with retention monitoring, and 48.5% attended a clinic with adherence monitoring. VS was achieved by 82% of participants. Clinic-level factors associated with the outcomes included attending a clinic with a high assessment score (for ART initiation adjusted Hazard Ratio (aHR)=1.41, 95% CI 1.14, 1.75; for VS aHR=1.50, 95% CI 1.19, 1.89); retention monitoring (for ART initiation aHR=1.37, 95% CI 1.02, 1.83; for VS aHR=1.43, 95% CI 1.15, 1.78); and adherence monitoring (for ART initiation aHR=1.32, 95% CI 1.07, 1.62; for VS aHR=1.26, 95% CI 1.00, 1.58) (Figure).

Conclusion: Clinics with services that increase accessibility and comprehensiveness of care as well as actively monitor retention and ART adherence have faster time to ART initiation and VS. Our findings highlight aspects of HIV care models that may optimize patient outcomes.







1124 PREDICTORS OF PERSISTENT LOW LEVEL VIREMIA AND TRANSIENT VIRAL BLIPS

Allahna L. Esber[1], Christina Polyak[1], Jonah Jonah Maswai[2], John Owuoth[3], Lucas Maganga[4], Akindiran Akintunde[5], Hannah Kibuuka[6], Julie Ake[7], Trevor Crowell[1]

[1]US Military HIV Research Program, Silver Spring, MD, USA, [2]KEMRI/Walter Reed Proj, Kericho, Kenya, [3]KEMRI/Walter Reed Proj, Kisumu, Kenya, [4]Walter Reed Program–Tanzania, Mbeya, Tanzania, United Republic of, [5]Walter Reed Program–Nigeria, Abuja, Nigeria, [6]Makerere Univ Walter Reed Proj, Kampala, Uganda, [7]Walter Reed Army Institute of Research, Silver Spring, MD, USA

Background: WHO guidelines identify HIV RNA less than 1000 copies/ml as the goal of antiretroviral therapy (ART). However, the clinical implications of and factors associated with persistent viremia below this threshold are unclear in the African context. We examined factors associated with persistent low level viremia (pLLV) and transient viral blips among HIV-infected participants in four African countries.

Methods: AFRICOS is an ongoing cohort enrolling HIV-infected and uninfected participants at 11 clinical sites in Uganda, Kenya, Tanzania, and Nigeria. Clinical assessments, including viral load testing, are performed every six months. We evaluated participants who were prescribed ART for at least six months without virologic failure for pLLV and blips. We defined pLLV as HIV RNA 20-999 copies/ml for at least two consecutive study visits, a blip as one HIV RNA 20-999 copies/ml preceded and followed by an undetectable measurement, and virologic failure as one HIV RNA ≥1,000 copies/ml. We used generalized estimating equations with a binomial distribution to calculate adjusted odds ratios (AORs) to assess associations between pLLV, blips, and factors of interest.
Results: As of June 1, 2017, we enrolled 2,635 HIV infected participants of which 1553 participants met our inclusion criteria. The median age was 40 years (IQR: 34-47) and 58% were female. PLLV was observed in 520 participants while blips were observed in 519 participants. In the multivariable analysis, Kenyan and Tanzanian sites (Kenya AOR: 0.18, 95% CI: 0.14, 0.24; Tanzania AOR: 0.64, 95% CI: 0.47, 0.88), duration of ART ≥5 years (AOR: 0.73, 95% CI: 0.57, 0.94), and higher CD4 count (AOR: 0.77, 95% CI 0.60, 0.99) were all associated with lower odds of pLLV. Participants on a protease inhibitor (PI) had a 3.28 times higher odds of pLLV (95% CI: 1.17, 9.19). Study site, longer duration of ART, and being on an NRTI were significantly associated with blips.
Conclusion: PLLV and blips were common with 1/3 of participants experiencing these outcomes. The difference in significant risk factors supports that those experiencing LLV blips may be clinically different than those with pLLV. The increased odds of pLLV among those on a PI may have implications for the rollout of tenofovir-lamivudiine-dolutegravir (TLD) and will warrant close monitoring. With the high incidence of pLLV in this population, a better understanding of the long-term impacts on virologic failure, drug resistance, and clinical outcomes is needed.

			Persistent low level viremia		Viral blips	
		N(%)[1]	AOR[2]	95% CI	AOR[2]	95% CI
Study site	Uganda	295 (19%)	-		-	
	Kenya	888 (57%)	**0.18**	**(0.14, 0.24)**	**0.83**	**(0.73, 0.95)**
	Tanzania	210 (13%)	**0.64**	**(0.47, 0.88)**	**1.49**	**(1.24, 1.78)**
	Nigeria	160 (10%)	0.96	(0.69, 1.33)	**1.54**	**(1.27, 1.86)**
On PI		138 (9%)	**3.28**	**(1.17, 9.19)**	1.52	(0.70, 3.27)
On NRTI		1540 (99%)	0.73	(0.31, 1.72)	**0.36**	**(0.14, 0.92)**
CD4 (cells/mm3)	<200	157 (10%)	-		-	
	200-349	399 (26%)	0.88	(0.69, 1.13)	1.27	(0.96, 1.68)
	350-499	394 (25%)	0.77	**(0.60, 0.99)**	1.26	(0.96, 1.66)
	≥500	573 (37%)	0.78	(0.60, 1.02)	1.30	(0.99, 1.70)
Duration on ART	6-11 months	474 (30%)	-		-	
	1-4 years	604 (39%)	0.88	(0.74, 1.05)	**2.06**	**(1.54, 2.75)**
	5+ years	475 (31%)	**0.73**	**(0.57, 0.94)**	**1.82**	**(1.36, 2.45)**

[1]At initial visit
[2]Adjusted for age and gender

1125 IMPROVED OUTCOMES WITH MAXIMUM ASSISTANCE, LOW-THRESHOLD HIV CARE (THE "MAX CLINIC")

Julia C. Dombrowski, Sean Galagan, Meena Ramchandani, Shireesha Dhanireddy, Robert D. Harrington, Matthew R. Golden
University of Washington, Seattle, WA, USA

Background: The MAX Clinic is designed for HIV+ persons with extensive psychosocial barriers who do not engage in standard HIV care. It includes walk-in access to primary care in an STD clinic, intensive coordinated case management, food vouchers, free bus passes and cell phones, and financial incentives for blood draws and achieving viral suppression. We conducted a retrospective cohort study comparing outcomes in the first 50 patients enrolled in the MAX Clinic to matched control patients attending a Ryan White Part C-funded clinic with wrap-around support services.
Methods: For each MAX patient we identified 2 control patients who had ≥1 encounter in the Madison Clinic within 2 months of the MAX patient's enrollment ("baseline") and had a most recent viral load (VL) >200 copies/mL. We examined outcomes at 6 and 12 months post-baseline. The primary outcome was viral suppression (≥1 VL <200 copies/mL). Continuous viral suppression (≥2 consecutive VL<200 copies/mL ≥60 days apart) and care engagement (≥2 visits ≥60 days apart) were secondary outcomes. We compared outcomes in the 12 months post- vs. 12 months pre-enrollment for each patient using $\chi 2$ tests. To compare the pre-post changes in MAX vs. control patients, we used generalized estimating equations adjusted for housing status, substance use, and psychiatric diagnoses.
Results: Compared to control patients (N=100), MAX Clinic patients enrolled 12/2014-11/2015 (N=50) had lower CD4 counts (median 172 vs. 262 cells/mm^3, p=0.03), higher viral loads (median 22,695 vs. 1,649 copies/mL, p<0.001), were less likely to have had any suppressed viral load measurements in the past year (20% vs. 51%, p=0.002), and more often had illicit substance or hazardous alcohol use (90 vs. 70%; p=0.006), unstable housing (64 vs. 36%; p=0.001), or a history of incarceration (68 vs. 31%, p <0.001) documented in medical records. The proportion with diagnosed psychiatric illness did not differ significantly (78 vs. 73%, p=0.51). Viral suppression increased in both groups from the 12 months pre-baseline to post-baseline (Table), but the improvement among MAX Clinic patients (20 to 82%) was significantly greater than control patients (51 to 65%). Continuous viral suppression and engagement in care increased from pre- to post-baseline among MAX patients, but not significantly compared to controls.
Conclusion: A low-threshold clinic with extensive support services and incentives can substantially increase viral suppression among high need, complex HIV+ patients.

Viral suppression among patients enrolled in the MAX Clinic and (N=50) and standard-of-care clinic (N=100) in the 12 months post-baseline compared to 12 months pre-baseline

	MAX pre	MAX post	Control pre	Control post
Viral suppression, N (%) [viral load (VL)<200 copies/mL at least once]	10 (20)	41 (82)	51 (51)	65 (65)
Within group pre-post comparison, OR (95% CI)*	4.1 (2.3 – 7.2)		1.3 (1.0-1.6)	
Between group pre-post comparison, OR (95% CI)*	3.2 (1.8 – 5.9)			
Continuous viral suppression, N (%) (≥2 consecutive VL<200 ≥60 days apart)	4 (8)	22 (44)	7 (7)	25 (25)
Within group pre-post comparison, OR (95% CI)*	5.5 (2.2 – 14.0)		3.6 (1.6 – 7.8)	
Between group pre-post comparison, OR (95% CI)*	1.5 (0.5 – 5.2)			
Engagement in care, N (%) (≥2 visits ≥60 days apart)	22 (44)	41 (82)	64 (64)	90 (90)
Within group pre-post comparison, OR (95% CI)*	1.9 (1.3 – 2.6)		1.4 (1.2 – 1.6)	
Between group pre-post comparison, OR (95% CI)*	1.3 (0.9 – 1.9)			

*Generalized estimating equations controlling for housing status, substance use and psychiatric diagnoses.

1126 CLINICAL OUTCOMES OF US YOUNG BLACK MEN WITH HIV RECEIVING MEDICAL CARE, 2009–2014

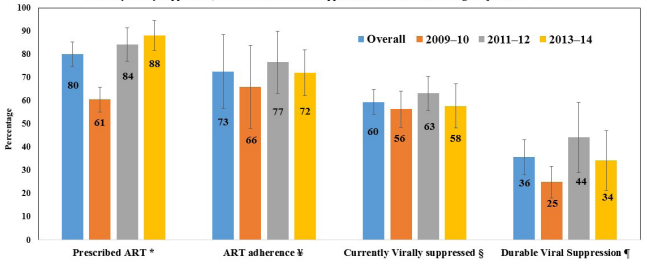
Pranesh P. Chowdury, Linda Beer, R. L. Shouse, Heather Bradley
CDC, Atlanta, GA, USA

Background: Nearly one-third of HIV diagnoses among blacks in the United States in 2015 occurred among young people aged 15–24 years, and three-quarters were among men. Viral suppression, which greatly reduces the risk of HIV transmission, increased from 72% in 2009 to 80% in 2013 among persons in HIV care. National data on viral suppression or other clinical outcomes among young black men in HIV care are lacking.
Methods: We analyzed 2009–2014 Medical Monitoring Project (MMP) interview and medical record data collected from 336 black men aged 18–24 years. MMP is a surveillance system that produces nationally representative information about adults with diagnosed HIV in the US. We estimated the proportion of young black men in HIV care who were virally suppressed at last test (current viral suppression) and at all tests in the previous 12 months (durable viral suppression). We also estimated the proportion prescribed antiretroviral therapy (ART) and adherent to ART. We assessed changes over time in all clinical outcomes and certain characteristics associated with each outcome.
Results: During 2009–2014, 60% of young black men in HIV care were currently virally suppressed, and 36% had durable viral suppression. There was no significant change over time in either viral suppression measure. ART prescription increased from 61% in 2009–2010 to 88% in 2013–2014 (β=0.13, P for trend <0.05). Overall, 73% of young black men were adherent to ART; this did not change significantly over time. Current viral suppression was lower among the 45% of young black men who used injection or non-injection drugs than among those who did not (49% vs. 68%, P <0.05). Durable HIV viral suppression was lower among the 12% of young black men who were homeless compared with those who were not homeless (23% vs. 38%, P <0.05) and also lower among those who used injection or non-injection drugs than among those who did not (28% vs. 42%, P <0.05). ART adherence was lower among the

20% of young black men who had current depression compared with who did not (53% vs. 78%, P <0.05) and among those who were homeless compared with those who were not (56% vs. 75%, P <0.05).

Conclusion: Viral suppression among young black men in HIV care was much lower than in the overall population receiving HIV care, and there were no increases in viral suppression or ART adherence among this group during 2009–2014. Improving viral suppression is essential to ensure health and reduce HIV transmission in this key population.

Figure 1: Proportion of young black men aged 18-24 years in HIV care who were prescribed ART, adherent to ART, currently virally suppressed, and had durable viral suppression: Medical Monitoring Project 2009–2014



* Antiretroviral therapy (ART) prescription document in medical record, significant trend test (β=0.13, *P* for trend <0.05)
¥ Self-reported 100% antiretroviral therapy (ART) adherence in past 3 days
§ Virally suppressed (<200 copies/mL) at last test documented in medical record
¶ Virally suppressed (<200 copies/mL) at all tests in past 12 months documented in medical record

Disclaimer: The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

1127 BEYOND VIRAL SUPPRESSION: BROADENING QUALITY MEASURES (QM) FOR TOTAL HIV PATIENT CARE

Michael A. Horberg[1], Jackie Blank[1], Kevin Rubenstein[1], Leo Hurley[2], Peter Kadlecik[1], Daniel B. Klein[2], Michael J. Silverberg[2]
[1]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [2]Kaiser Permanente Northern California, Oakland, CA, USA

Background: The HIV Cascade emphasized the importance of linkage, retention, and viral suppression as outcomes, but comprehensive care of HIV patients requires a broader view of what constitutes quality care. At Kaiser Permanente Mid-Atlantic States (KP), an integrated health system providing comprehensive HIV care in District of Columbia, Maryland, and Virginia, we strove to define a more composite measure of quality care for our HIV patients, considering both process and outcome QMs, obtained from the electronic health record.

Methods: Study population: HIV+ patients ≥18 years old with ≥6 months KP membership in both calendar years 2015 and 2016 (N=2,307). Process QM (based on expert panel) are: ever vaccination for Prevnar, Pneumovax, and flu (either year); ≥1 visit to primary care provider (PCP) and HIV/ID specialist each year; screening for syphilis and gonorrhea/chlamydia (either year). Outcome QM are: HIV RNA<200 copies/mL at last measure each year; no hospitalization or ED visit either year; non-smoker, blood pressure <140 systolic and <90 diastolic as of last office visit; no incident diagnosis of depression in time span (either year); hemoglobin ≥12g/dL, blood sugar <140mg/dL, ALT <51U/L, LDL cholesterol <130mg/dL, and eGFR ≥60 (all labs as last measured). Patients needed to achieve all process or outcome measures to meet the QM. Missing data was considered unachieved. We used a logistic model to estimate odds of achieving these QM associated with sex, age, race/ethnicity, coverage plan, and HIV risk.

Results: 33.0% met all process QM, while only 17.0% met all outcome QM (Table). Only 1.1% and 1.9% met no process or outcome QM, respectively. Least frequently met process QM was visit to PCP (59.4%; but visit to HIV/ID was 81.7%); least met outcome QM was LDL <130 mg/dL (67.9%). Significantly greater odds of achieving all process QM was associated with female sex (versus males; OR=1.37 [95% CI: 1.08,1.74]); Black (vs. White; OR=1.38 [1.06,1.81]); MSM (vs. heterosexual; OR=1.45 [1.12,1.89]); Medicaid and Medicare (vs. Commercial; OR=1.93 [1.34,2.78] and 1.50 [1.09,2.06], respectively). Medicare was the only coverage plan significantly less likely to achieve all outcome QM (vs. Commercial; OR=0.52 [0.33,0.85]).

Conclusion: Broadening the scope of HIV patient care QM beyond viral suppression helps identify opportunities for improvement. Successful process QM does not necessarily translate into higher outcome QM. Certain measures merit attention, particularly for selected subgroups.

Table: Patient Demographics, Number, and Percent Achieving Process and Outcome QM

Variable (Total Patients=2,307)	Number	%
Sex: Male	1612	69.9%
Female	695	30.1%
Age: Median years (IQR)		50 (41-58)
18-29 years	215	9.3%
30-49 years	871	37.8%
50-64 years	1022	44.3%
65+	199	8.6%
Race/Ethnicity: White	352	15.3%
Black	1753	76.0%
Latino	104	4.5%
Asian	30	1.3%
Coverage Plan: Commercial	1669	72.3%
Medicare	263	11.4%
Exchange (ACA)	236	10.2%
Medicaid	139	6.0%
HIV Risk: Men having sex with men (MSM)	840	36.4%
Heterosexual	861	37.3%
IDU	243	10.5%
Process QM: Prevnar vaccinated ever by end of 2016	2157	93.5%
Pneumovax vaccinated ever by end of 2016	2101	91.1%
Flu vaccination in 2015 or 2016	1869	81.0%
≥1 visit to PCP in both 2015 and 2016	1372	59.5%
≥1 visit to HIV/ID in both 2015 and 2016	1887	81.8%
Screened for Syphilis in 2015 or 2016	1968	85.3%
Screened for Gonorrhea/Chlamydia in 2015 or 2016	1721	74.6%
Outcome QM: HIV RNA < 200 copies/mL at last measure in both 2015 and 2016	1637	71.0%
NOT hospitalized in calendar year (except pregnancy) in either 2015 or 2016	1981	85.9%
No visit to emergency department in either 2015 or 2016	1777	77.0%
Non-Smoker at last visit	1875	81.3%
BP<140 systolic at last visit	1865	80.8%
BP<90 diastolic at last visit	1957	84.8%
No new diagnosis of depression in 2015 or 2016	2088	90.5%
Hemoglobin ≥12 g/dL at last measured	1766	76.5%
Blood Sugar <140 mg/dL at last measured (random or fasting)	2045	88.6%
ALT <51 U/L at last measured	1996	86.5%
eGFR≥60 at last measured	2011	87.2%
LDL Cholesterol <130 mg/dL at last measured	1567	67.9%

1128 HIV STIGMA IS ASSOCIATED WITH RETENTION AND VIRAL LOAD AMONG US PATIENTS IN CARE

Katerina A. Christopoulos[1], Torsten B. Neilands[1], Wendy Hartogensis[1], Michael J. Mugavero[2], Heidi M. Crane[3], Rob Fredericksen[3], Elvin Geng[1], W. C. Mathews[4], Geetanjali Chander[5], Joseph J. Eron[6], Kenneth H. Mayer[7], John Sauceda[1], Kimberly Koester[1], Troy Wood[1], Mallory Johnson[1]
[1]University of California San Francisco, San Francisco, CA, USA, [2]University of Alabama at Birmingham, Birmingham, AL, USA, [3]University of Washington, Seattle, WA, USA, [4]University of California San Diego, San Diego, CA, USA, [5]Johns Hopkins University, Baltimore, MD, USA, [6]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [7]Fenway Health, Boston, MA, USA

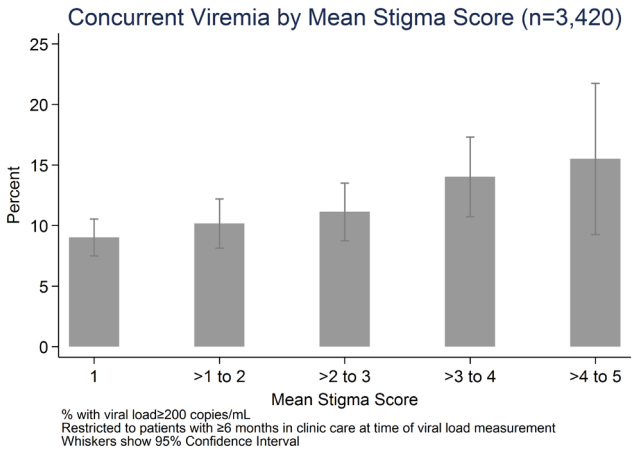
Background: HIV-related stigma is a barrier to engagement in care, yet few large-scale assessments of stigma and HIV outcomes exist in the United States (US).

Methods: The Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort study integrates medical record and survey data from patients in primary care at seven academic HIV clinics across the US. We incorporated a yearly, validated 4-item assessment of internalized HIV stigma (1=strongly disagree to 5=strongly agree, α=0.91) into patient surveys administered every 4-6 months. We used multivariable logistic regression models to evaluate associations between mean stigma and: 1) poor retention in care (≥ 2 missed primary care visits in the year prior to stigma assessment); 2) concurrent viremia (viral load >200 copies/mL +/- 90 days of the stigma assessment), and controlled for age, gender, race/ethnicity, sexual orientation, time since CNICS enrollment, and site. We assessed linearity of stigma as a continuous predictor with the log odds of outcomes using cumulative sums of residuals.

Results: From March 2016 - April 2017, 4,428 patients completed the stigma assessment. Median (IQR) age was 48 (39-55) years; 83% were male, 36% were black, 14% were Hispanic, and 27% identified as heterosexual. Median (IQR) CNICS enrollment was 6 (3-11) years. Mean stigma was 1.99 (SD 1.07) and 28.3% agreed/strongly agreed with ≥1 stigma question. Among 3,345 patients with missed visit/covariate data, 19.0% had poor retention. Higher stigma was associated with increased odds of poor retention (aOR=1.13, 95% CI 1.04-1.22, p 0.004). The proportion of patients with concurrent viremia increased as mean stigma increased (Figure). In 3,290 patients with viral load/covariate data, 10.2% had concurrent viremia. Higher stigma was associated with increased odds of viremia (aOR=1.13, 95% CI 1.02-1.25, p 0.024). In both models, younger

age and black race were also associated with poor retention and concurrent viremia.

Conclusion: In one of the first multi-site, clinic-based studies of HIV stigma in the US, we found that higher stigma had a modest but statistically significant independent effect on the likelihood of poor retention and concurrent viremia. These findings suggest that ameliorating stigma will be necessary to optimize HIV outcomes in pursuit of "getting to zero." Future research will examine prospective associations between stigma and HIV outcomes and the role of potential mediators such as depression and antiretroviral adherence.



1129 HIGH VIREMIA AMONG 'STABLE' PATIENTS RECEIVING ANTIRETROVIRAL THERAPY IN ZAMBIA

Mpande Mukumbwa-Mwenechanya[1], Emilie Efronson[1], Paul Somwe[1], Jillian L. Kadota[1], Monika Roy[2], Samuel Bosomprah[1], Kelvin Kaputula[1], Jake Pry[1], Nancy Padian[3], Elvin Geng[2], Charles B. Holmes[4], Izukanji Sikazwe[1], Anjali Sharma[1], Carolyn Bolton Moore[1]

[1]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, [2]University of California San Francisco, San Francisco, CA, USA, [3]University of California Berkeley, Berkeley, CA, USA, [4]Georgetown University, Washington, DC, USA

Background: Despite widespread availability of ART in Zambia, only 59.8% HIV-positive adults 15-59 years old on ART were found to have viral load (VL) suppression (<1000 copies of viral RNA/ml) in a recent community based study (1). This high level of silent non-suppression threatens to undermine the country's ability to attain the UNAIDS 2020 treatment target of 90-90-90.
1.Zambia Population Based HIV Impact Assessment, 2015-2016

Methods: A systematic sample of eligible stable patients (HIV+, on ART > 6 months, not acutely ill, CD4 >200/µl (if available)) in two purposively selected urban and heavy clinic patient load (>4500) sites were selected to assess the FastTrack model (accelerated pharmacy pick-ups to receive ART every 3 months (FastTrack model)). We collected dry blood spots (DBS) to test for baseline VL and extracted current socio-demographic and, clinical and pharmacy data retrospective to 12 months from study enrolment. Bivariate and backward stepwise logistic regression analyses were conducted to assess viral suppression rates and factors associated with odds of unsuppressed HIV VL at enrollment.

Results: Of the 407 enrolled, 308 patients had complete clinical data; 73% were female (n=225), median age was 34.7 years (IQR: 29.7-39.9) and median time on ART was 2144 days (IQR: 1087-2947). 43.5% (n=134) had no CD4 test result within the last 6 months and were enrolled based on clinical judgement of 'stability.' At enrollment into the FastTrack model, 40.3% (n=124) had >1000 copies of viral RNA/MI. Analyses showed no significant association of unsuppressed HIV VL with gender, age, WHO staging, time on ART and missed pharmacy appointments. Odds of unsuppressed VL was greater for those in WHO clinical stage 2 (OR: 1.25 (95% CI: 0.65, 2.42) and stage ≥3 (OR: 1.47 (95% CI: 0.87, 2.50) compared to those in stage 1, although effect sizes were statistically insignificant.

Conclusion: Rates of VL non-suppression among patients identified as stable were high and did not appear to have a specific age/ gender distribution. Clinical judgment combined with CD4 did not identify a large proportion of at risk patients. Strengthening access to routine VL testing is essential in order to ensure viremic patients are provided linkages to additional adherence and support services and that stable patients are correctly identified.

TABLE 1 . Characteristics associated with viral nonsuppression (defined as >=1000 copies) at baseline visit (N=308).[1]

Patient Characteristic at Baseline		Unadjusted OR (CI)	p-value
Sex			
	Female	*Reference*	0.37
	Male	0.79 (0.47, 1.33)	
Age category			
	>45 years	*Reference*	0.93
	36-45 years	0.89 (0.43, 1.85)	
	26-35 years	1.00 (0.49, 2.06)	
	<=25 years	1.14 (0.47, 2.75)	
WHO Stage			
	1	*Reference*	0.36
	2	1.25 (0.65, 2.42)	
	3 or 4	1.47 (0.87, 2.50)	
Time on ART			
	> 4 years	*Reference*	0.49
	2-4 years	0.71 (0.37, 1.35)	
	1-2 years	1.46 (0.66, 3.22)	
	<1 year	0.87 (0.36, 2.09)	
Number of late appointments w/in 12 months			
	0-3 late	*Reference*	0.48
	4-7 late	1.36 (0.82, 2.25)	
	8-11 late	1.07 (0.56, 2.04)	
ART Regimen			
	Old	*Reference*	0.82
	Current	0.99 (0.49, 2.00)	
	2nd line	0.59 (0.10, 3.43)	

1. All values had less than 5% missing
*p<0.05

1130 COMPLIANCE TO GUIDELINES FOR ROUTINE VIRAL LOAD TESTING IN RESOURCE LIMITED SETTINGS

Barbara Castelnuovo[1], Frank Mubiru[1], Mark Nsumba[1], Isaac Lwanga[1], Ivan Lumu[1], Agnes Kiragga[1], Steven J. Reynolds[2]

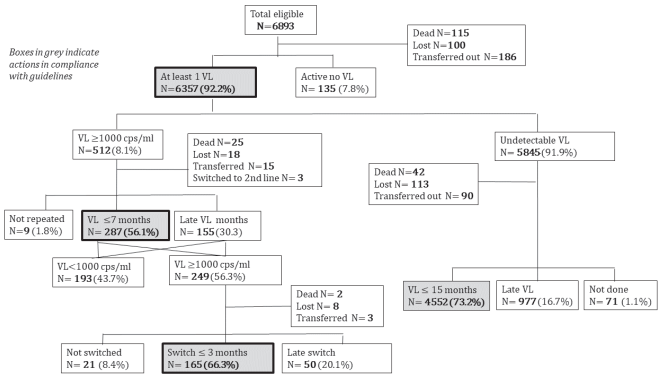
[1]Infectious Disease Institute, Kampala, Uganda, [2]NIH, Bethesda, MD, USA

Background: To achieve the final 90 of the UNAIDS 90-90-90 targets, it is critical that timely viral load (VL) testing is offered to all patients on ART. The WHO guidelines recommend VL every 12 months; patients with VL≥1000 copies/ml should repeat VL after 6 months and be promptly switched to 2nd line ART if treatment failure is confirmed. We aimed to evaluate the compliance to the WHO guidelines in implementing VL testing and managing patients according to guidelines in a large urban clinic in Uganda.

Methods: This analysis included all patients at the Infectious Diseases Institute in Kampala on 1st line ART after December 2014 (date of VL monitoring implementation). Patients not yet due for a repeat VL at database closure were excluded. We describe the "cascade" of VL management by reporting the proportion who received a VL test. Among those with VL15 months), and never. For those with VL≥1,000 copies/ml we evaluated the proportion with a VL repeated within 7 months (6 months per guidelines+ 1-month window for patients on 1-month prescription), late (>7 months), and never. For those with 2 VL≥1000 copies/ml we evaluated the proportion promptly switched to 2nd line defined as within 3 months, late (>3 months) and not switched.

Results: Among 9599 registered patients, 6,893 were eligible; 61.0% were female, median age at ART start was 36 years (IQR: 30-42), CD4 count was 166 (IQR: 68-293) cell/µL and median(IQR) duration on ART was 41(IQR: 17-87) months 6,357 (92.6%) had at least 1 VL, of which 512 (8.1%) was ≥1000 copies/ml. Figure 1 shows compliance to WHO guidelines. Among patients with VL<1000 copies/ml, VL was repeated ≤ 15 months in 73.2% and totally in 89%. In patients with VL≥1000 copies/ml VL was repeated in 56.1% (287/512) within 7 months, totally in 86.3%, and was confirmed ≥1000 copies/ml in 249 (56.3%). Of the latter only 165 (66.3 %) were switched to 2nd line within 3 months with a total of being switched of 86.4%. Details for all the other patients are shown in the figure.

Conclusion: We found a high rate of viral suppression (92%) in a population where the majority of the patients had been on long term ART with no VL monitoring. Compliance to timing of repeated VL in any category (VL < and ≥1000 copies/ml) was sub-optimal, however the proportion of patients for which no action was taken at the different steps was low.



1131 HEALTHCARE PROVIDER TRUST LINKED TO LONG-TERM HIV VIRAL SUPPRESSION

Kate G. Michel[1], Cuiwei Wang[1], Tracey Wilson[2], Kathryn Anastos[3], Mardge H. Cohen[4], Ruth Greenblatt[5], Margaret Fischl[6], Igho Ofotokun[7], Mirjam-Colette Kempf[8], Adaora Adimora[9], Joel Milam[10], Joanne Michelle F. Ocampo[1], Stephen J. Gange[11], Michael Plankey[1], Seble Kassaye[1]

[1]Georgetown University, Washington, DC, USA, [2]SUNY Downstate Medical Center, Brooklyn, NY, USA, [3]Montefiore Medical Center, Bronx, NY, USA, [4]Cook County Health & Hospitals System, Chicago, IL, USA, [5]University of California San Francisco, San Francisco, CA, USA, [6]University of Miami, Miami, FL, USA, [7]Emory University, Atlanta, GA, USA, [8]University of Alabama at Birmingham, Birmingham, AL, USA, [9]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [10]University of Southern California, Los Angeles, CA, USA, [11]Johns Hopkins Hospital, Baltimore, MD, USA

Background: Trust in the healthcare system (HS) and health providers (HP) is linked to medication adherence; however, many studies do not link to biological data. We hypothesize that trust differs by HIV status and is associated with longitudinal patterns of viremia.

Methods: A 2006 cross-sectional survey assessed the Healthcare System Distrust Scale (HSDS, 0=trust; 50=distrust), an adapted Patient-Physician Trust Scale (PPTS, 0=distrust; 25=trust), HIV medication distrust and demographics in 1049 HIV+ and 463 high-risk HIV-negative women from the Women's Interagency HIV Study. This study identified HIV viral load trajectories in 2440 HIV+ women who contributed ≥ 4 semi-annual visits from 1994-2015. Viral suppression was defined by assay detection limits (<80 to <20 copies/mL). Group-based probability trajectory analyses categorized women based on longitudinal viral load patterns, and identified 3 groups: sustained viremia (SV; n=1,010), intermittent viremia (IV; n=719), and non-viremia (NV; n=711). Ordinal logistic regression models assessed trajectory group and HP/HS trust, controlling for demographics.

Results: Most women were African American (60%), currently insured (89%) non-smokers (56%). HIV+ women were more trusting of HS (HSDS 12.6 vs. 13.8, p=0.02) and HP (PPTS 20.6 vs. 18.8, p<0.0001) compared to HIV- women. HIV+ women with NV had higher HP trust compared to SV women (PPTS: SV 19.9, IV 20.6, NV 21.4, p<0.0001); there was no difference in HS trust between viral trajectory groups. Compared to NV women, SV women were less likely to agree that HIV medicines help people live longer (86% vs. 94%, p<0.0002) or that HIV medicines prevent hospitalizations (73% vs. 87%, p<0.0001). Only 52% of SV women believed HIV medicines work as well for African American/Latina women compared to white women (IV 61%, NV 66%, p=0.0005). In ordinal logistic regression, groups with higher viremia were associated with HP distrust (OR 1.49; 95% CI 1.12, 1.98), HS distrust (OR 1.49; 95% CI 1.13, 1.98), African American race (OR 1.70; 95% CI 1.1.29, 2.24), current smoking (OR 2.42; 95% CI 1.84, 3.19), and current unemployment (OR 1.62; 95% CI 1.23, 2.14).

Conclusion: HIV+ women express high levels of HS and HP trust. HIV-negative women's low trust in HS, HP, and HIV medicines may have implications for PrEP use. Trust in HPs and HIV medicines is less common among SV women. Successful long-term HIV management depends on HP and HS trust; current data is needed on healthcare perceptions linked to HIV biological data.

1132 CHARACTERIZING HIV CARE TRAJECTORIES AND DIFFERENCES IN PATIENT OUTCOMES

Eva A. Enns[1], Cavan Reilly[1], Karen Baker[2], Keith Henry[2]

[1]University of Minnesota, Minneapolis, MN, USA, [2]Hennepin County Medical Center, Minneapolis, MN, USA

Background: Standard measures of retention in HIV care are all-or-nothing classifications: persons living with HIV (PLWH) are either "in care" or "out of care". However, in reality, engagement in care is an evolving process, with periods of more or less frequent care encounters. The goal of this analysis was to classify PLWH into different "care trajectory" classes based on longitudinal patterns of care and to determine how patient outcomes differ across care classes.

Methods: We conducted a retrospective analysis of all PLWH ≥18 years-old who received medical care at a public, hospital-based clinic in Minneapolis, MN between 2008-2013. We analyzed clinic visit and laboratory test data from 2008-2015 merged with surveillance records to account for HIV care at other clinics, out-of-state relocation, and mortality. Individual HIV care trajectories were constructed in six-month intervals starting from first observed care event until death, relocation, or the end of 2015. PLWH observed for less than 1 year were excluded from analysis. Latent class analysis was used to identify care trajectory classes, described by the probability of having a clinical encounter in each six-month interval. The number of care classes was chosen to maximize model fit. Patient outcomes included retention (≥1 care events in every six-month interval), mortality, and sustained viral suppression (all viral loads <50 copies/mL in last 12 months of care).

Results: The study population (N=2,110) was best divided into 5 care trajectory classes: (1) consistent care; (2) less frequent care; (3) return to care after initial attrition; (4) moderate attrition; and (5) rapid attrition. Only Class 1 had a substantial (78.4%) level of retention using standard measures. PLWH in Class 1 were also the most likely to have sustained viral suppression in the last 12 months of care. Though retention was consistently low among the other care classes, there was substantial variation in viral suppression, from 63.2% in Class 2 to 24.2% in Class 5. Mortality was greatest for those in Class 1, but the total number of deaths over the study period was relatively small.

Conclusion: Characterizing the longitudinal patterns of HIV care identified five intuitive care trajectories, including four distinct patterns of suboptimal retention with differing levels of viral suppression. Care trajectories could be used to prioritize re-engagement efforts.

	Class 1	Class 2	Class 3	Class 4	Class 5
N (%)	1225 (58.1)	307 (14.5)	184 (8.7)	163 (7.7)	231 (10.9)
Probability of care – mean % (95% CI)					
6-12 months	99 (97, 100)	92 (88, 97)	54 (44, 64)	94 (88, 99)	41 (33, 49)
12-18 months	97 (96, 99)	92 (87, 98)	30 (19, 41)	91 (84, 98)	15 (8, 22)
25-30 months	98 (97, 99)	84 (79, 90)	50 (40, 60)	58 (48, 69)	0 (0, 2)
48-54 months	96 (95, 98)	79 (72, 86)	60 (48, 72)	11 (3, 18)	1 (0, 4)
72-78 months	96 (94, 98)	53 (43, 62)	86 (75, 97)	8 (0, 16)	7 (0, 15)
Outcomes by class – N (%)					
Retained in care	960 (78.4)	2 (0.7)	7 (3.8)	9 (5.5)	0 (0.0)
Died by study end	37 (3.0)	1 (0.3)	4 (2.2)	0 (0.0)	3 (1.3)
Sustained viral suppression	862 (70.4)	194 (63.2)	98 (53.3)	84 (51.5)	56 (24.2)

1133 FROM PRISON'S GATE TO DEATH'S DOOR: SURVIVAL ANALYSIS OF RELEASED PRISONERS WITH HIV

Kelsey B. Loeliger[1], Jaimie P. Meyer[1], Maria M. Ciarleglio[1], Mayur M. Desai[1], Colleen Gallagher[2], Frederick Altice[1]

[1]Yale University, New Haven, CT, USA, [2]Connecticut Department of Correction, Wethersfield, CT, USA

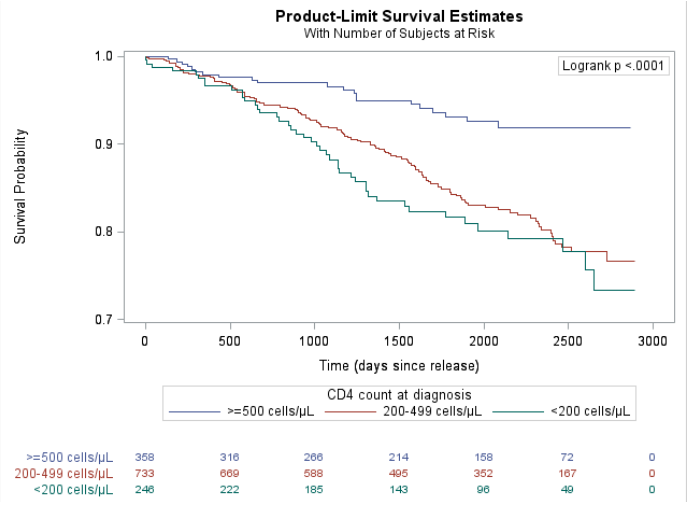
Background: Prisoners returning to the community have high mortality, but there is limited data on death among those living with HIV (PLH). This study evaluates causes of and risk factors for death among PLH after prison or jail release.

Methods: We created a retrospective cohort of all PLH released from a Connecticut jail or prison in 2007–14 (n=1,350) by linking prison pharmacy and custody data with state death indices and HIV surveillance data. Cox proportional hazards regression identified predictors of death.

Results: Overall, 184 (13.6%) died during a median of 5.2 (IQR 3.0-6.7) years follow-up after release (crude mortality rate of 28/1,000 person-years). Among PLH who died, median time to death was 3.0 years (IQR 1.5-4.5); 179 died in the community and 5 died during a later re-incarceration. Among the 175 deaths with available data, main primary causes included HIV (n=76, 43.4%), drug overdose (n=26, 14.9%), liver disease/failure or hepatitis C (n=16, 9.1%), heart disease (n=11, 6.3%), infection (n=9, 5.1%), accidental injury or homicide (n=9, 5.1%), non-AIDS related cancer (n=5, 2.9%), diabetes (n=4, 2.3%), and suicide (n=2, 1.1%). Independently significant (p<0.05) predictors of death

were HIV acquisition from injection drug use (adjusted hazard ratio [aHR] 1.53), low CD4 count at diagnosis (200-499 cells/μL: aHR 2.37; <200 cells/μL: aHR 3.26), higher re-incarceration rate during follow-up (aHR 5.62), HIV virologic failure within 6 months of death/censoring (aHR 2.91), and ≥1 medical comorbidity (1 comorbidity: aHR 1.51; ≥2 comorbidities: aHR 1.82). Protective factors were black race (aHR 0.53), at least a high school diploma (aHR 0.72), medical insurance (aHR 0.09), at least one long (>1 year) re-incarceration during follow-up (aHR 0.42), higher percentage of re-incarcerations in which ART was prescribed (compared to never re-incarcerated, 0-10%: aHR 0.45; 11-50%: aHR 0.16; 51-90%: aHR 0.04; 91-100%: aHR 0.13), and a moderate addiction severity score during one's last incarceration (aHR 0.53).

Conclusion: Among PLH, there is a high rate of death after release. Advanced HIV disease, substance use disorders, and lack of medical insurance strongly predict death post-release. Long re-incarcerations and those involving ART are protective, but frequent re-incarceration is highly detrimental. While healthcare provided during incarceration is beneficial, linkage to and retention in community-based healthcare, addiction treatment, and other resources are crucial to reducing mortality after release.



1134 DISCRIMINATION IN HEALTHCARE SETTINGS AMONG PATIENTS WITH RECENT HIV DIAGNOSES

Amy R. Baugher, Linda Beer, Jennifer Fagan, Christine Mattson, R. L. Shouse
CDC, Atlanta, GA, USA

Background: Discrimination in healthcare settings has been associated with sub-optimal healthcare utilization and medication adherence among persons living with HIV (PLWH). Reducing discrimination is a national HIV prevention goal. We estimated the prevalence of healthcare discrimination among PLWH with recent diagnoses. We examined the association between discrimination and poverty and homelessness by whether patients attended a facility funded by Ryan White HIV/AIDS Program (RWHAP), which was designed to assist vulnerable PLWH.

Methods: We used nationally representative data from the Medical Monitoring Project, a surveillance system of PLWH receiving HIV care. We analyzed pooled data from 2011–2014 on self-reported discrimination among PLWH with diagnoses ≤5 years before interview (N=3,770). Discrimination was defined as reporting ≥1 of the following experiences since testing positive for HIV: a healthcare worker exhibited hostility towards them, gave them less attention than other patients, or refused them service. We assessed whether RWHAP facility attendance modified the relationship between discrimination and poverty and homelessness using chi-square tests.

Results: Of PLWH with recent diagnoses, 13.8% experienced discrimination since receiving the diagnosis. Overall, PLWH were more likely to report discrimination if their income was below the poverty level (15.3%) vs. above (13.0%), they experienced homelessness in the past 12 months (22.1%) vs. no homelessness (12.8%), or they attended a non-RWHAP facility (17.4%) vs. RWHAP facility (13.1%). Among patients attending RWHAP facilities, discrimination was similar by poverty status (12.5%–14.9%); among patients attending non-RWHAP facilities, discrimination was higher among those in poverty (27.5%) vs. not in poverty (15.1%). Homelessness was associated with higher discrimination regardless of facility type, but was less common in RWHAP (21.5%) vs. non-RWHAP facilities (34.0%; Table 1).

Conclusion: More than 1 in 10 PLWH with recent diagnoses experienced discrimination in healthcare settings. PLWH reporting poverty or homelessness were disproportionately affected, particularly those attending non-RWHAP facilities. Ensuring PLWH receive HIV care in settings free of discrimination may improve outcomes in the HIV care continuum. Incorporating practices typical of RWHAP facilities, such as anti-discrimination training and the medical home model may reduce discrimination in non-RWHAP healthcare settings.

Table 1. Discrimination[a] experienced by patients recently diagnosed with HIV stratified by poverty[b], homelessness[c], and receiving care at a facility funded by Ryan White HIV/AIDS Program (RWHAP)[d], MMP 2011–2014 (N=3,770)

	Discrimination	
	n (%) (95%CI)	OR (95%CI)*
RWHAP		
Poverty	213 (14.9%) (13.0, 16.8)	1.2 (0.9, 1.5)
No poverty	132 (12.5%) (10.4, 14.5)	-
Non-RWHAP		
Poverty	42 (27.5%) (18.0, 36.9)	2.1 (1.3, 3.5)*
No poverty	69 (15.1%) (10.5, 19.7)	-
RWHAP		
Homeless	68 (21.5%) (15.0, 27.9)	1.9 (1.3, 2.9)*
Not homeless	291 (12.3%) (11.0, 13.6)	-
Non-RWHAP		
Homeless	17 (34.0%) (20.7, 47.2)	2.5 (1.4, 4.6)*
Not homeless	98 (17.0%) (12.3, 21.6)	-

[a]Discrimination was defined as reporting at least one discriminatory experience in an HIV healthcare setting: exhibited hostility or a lack of respect towards you, given you less attention than other patients, or refused you service.
[b]Poverty guidelines as defined by the Department of Health and Human Services (HHS). More information regarding the HHS poverty guidelines can be found at http://aspe.hhs.gov/poverty/faq.cfm
[c]Living on the street, in a shelter, in a single-room-occupancy hotel, or in a car in the past 12 months
[d]Ryan White HIV/AIDS Program (RWHAP) was defined as a facility receiving any Ryan White funding from any source
[e]Odds ratio (OR); 95% confidence interval (CI) assessed using Rao-Scott chi-square tests
*$p<0.05$

1135 LONGITUDINAL DIFFERENCES IN POOR ADHERENCE AMONG YOUTH AND ADULTS LIVING WITH HIV

Kalysha Closson[1], Alexis Palmer[1], Cathy Puskas[1], Kate Salters[1], Surita Parashar[1], Karyn Gabler[1], Lateefa Tiamiyu[1], Wendy Zhang[1], Angela Kaida[2], Robert S. Hogg[1]
[1]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, [2]Simon Fraser University, Burnaby, BC, Canada

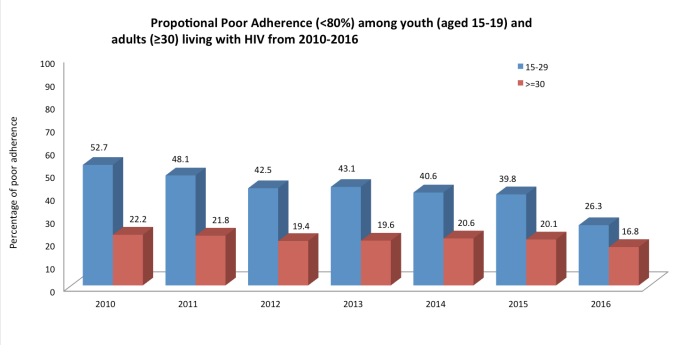
Background: Youth (aged <30) living with HIV (YLWH) experience worse HIV treatment outcomes compared with adults. This inequity may be due, in part, to differences in adherence to combination antiretroviral therapy (cART). Few studies have examined longitudinal differences in cART adherence between youth and adults. As such, we examined cART adherence differences among YLWH and adults with HIV and the factors associated with sub-optimal adherence from 2010-2016.

Methods: Data from the British Columbia (BC) Centre for Excellence in HIV/AIDS Drug Treatment Program, a population-level provincial database of all individuals living with HIV who have been linked to care in the universal care setting of BC. Adherence was measured based on pharmacy refill compliance. Poor cART adherence was defined as <80% pharmacy refill vs ≥80% adherence. The proportion of participants with sub-optimal adherence (<80%) among youth (15-29 years) and among adults (30+) was compared per year from 2010-2016. Univariable and multivariable generalized estimating equation (GEE) confounding models assessed the independent association between sub-optimal adherence and being a youth (vs. adult). An explanatory GEE model was conducted to examine factors associated with poor adherence from 2010-2016 among YLWH specifically.

Results: A total of 7485 individuals were included in this analysis, 291 (3.9%) of which were youth. Of the YLWH, 39 (13.3%) had a history of injection drug use (IDU), and were on cART for a median of 2 years (Q1, Q3: 1-5). Over the study period YLWH showed significant time-trend reductions in poor adherence from 53% in 2010 to 26% in 2016 (p=<0.001) (See Figure 1), however this remained to be significantly higher than adults. In adjusted analyses, youth had significantly higher odds of poor adherence compared to adults (OR= aOR=2.00, 95%CI=1.85-2.17), controlling for IDU history and years on cART.

Poor adherence among YLWH was independently associated with a history of IDU (aOR=1.69, 95%CI=1.08-2.63).

Conclusion: Between 2010-2016, we observed significant improvements in the proportion of YLWH adhering to cART. Despite these improvements, YLWH in BC continue to have significantly poorer adherence compared to adults. Such inequities are aggravated among youth with a history of IDU. Scale-up in youth-focused and harm-reduction adherence supports, are needed to address persistent gaps in adherence among YLHIV accessing care within settings where cART is universally available.



1136 VIRAL SUPPRESSION AFTER INTERMITTENT VIREMIA: WOMEN'S INTERAGENCY HIV STUDY 1994-2015

Amanda B. Spence[1], Cuiwei Wang[1], Tracey Wilson[2], Kathryn Anastos[3], Mardge H. Cohen[4], Ruth Greenblatt[5], Margaret Fischl[6], Igho Ofotokun[7], Mirjam-Colette Kempf[8], Adaora Adimora[9], Joel Milam[10], Joanne Michelle F. Ocampo[1], Kate G. Michel[1], Seble Kassaye[1]

[1]Georgetown University, Washington, DC, USA, [2]SUNY Downstate Medical Center, Brooklyn, NY, USA, [3]Albert Einstein College of Medicine, Bronx, NY, USA, [4]Stroger Hospital of Cook County, Chicago, IL, USA, [5]University of California San Francisco, San Francisco, CA, USA, [6]University of Miami, Miami, FL, USA, [7]Emory University, Atlanta, GA, USA, [8]University of Alabama at Birmingham, Birmingham, AL, USA, [9]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [10]University of Southern California, Los Angeles, CA, USA

Background: Long term HIV viral suppression (VS) decreases morbidity, mortality, and limits transmission. Previous studies suggest that failure to an initial treatment regimen decreases the likelihood of subsequent VS. We studied viral outcomes among women in the nationwide Women's Interagency HIV Study (WIHS) with intermittent viremia (IV).

Methods: This study included women in the multisite WIHS who contributed ≥ four semi-annual visits from 1994-2015. Trajectory analysis identified the number of groups that fit the HIV RNA viral load (VL) data, and assigned women to a group based on their VL pattern over time. We determined the proportion of women with VS (VL<80 c/mL) at each visit for each trajectory group. We compared differences between IV and non-viremia (NV) groups, before and after 2006 when viral suppression in the IV group exceeded 50% (fig. 1). Univariate and multivariable generalized linear modeling for repeated measures accounted for correlated responses from the same woman. All variables were time-varying, except race/ethnicity. We used SAS v9.1.3. for all analyses.

Results: Three groups emerged: sustained viremia (N=1010); IV (N=719); and NV (N=711). Before 2006, comparing IV and NV groups, the IV group had lower mean CD4+ (387 vs 544/mm^3, aOR 0.78, p<0.0001) higher depression CES-D ≥16 (47.0% vs 36.2%, aOR 1.28, p=0.02), were more likely African American (55.5% vs 46. 2%, aOR 1.86, p=0.004) and had lower NNRTI use (17.2% vs 30.2%, aOR 0.7, p=0.006), adjusted for age, employment, alcohol and drug use, depression, cART use and adherence. After 2006, women with IV had lower CD4+ (583 vs 670, aOR 0.91, p<0.0001), higher depression (31.6% vs 26. 5%, aOR 1.30, p=0.01); were more likely to be African American (58% vs 51%, aOR 1.8, p=0.007); were more likely to use integrase (15.4% vs 10.1%, aOR 1.60, p=0.004) and protease inhibitors (59.9% vs 40.3%, aOR 1.85, p=0.0003), adjusted for age, employment, and insurance. Alcohol, drug use, cART uptake, and adherence were similar between IV and NV groups after 2006.

Conclusion: The majority of women in the IV group were able to achieve viral suppression with potent, better tolerated protease and integrase inhibitors. This provides ecological support for the use of these agents even in the setting of substance use and depression. Despite these advances, health disparities remain a significant challenge that need to be addressed to meet national viral suppression goals.

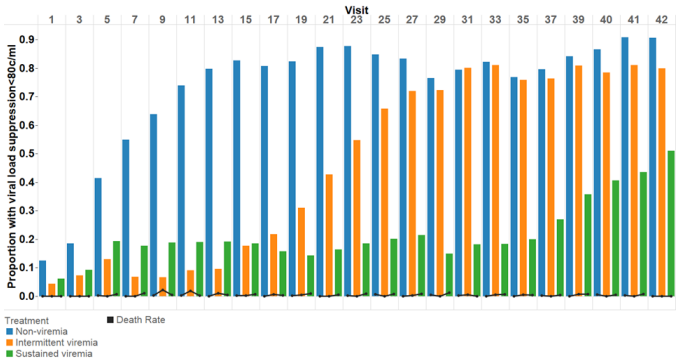


Figure 1: Viral suppression over time by trajectory group
2,440 women contributed 56,209 semi-annual visits from 1994-2015, with a baseline median age of 36.4 years, CD4+ T cell count of 464/mm3, and HIV RNA of 7,000 c/mL. We identified three trajectory groups: sustained viremia (N=1010); intermittent viremia (N=719); and non-viremia (N=711) for a viremia cutoff of 80 copies/mL.

1137 EVALUATING CARE OUTCOMES FOR ACUTE HIV INFECTION IN PHILADELPHIA, 2014-2016

Melissa Miller[1], Tanner Nassau[1], Coleman Terrell[1], Kathleen Brady[1]

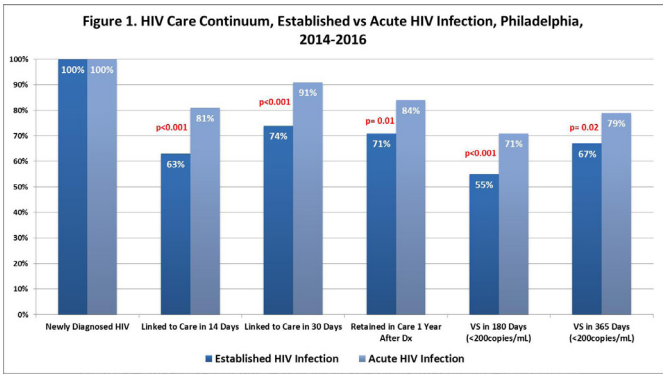
[1]Philadelphia Department of Public Health, Philadelphia, PA, USA

Background: Detection and treatment of acute HIV infection (AHI) improves both individual-level health by preserving immune function and community-level health by reducing infectiousness and HIV transmission. The implementation of 4th generation HIV testing has resulted in an increase in the proportion of individuals identified as AHI in Philadelphia from 3.2% in 2014 to 6.3% in 2016. This analysis aims to evaluate characteristics and care outcomes associated with AHI among individuals newly diagnosed with HIV in Philadelphia.

Methods: Data were extracted from the Enhanced HIV/AIDS Reporting System (eHARS) for individuals aged 13+ and newly diagnosed with HIV between 2014 and 2016. Chi-square tests were used to assess significant differences in continuum measures including: linkage to care at 14 and 30 days after diagnosis, retention in care at 1 year after diagnosis (2 CD4/VL > 90 days apart), and viral suppression (VS; VL <200 copies/ml) at 180 and 365 days after diagnosis between AHI and established infections. Bivariate and multivariable regression models assessed primary outcomes linkage to care < 30 days of diagnosis, retention in care at 1 year after diagnosis, and VS in 180 days of diagnosis. Multivariable models were adjusted for potential demographic and clinical confounders.

Results: 1,827 Philadelphia residents were eligible for inclusion in analysis, of which 86 (4.6%) were categorized as AHI and 1752 (95.4%) as established infection. Cases of AHI were significantly more likely to be male, aged 13-24, HIV-non AIDS cases, and report MSM as their transmission risk. Care continuum data for each outcome is presented in Figure 1. Results indicated that AHI were three times more likely to be linked to care within 30 days of diagnosis compared to those diagnosed with established infection (AOR,3.3; 95%CI:1.5-6.8). AHI were twice as likely to be retained in care in the year following diagnosis (AOR,2.1; 95%CI:1.1-3.7) and achieve VS within 180 days of diagnosis (AOR,2.0; 95%CI:1.2-3.3) when compared to those with established infections.

Conclusion: Detecting AHI is vital for both individual and community-level health. Our data show that individuals diagnosed with AHI have better engagement in care and VS outcomes in the year following diagnosis than those with established infection. Further increasing early detection of HIV may be impactful in improving engagement in care among newly diagnosed individuals and reducing HIV transmission overall.



1138 HIV CARE TRAJECTORIES IN THE ERA OF UNIVERSAL TEST-AND-TREAT IN RURAL SOUTH AFRICA

Delphine Perriat[1], Hassimiou Diallo[2], François Dabis[3], Deenan Pillay[4], Joanna Orne-Gliemann[3], Joseph Larmarange[2]

[1]L'Université de Bordeaux, Bordeaux, France, [2]IRD, Paris, France, [3]INSERM, Bordeaux, France, [4]Africa Health Research Institute, Mtubatuba, South Africa

Background: The test-and-treat strategy requires that HIV-infected individuals enter care and start an antiretroviral treatment (ART) as soon as possible after diagnosis. Little is known yet about the care continuum in such context. We aimed to describe the timing and sequencing of individual HIV care events from referral to viral suppression by identifying groups of individuals with similar care trajectories and identifying factors associated with each group.

Methods: We used prospective longitudinal data from the ANRS 12249 TasP trial, a cluster-randomized trial that investigated the impact of universal ART following home-based testing, on HIV incidence in rural KwaZulu-Natal, South Africa (2012-2016). The care status of all participants >16 years, identified HIV+, not in care at referral and followed-up for ≥18 months was classified at each calendar day: not in care, in care but not on ART, on ART but not virally suppressed, virally suppressed. We used state sequence data analysis to identify homogeneous groups of care trajectories. Individual and cluster characteristics at referral were analysed using multinomial logistic regression to characterize the profile of each group.

Results: 1,827 HIV+ participants were included. Median age was 34 years [IQR 27-45], 75% were female. We identified four groups of care trajectories (Figure): (i) participants who mostly did not enter care (53%), (ii) participants with inconstant care, visiting a clinic occasionally but leaving care thereafter (median time to exit care: 8.3 months [3.9-10.5]) (12%), (iii) participants who took extensive time at each step of the care continuum (median time between care referral and ART initiation: 7.6 months [5.8-9.4]) (11%) and (iv) participants who rapidly progressed towards continuous care (median time between care referral and ART initiation: 1.5 month [0.7-4.2]) (23%). Participants who were living further than a kilometre from a clinic, who were newly diagnosed and who were offered pre-ART services (vs immediate ART), were more likely to present with incomplete, inconstant and slow care trajectories.

Conclusion: Care trajectories are heterogeneous. To maximise the impact of test-and-treat strategies, differentiated care and support should be scaled-up, especially between diagnosis and ART initiation, which constitutes the main bottleneck of HIV programs in this South African rural study area.

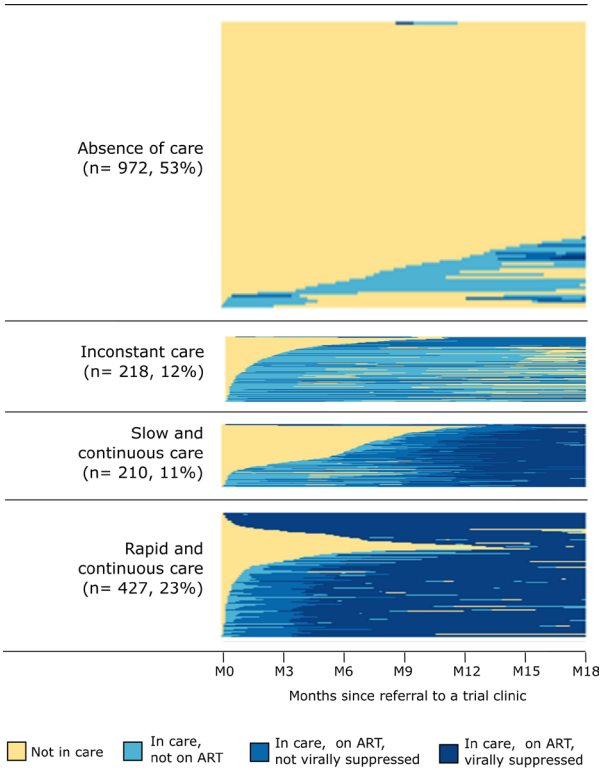


Figure: Homogeneous groups of HIV care trajectories of participants to the ANRS 12249 TasP trial who were not already in care when referred to a trial clinic (n=1,827).

ART: antiretroviral treatment. Each panel represents a group of homogeneous trajectories computed using clustering analysis. Each group includes participants to the TasP trial with similar sequences of care trajectories (representing specific care events from the day they were identified as HIV-positive by the trial and referred to care up to 18 months). Each horizontal line (Y-axis) represents a unique individual and the height of the group represents its proportion of the studied population. The X-axis represents time since referral to HIV care. The colours represent the daily care status.

1139 THE IMPACT OF "TREATMENT FOR ALL" ON EARLY GAPS IN ART- A MULTISITE COHORT STUDY

Ingrid Katz[1], Nicholas Musinguzi[2], Kathleen Bell[3], Anna Cross[4], Bosco M. Bwana[2], Gideon Amanyire[2], Stephen Asiimwe[5], Catherine Orrell[4], David R. Bangsberg[6], Jessica E. Haberer[3]

[1]Brigham and Women's Hospital, Boston, MA, USA, [2]Mbarara University of Science and Technology, Mbarara, Uganda, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Desmond Tutu HIV Foundation, Cape Town, South Africa, [5]Kabwohe Clinical Research Center, Kabwohe, Uganda, [6]Oregon Health and Sciences University, Portland, OR, USA

Background: Treatment eligibility has expanded throughout sub-Saharan Africa (SSA) in response to the WHO 2015 policy promoting "treatment for all" people living with HIV (PLWH). We evaluated the impact of early vs. late treatment initiation on early gaps in ART usage across two countries in SSA – South Africa (SA) and Uganda (UG) – and identified clinical and psychosocial predictors of losses.

Methods: Two cohorts of men and women initiating ART in routine care were prospectively enrolled in Cape Town, SA and southwestern UG: one initiating early (CD4>350 cells/ml) and one initiating late (CD4<200 cells/ml). Participants were seen at 0, 6 and 12 months for socio-behavioral questionnaires and HIV RNA levels. Adherence was monitored in real-time (Wisepill); early gaps were defined as >30 consecutive days without evidence of adherence in the first 6 months of ART. Demographic and clinical factors were compared across groups using chi-square to identify potentially confounding covariates, and logistic regression models were used to estimate predictors of early gaps in ART usage, adjusting for age, gender, employment, education and marital status.

Results: Of the 904 PLWH who were enrolled, 868 (96%) completed follow up, and 670 (77%) were eligible for this analysis (pregnant women were excluded). There were 92 (14%) early gaps in ART use, with a median time to early gap

of 80 days (IQR: 45-102). Given the limited number of early gaps in UG (n=21), we explored associated findings in an adjusted model in SA (n=71) (see Table 1). In the adjusted model, PLWH in SA who initiated ART later had double the odds of early gaps in treatment (aOR=2.0, 95%CI: 1.0-4.0). Those who used denial to cope were also at higher odds of early losses (aOR=1.2, 95%CI: 1.0-1.4). Education provided a protective effect against early losses (aOR=0.4, 95%CI: 0.2-0.8). There was no significant difference across age, gender, marital status or employment. Those with early gaps were more likely to have detectable viremia across sites (OR:6.3, p=0.001 in UG vs. OR:2.6, p=0.008 in SA).
Conclusion: Despite global efforts to promote early and enduring treatment, early gaps in ART persist, resulting in higher odds of detectable viremia. These gaps remain significant for key vulnerable populations, specifically those who present late to care, who lack educational opportunities, and who use denial to cope.

Table 1: Adjusted Analyses of Factors Associated with Early Gaps among South African participants living with HIV

	aOR	95% CI	p-value
Cohort			
Early	ref	--	
Late	2.0	1.0, 4.0	0.03
Age	1.0	1.0, 1.0	0.76
Female Sex	1.0	0.5, 1.9	0.96
High School			
Never Completed	ref	--	--
Completed High School	0.4	0.2, 0.8	0.01
Married or Living Together	0.7	0.3, 1.5	0.31
Employed	0.8	0.4, 1.5	0.42
Started ART because feel sick	1.6	0.8, 3.2	0.16
Coping through Denial	1.2	1.0, 1.4	0.03

1140 VIRAL SUPPRESSION EFFECTS OF INTERVENTIONS FOR UNSTABLE ART PATIENTS IN SOUTH AFRICA

Matthew P. Fox[1], Sophie Pascoe[2], Amy Huber[2], Joshua Murphy[2], Mokgadi Phokojoe[3], Marelize Gorgens[4], **Sydney Rosen**[1], David Wilson[4], Yogan Pillay[3], Nicole Fraser[4]
[1]Boston University, Boston, MA, USA, [2]Health Economics and Epidemiology Research Office, Johannesburg, South Africa, [3]South African National Department of Health, Pretoria, South Africa, [4]World Bank, Washington, DC, USA

Background: As loss from HIV care is an ongoing challenge globally, interventions are needed for patients who don't achieve or maintain ART stability. The 2015 South African National Adherence Guidelines (AGL) for Chronic Diseases include two interventions targeted at unstable patients: rapid tracing of patients who miss visits (TRIC) and enhanced adherence counselling (EAC).
Methods: As part of a cluster-randomized evaluation at 12 intervention and 12 control clinics in 4 provinces, intervention sites implemented the AGL interventions, while control sites retained standard care. We report early outcomes of EAC for patients with an elevated viral load (>400 copies/ml3) and on TRIC who missed a visit by >5 days. We included patients meeting these criteria from 20 June 2016 and 16 December 2016 and followed them through record review. We estimated risk differences (RD) of 3 month viral resuppression (<400 copies/ml3) with cluster adjustment using generalized estimating equations and controlled for imbalances using difference in differences compared to all eligible for these strategies in 2015, prior to intervention roll out.
Results: For EAC, we had 358 intervention site and 505 control site patients (61% female, median ART initiation CD4 count 157 cells/µl3). Few in either group had evidence of resuppression by 3 months (4.2% EAC vs 4.7% control) but few had a three-month repeat viral load recorded (71/358 intervention, 68/505 control). Among all eligible for EAC with a repeat viral load in the intervention-period (n=934), EAC showed a small increase in resuppression (28% vs 25%, RD 3.0%; 95% CI-2.7% to 8.8%)(Table). Adjusting for baseline differences increased the RD to 8.1% (-0.1% to 17.2%). For TRIC, we enrolled 155 at intervention sites and 245 at control sites (44% > 40, 67% female, median CD4 count 212 cells/µl3). We found no difference between groups in resuppression. During the study period, control sites incorporated rapid tracing into standard care, however, potentially masking intervention effects.
Conclusion: EAC appears to increase viral re-suppression modestly for patients who return to the clinic for a three-month viral load but as most did not return, the overall effect was small. Implementation of the tracing intervention under the new guidelines did not differ from standard care. Interventions that aim to return unstable patients to care should incorporate active monitoring to determine if the interventions are effective.

Difference-in-differences comparison of resuppression within 3 months among all eligible for enhanced adherence counselling and who had a supressed 3-month viral load at intervention and control sites during a period prior to the intervention compared to the intervention period.

3-month Follow-up Viral Load Supressed	Intervention	%	Control	%	Difference
All enrolled intervention period	11/358	4.3%	24/505	4.7%	-0.5% (-3.6% to 2.6%)
All at site					
Pre-intervention period	93/304	31%	108/307	35%	-4.6% (-12.0% to 2.9%)
Intervention-period	143/504	28%	109/430	25%	3.0% (-2.7% to 8.8%)
Difference-in-differences					**7.6% (-1.7% to 16.9%)**
Difference-in-differences (cluster and covariate adjusted)*					**8.1% (-0.1% to 17.2%)**

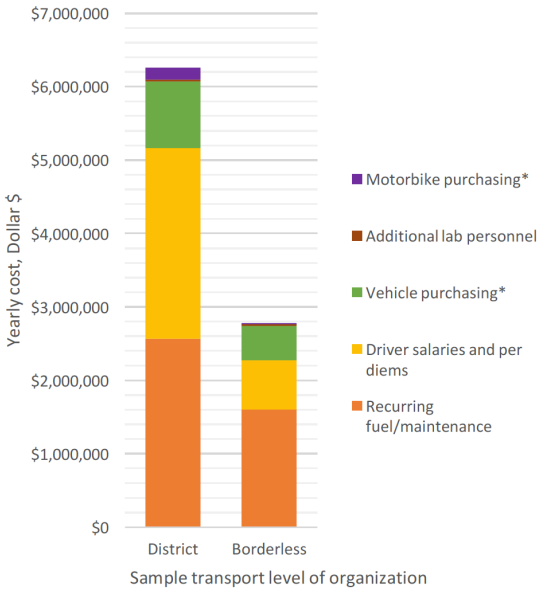
* Analyses are adjusted for clustering by site using a generalized estimating equation with site level clustering and an unstructured correlation matrix

1141 SUSTAINABLE VIRAL LOAD MONITORING SCALE-UP: GEOSPATIAL OPTIMIZATION MODEL FOR ZAMBIA

Brooke E. Nichols[1], Sarah Girdwood[2], Thomas Crompton[3], Lynsey E. Stewart-Isherwood[4], Leigh Berrie[4], Dorman Chimhamhiwa[3], Crispin Moyo[5], John Kuehnle[6], **Sydney Rosen**[1]
[1]Boston University, Boston, MA, USA, [2]Health Economics and Epidemiology Research Office, Johannesburg, South Africa, [3]Right to Care, Johannesburg, South Africa, [4]National Health Laboratory Service, Johannesburg, South Africa, [5]EQUIP Health Zambia, Lusaka, Zambia, [6]United States Agency for International Development, Washington, DC, USA

Background: WHO recommends viral load monitoring at 6 and 12 months, then annually, after initiating ART. Expansion of viral load testing has been slow in many countries due to lack of an efficient system for blood sample transportation. An estimated 1.2 million people are infected with HIV in Zambia. To assist Zambia in scaling up testing capacity, we designed a geospatial optimization model to minimize the cost of a national viral load sample transportation network (STN).
Methods: The model optimizes an STN in Zambia for the anticipated 1.5 million viral load tests that will be needed in 2020, taking into account the country's geography, infrastructure, and district political boundaries. Data incorporated into the model included the location of all 2,500 Zambian health facilities and laboratories, lab and hub infrastructure and capacity, driving distances and driving times for different types of vehicles, and expected future viral load demand by health facility. Under the status quo, each district independently provides sample transport for facilities within its borders. We evaluated the all-inclusive STN costs of 2 alternative scenarios: 1) an optimized status quo where each district provides its own weekly or daily sample transport for the anticipated viral load volume; and 2) an optimized borderless STN that ignores district boundaries, provides weekly or daily sample transport, and reaches the same facilities/viral load volumes as scenario 1.
Results: Under both scenarios, coverage of viral load testing would increase from 10% in 2016 to 89% in 2020. Mean transport cost per viral load in scenario 2 was $1.86 per test (SD $0.27), 55% less than the mean cost/test in scenario 1 of $4.14 (SD $0.70). When fully scaled-up to the anticipated 2020 volumes, the borderless system would save the government of Zambia $3,537,000 annually (SD $660,000) compared to the district-based system. This saving is primarily due to a reduction in the number of vehicles and drivers needed, along with more efficient routes enabled by intra-district routing.
Conclusion: We found that an efficient STN that optimizes sample transport on the basis of geography and test volume, rather than political boundaries, can cut the cost of sample transport by more than half. This model, which can be used in other countries and for other types of samples, has the potential to increase the sustainability of ART programs throughout Africa.

Figure 1. The average annual operating cost of an optimized viral load sample transportation network in Zambia, borderless and by district.



*Annualized cost (assumed write-off period of 4 years)

1142 EXPANDING VIRAL LOAD TESTING ACCESS THROUGH EVALUATION OF THE GENEXPERT IN BOTSWANA

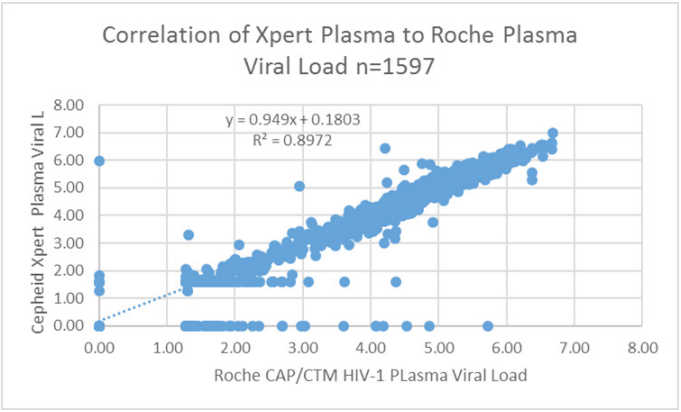
Rachel S. Beard[1], Anikie Mathoma[2], Mackenzie Hurlston[1], Naledi Nyepetsi[3], Christopher Serumola[2], Joyce Basotli[2], Ritah Moatlhodi[3], Unami Mathebula[2], Otsile Meswele[4], Charity Ralegoreng[4], Tefera Agizew[2], Rosanna Boyd[2], Madisa Mine[5], Ishmael Kasvosve[3]
[1]CDC, Atlanta, GA, USA, [2]CDC Botswana, Gaborone, Botswana, [3]University of Botswana, Gaborone, Botswana, [4]African Society for Laboratory Medicine, Gaborone, Botswana, [5]Botswana Ministry of Health, Gaborone, Botswana

Background: With the UNAIDS target to reach 90% HIV viral suppression of those on treatment by 2020, access to viral load (VL) testing is essential. However, VL testing for monitoring of treatment efficacy remains limited and confined to centralized laboratories with demanding infrastructural and technical requirements. Large field evaluations for point of care (POC) and near POC VL instrumentation and assays are lacking. We assessed the performance and operational characteristics of the Xpert HIV-1 VL assay and the GeneXpert near (POC) platform, in clinics with limited laboratory infrastructure in Botswana.

Methods: In a multi-site cross-sectional study, people living with HIV, including those currently on antiretroviral therapy (ART) and ART naïve patients, were enrolled beginning in May 2016 from four HIV clinics, 2 in Francistown and 2 in Gaborone. Plasma samples from consenting patients were prepared and tested on Xpert HIV-1 VL and a reference assay, Roche COBAS AmpliPrep/ COBAS TaqMan HIV-1 v2.0 (CAP/CTM HIV-1 v2), according to manufacturers' recommendations. Correlation was assessed via linear regression. Sensitivity and specificity were determined at the World Health Organization (WHO) recommended clinical cut-off of 1000 copies/mL and the Botswana National Guidelines' cut-off of 400 copies/mL.

Results: Of the 1600 patients enrolled, 1597 patients' plasma were tested on both the Xpert HIV-1 VL and the reference assays. Of the plasma samples tested, 583 (36.5%) are from patients on ART. Gender information was available for 1585 patients of which 1379 (87.0%) were female. Sensitivity and specificity of Xpert HIV-1 VL from the 1597 tested was 98.2% and 98.7% at 1000 copies/mL and 97.7% and 98.6% at 400 copies/mL, respectively. Linear regression analysis (Figure 1) demonstrated good correlation between Xpert HIV-1 VL and CAP/CTM HIV-1 v2 ($R2$=0.897). The upward and downward misclassification was 1.34% and 1.81% at 1000 cps/mL and 1.42% and 2.32% at 400 cps/mL, respectively. Twenty-nine GeneXpert instrumentation errors occurred, yielding an error rate of 1.8%.

Conclusion: Findings indicate that at both the WHO cutoff of 1000 copies/mL and the Botswana cutoff of 400 copies/mL, the Xpert HIV-1 VL performs well compared to the CAP/CTM HIV-1 v2 in a setting of intended use. These findings suggest that the assay is suitable to complement conventional platforms, particularly for target populations in resource-limited settings where VL testing is lacking.



1143 THE ECONOMIES OF SCALE OF TEST AND TREAT: A LONGITUDINAL COSTING STUDY IN SWAZILAND

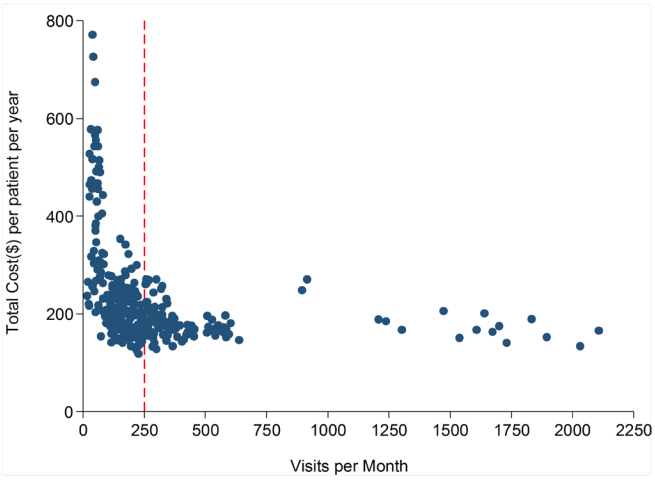
Shaukat Khan[1], Cebele Wong[1], Pascal Geldsetzer[2], Gerda Asmus[3], Thomas How[1], Charlotte Lejeune[1], Velephi Okello[4], Till Bärnighausen[3]
[1]Clinton Health Access Initiative, Mbabane, Swaziland, [2]Harvard University, Cambridge, MA, USA, [3]Heidelberg University, Heidelberg, Germany, [4]Ministry of Health, Mbabane, Swaziland

Background: Swaziland has one of the highest adult HIV prevalence rates worldwide, 27%; with approximately 200,000 people 15 years and older living with HIV. Swaziland and many other countries in sub-Saharan Africa have adopted universal test-and-treat (UTT) policies. As the number of people needing and receiving ART in Swaziland is rapidly increasing, it is critical to understand the cost of UTT scale-up and its implications for the health system. The study presented here is the first empirical longitudinal costing study of annual ART patient costs under a public-sector UTT policy with routine viral load monitoring.

Methods: We collected comprehensive monthly facility-level data on ART patient costs from 14 facilities implementing UTT as part of a large-scale randomized stepped-wedge health systems trial (September 2014-December 2016). In addition to a comprehensive time-and-motion study, we used extracted cost data from facility budgets, expenditure reports, and patient records. Items included in this "bottom-up costing" included direct personnel, medications, laboratory services including viral load, and treatment for opportunistic infections (OI). We express all costs per patient per year (PPPY). Costs were converted from local currency to U.S. Dollars using annualized exchange rates.

Results: Total ART costs PPPY were $214 (95% CI: 201-226). ARVs costs accounted for the largest proportion at $102 (95% CI: 101-103), followed by personnel $77 (95% CI: 67-88), laboratory services (including viral load) $31 (95% CI: 27-35) and OI costs $4 (95% CI: 3-4). In the descriptive data (Figure 1) and in multilevel regression analysis controlling for time fixed effects and facility random effects, we identified strong economies of scale in the relationship between costs PPPY and facility size (measured in the number of visits per month). As facility size increases, costs initially decrease rapidly (from about $800 PPPY) and then plateau (below $200 PPPY) approximately at 250 patient visits.

Conclusion: Swaziland's public-sector ART program displays strong economies of scale under UTT, with far less efficiency achieved in clinics reaching less than 250 patient visits per month. In the context of scaling up UTT, increases in patient volumes are efficient trajectories but where not feasible (such as rural and remote populations), alternative delivery models could provide efficiency gains; including community health worker delivered ART.



1144 DECREASED ALCOHOL USE (EVEN WITHOUT ABSTINENCE) IS ASSOCIATED WITH BETTER VIRAL LOAD

Heidi M. Crane[1], Robin M. Nance[1], Andrew Hahn[1], Judith I. Tsui[1], Michael J. Mugavero[2], Bryan Lau[3], Geetanjali Chander[3], Sonia Napravnik[4], Karen Cropsey[2], Katerina A. Christopoulos[5], Rob Fredericksen[1], Dennis Donovan[1], Jane M. Simoni[1], Mari Kitahata[1], Joseph Delaney[1]

[1]University of Washington, Seattle, WA, USA, [2]University of Alabama at Birmingham, Birmingham, AL, USA, [3]Johns Hopkins University, Baltimore, MD, USA, [4]University of North Carolina Chapel Hill, Chapel Hill, NC, USA, [5]University of California San Francisco, San Francisco, CA, USA

Background: Alcohol use is common among people living with HIV (PLWH) and associated with poor antiretroviral treatment (ART) adherence and detectable viral load (VL). Interventions for hazardous alcohol use exists; however, many PLWH may moderate their use but not abstain. We conducted this study to examine the potential impact of decreasing alcohol use on VL without abstinence and how this differs based on alcohol use patterns.

Methods: We used data from 7 U.S. sites in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort. Eligible PLWH completed the CNICS clinical assessment including alcohol use on the AUDIT-C on or after 2010, reported alcohol use, and had 2 VL measures collected as part of clinical care. We examined frequency of alcohol use, frequency of binge drinking, and alcohol use severity (AUDIT-C score). Linear mixed models with time-updated alcohol use and VL were used to examine associations between changes in alcohol use and VL (log_{10} transformed) adjusting for age, sex, race, frequency of illicit substance use by individual drug category, and calendar year. Models were repeated, stratified by Hepatitis C virus (HCV) status.

Results: Among 7137 PLWH who drank alcohol there were 61,315 VL measures, mean baseline VL was 22,709 copies/mL (geometric mean 118) and 71% were undetectable (<100 copies/mL). Stopping alcohol use was associated with decreased VL for all alcohol measures (p values<0.05). Decreased alcohol use among those who continued to drink (not abstinent) was associated with lower VL for all 3 alcohol measures. Compared to those who did not decrease alcohol, those who decreased alcohol frequency had a mean 18% lower VL (95% confidence interval (CI) 11%-24%, p <0.001), those who decreased their binge drinking frequency had 26% lower VL (95% CI 15%-36%, p <0.001), and those who decreased their AUDIT-C score had 26% lower VL (95% CI 21%-31%, p <0.001). Even a 1-point AUDIT-C score decrease was significant. Impacts were attenuated among PLWH with HCV.

Conclusion: We demonstrated alcohol cessation was associated with decreased VL. In addition, decreasing alcohol use without abstinence was associated with a lower VL, which could lead to improved health outcomes and public health benefits in terms of decreased transmissibility. The decreased VL could be via improved ART adherence or more direct biological effects of alcohol. This suggests that supporting decreased alcohol use could help patients achieve VL goals regardless of achieving abstinence.

1145 DURABILITY OF FINANCIAL INCENTIVES EFFECT ON VIRAL SUPPRESSION AND CONTINUITY IN CARE

Wafaa M. El-Sadr[1], Geetha Beauchamp[2], Irene Hall[3], Lucia V. Torian[4], Barry S. Zingman[5], Garret Lum[6], Richard A. Elion[7], Kate Buchacz[3], David Burns[8], Allison Zerbe[1], Theresa Gamble[9], Deborah J. Donnell[2]

[1]ICAP at Columbia University, New York, NY, USA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [3]CDC, Atlanta, GA, USA, [4]New York City Department of Health and Mental Hygiene, Long Island City, NY, USA, [5]Montefiore Medical Center, Bronx, NY, USA, [6]District of Columbia Department of Health, Washington, DC, USA, [7]George Washington University, Washington, DC, USA, [8]NIAID, Bethesda, MD, USA, [9]FHI 360, Durham, NC, USA

Background: There is increased interest in use of financial incentives to achieve desired health, including HIV-related, behaviors. The HPTN 065 study demonstrated that financial incentives (FI) were associated with 3.8% [(0.7%-6.8%), p=0.014) higher viral suppression (VS) and with 8.7% [(4.2%,13.2%), p=0.0001] higher continuity in care (CC) among patients at sites randomized to FI versus (vs) standard of care (SOC) in the Bronx, NY (BNY) and Washington, DC (DC). Whether the effects of FI are durable beyond withdrawal of FI is unclear. We assessed VS and CC at FI versus SOC sites post-intervention to determine durability of FI.

Methods: A total of 37 (20 BNY/ 17 DC) care sites with 51,782 patients in care (28,439 BNY/23,343 DC), were site-randomized to FI or SOC. At FI sites, patients on ART could earn $70 gift card per quarter with VS. Lab data reported to HIV Surveillance were used for site-level outcomes: for VS, VL less than 400 copies/ml in engaged patients (≥2 visits in last 15 months); for CC, CD4 or VL in 4 of prior 5 quarters. Post-intervention effects were assessed for the three quarters after discontinuation of FI (Apr-Dec 2013). GEE was used to compare FI and SOC site-level outcomes during the FI intervention and post-intervention (Table).

Results: Post-intervention, a trend remained for an increase in VS by 2.7% (-0.3%, 5.6%, p=0.076) was noted at FI vs SOC sites. This difference in VS between FI and SOC sites was reduced from the 3.8% increase in VS to 2.7%, but was persistent nonetheless. Notably, in the subgroups of sites where FI achieved a significant increase in VS during the intervention, we noted a reduced but durable effect post-intervention at FI vs SOC sites: at DC sites 4.4% higher (p=0.057), at hospital-based sites 4.8% higher (p=0.003) and at sites with high baseline VS 3.2% higher (p=0.066). The significant increase in CC during FI intervention was sustained post-intervention with 7.5% (p=0.007) higher CC at FI vs SOC sites. A durable significant effect of FI post-intervention on CC persisted at sites randomized to FI vs SOC in BNY (p=0.010), at hospital-based sites (p=0.019) and at sites with higher baseline VS (p=0.014).

Conclusion: Post discontinuation of FI, data from this large study showed evidence of durable effects of FI, both on VS and CC, at sites that were previously randomized to FI vs SOC. These findings suggest that behaviors motivated by FI may last beyond the provision of the FI, increasing the potential cost-effectiveness of FI strategies.

Effects of Financial Incentives During and Post-Intervention on Viral suppression and Continuity in care [*#]

		Viral Suppression (VS)		Continuity in Care (CC)	
	Number of Sites	Intervention increase in percent with VS (95% CI), P Value	Post-intervention increase in percent with VS (95% CI), P Value	Intervention increase in percent of CC (95% CI), P Value	Post-intervention increase in percent of CC (95% CI), P Value
Overall	FI (N=17) SOC (N=20)	3.8% (0.7%, 6.8%) **p=0.014**	2.7% (-0.3%, 5.6%) *p=0.076*	8.7% (4.2%,13.2%), **p=0.0001**	7.5% (2.0%, 12.9%) **p=0.007**
Bronx, NY	FI (N=10) SOC (N=10)	1.6% (-0.6%, 3.9%) p=0.143	1.6% (-2.1%, 5.2%) p=0.398	8.0% (4.1%,11.9%) **p<0.0001**	5.9% (1.4%, 10.4%) **p=0.010**
Washington, DC	FI (N=7) SOC (N=10)	6.6% (1.9%, 11.3%) **p=0.006**	4.4% (-0.1%, 9.0%) *p=0.057*	10.1% (1.2%,19%) **p=0.026**	9.4% (-1.9%, 20.7%) p=0.1017
Hospital-based	FI (N=7) SOC (N=7)	4.9% (1.4%, 8.5%) **p=0.007**	4.8% (1.6%, 7.9%) **p=0.003**	8.7% (3.4%,14%) **p=0.001**	8.0% (1.3%, 14.6%) **p=0.019**
Community-based	FI (N=10) SOC (N=13)	1.2% (-2.0%, 4.3%) p=0.468	-0.1% (-3.9%, 3.6%) p=0.945	9.4% (1.7%,17.1%) **p=0.017**	6.9% (-2.7%, 16.4%) p=0.160
Smaller (≤196 at baseline)	FI (N=9) SOC (N=10)	11.8% (-0.1%, 23.7%) *p=0.052*	11.5% (1.9%, 21.1%) **p=0.019**	10.3% (1.5%, 19.2%) **p=0.022**	6.9% (-1.5%, 15.3%) p=0.108
Larger (>196 at baseline)	FI (N=8) SOC (N=10)	2.7% (-0.3%, 5.7%) *p=0.076*	1.9% (-1.3%, 5.0%) p=0.249	8.0% (2.4%,13.6%) **p=0.0053**	6.6% (-0.8%, 13.9%) *p=0.080*
Lower base VS (Baseline≤66%)	FI (N=11) SOC (N=9)	5.6% (0.0%, 11.3%) **p=0.049**	2.2% (-2.6%, 7.1%) p=0.372	5.7% (-4.4%,15.8%) p=0.27	1.5% (-10.1%, 13.1%) p=0.7988
Higher base VS (Baseline>66%)	FI (N=6) SOC (N=11)	3.6% (0.3%,7.0%) **p=0.034**	3.2% (-0.2%, 6.7%) *p=0.0662*	8.7% (3.6%,13.8%) **p=0.0008**	7.9% (1.6%, 14.2%) **p=0.014**

*bold: p<=0.05
#italics: 0.05<p<=0.10

1146 COST-EFFECTIVENESS OF REGULAR HIV SCREENING FOR YOUNG MEN WHO HAVE SEX WITH MEN

Anne M. Neilan[1], Alexander Bulteel[1], Kenneth Freedberg[1], Sybil Hosek[2], Raphael J. Landovitz[3], Rochelle P. Walensky[1], Craig M. Wilson[4], Andrea L. Ciaranello[1]

[1]Massachusetts General Hospital, Boston, MA, USA, [2]Cook County Health & Hospitals System, Chicago, IL, USA, [3]University of California Los Angeles, Los Angeles, CA, USA, [4]University of Alabama at Birmingham, Birmingham, AL, USA

Background: Of new HIV diagnoses among US youth, 81% occur among young men who have sex with men (YMSM). Using data from Adolescent Trials Network (ATN) studies 110/113 of high-risk US YMSM ages 15-22, we examined the clinical impact, cost, and cost-effectiveness of 4 HIV screening strategies for high-risk YMSM starting at age 15.

Methods: We simulated a cohort of high-risk HIV-uninfected 14-year-old MSM in the US who faced age-specific risks of HIV infection (0.91-6.41/100,000PY, peak incidence ages 15-18) based on ATN 110/113 (observational; incident infections despite PrEP adherence of 34-56%). We modeled HIV screening ($36/test) every 3 years, annually, biannually, and quarterly beginning at age 15, each in addition to current US screening practices for YMSM (16-53% screened at least once by ages 15-22). We used published YMSM HIV care continuum data, including screen acceptance (80%), linkage-to-care/antiretroviral therapy (ART) initiation (76%), disease progression, and HIV care costs. Outcomes included CD4 count at diagnosis, the HIV care continuum (proportions HIV-diagnosed, linked to care, retained in care, and virologically suppressed), one generation of secondary HIV transmissions, life expectancy, lifetime costs, and incremental cost-effectiveness ratios (ICER) in $/year-of-life saved (YLS) from the healthcare system perspective. In sensitivity analyses, we varied HIV incidence, screening and linkage rates, and costs.

Results: All screening strategies beginning at age 15 diagnosed greater proportions of lifetime infections compared to current practice alone (81-99% vs. 35%). Compared to the next most effective strategy, quarterly screening beginning at age 15 was cost-effective ($84,000/YLS) by US standards (<$100,000/YLS) (Table). Including just first-generation HIV transmissions averted, the ICER was markedly lower ($20,900/YLS). These results were most sensitive to current HIV screening practice rates and linkage-to-care/ART initiation. If HIV incidence peaked at older ages, an older starting age for HIV screening had more favorable cost-effectiveness outcomes; if absolute HIV incidence was lower, less frequent screening was more favorable.

Conclusion: For high-risk US YMSM, quarterly HIV screening beginning at age 15, compared to less frequent screening beginning at age 15, would improve clinical outcomes and be cost-effective. To optimize clinical outcomes, screening should begin at or after the peak of population-specific HIV incidence.

Table: Modeled outcomes of 4 HIV screening strategies for high-risk YMSM in the US

Screening strategy starting at age 15 in addition to current practice	Without HIV transmission: Mean CD4 at diagnosis (cells/μL)	Without HIV transmission: Life expectancy (months from age 14): HIV-infected (undiscounted)	Without HIV transmission: Life expectancy (months from age 14): Population (undiscounted)	Without HIV transmission: Life expectancy (months from age 14): Population (discounted) [a]	Without HIV transmission: Population lifetime cost per-person ($) [a,b]	Without HIV transmission: ICER ($/YLS) [a,b,c]	With HIV transmission: Life expectancy (months from age 14): Population (discounted) [a]	With HIV transmission: Population lifetime cost per-person ($) [a,b]	With HIV transmission: ICER ($/YLS) [a,b,c]
Current practice	269	491.26	597.65	287.28	119,900	*Reference*	287.28	119,900	*Reference*
Every 3 years	459	533.58	621.84	296.01	164,100	60,700	309.88	164,100	weakly dominated
Annual	568	548.18	630.14	299.24	182,400	68,000	321.41	182,400	weakly dominated
Every 6 months	608	553.14	633.02	300.31	189,700	81,400	326.46	189,700	weakly dominated
Every 3 months	630	556.63	635.00	301.16	195,600	84,100	330.82	195,600	20,900

YMSM: young men who have sex with men; ICER: Incremental cost-effectiveness ratio; YLS: Year of life saved

[a] Results are discounted at 3 percent per year.
[b] Results are rounded to the nearest $100.
[c] Cost-effectiveness is the difference in cost divided by the difference in life expectancy for each strategy compared with the next most costly strategy. When comparing three or more strategies, if a strategy has a higher ICER than a competing strategy with a higher lifetime cost (as is the case here), then the strategy is said to be "dominated," reflecting an inefficient use of healthcare resources, and the ICERs of all strategies are recalculated with that strategy omitted.

1147 REPEAT HIV TESTING DURING PREGNANCY IN KENYA: AN ECONOMIC EVALUATION

Anna Joy Rogers, **Janet M. Turan**, Ellen F. Eaton, Stephen T. Mennemeyer

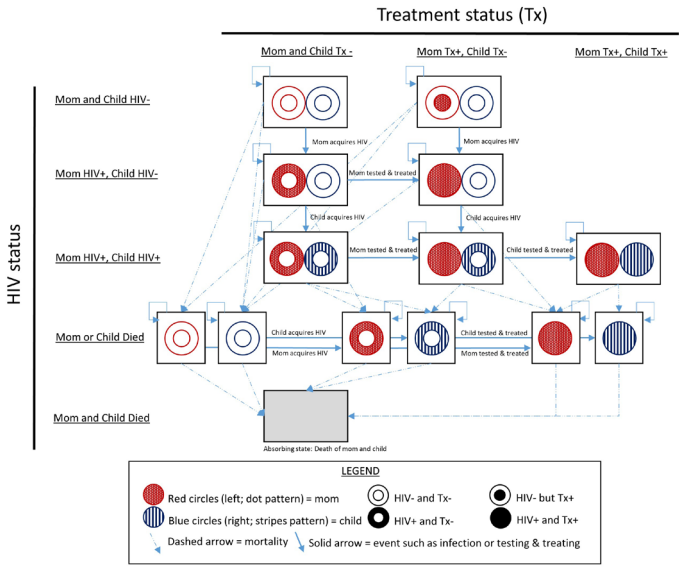
University of Alabama at Birmingham, Birmingham, AL, USA

Background: Repeat HIV testing during late pregnancy may identify women who seroconvert after an initial negative HIV test early in pregnancy, allowing these women to adopt lifelong antiretroviral therapy (ART) for the sake of their own health as well as to prevent mother-to-child transmission of HIV. We evaluated the cost-effectiveness of repeat HIV testing during late pregnancy in Kenya, hypothesizing that retesting would be cost-effective when compared to initial HIV testing alone due to health benefits accrued by mother and child.

Methods: We used TreeAge software to model a decision tree with the initial decision node comparing the alternative HIV testing strategies (a single antenatal HIV test early in pregnancy, or the initial antenatal HIV test plus a repeat HIV test three months later) and the successive chance nodes representing antepartum possibilities including maternal seroconversion, maternal ART uptake, fetal HIV acquisition, facility delivery, and mortality during delivery. At delivery of the infant, each branch culminates in a state-transition model that jointly tracks the mother-infant pair in one-month cycles for a ten-year horizon (Figure 1). All inputs were drawn from the literature and were varied across their range or distribution in univariate and probabilistic sensitivity analyses.

Results: In the base case, the retesting strategy was cost-effective for the Kenyan setting at $1,098 per quality-adjusted life year (QALY) saved, yielding fewer infant HIV infections during pregnancy and breastfeeding (n=504 and 253, respectively), infant deaths (n=30), and maternal deaths (n=178) per 100,000 women. Results were sensitive to low cumulative incidence of HIV during pregnancy and monthly cost of maternal ART (thresholds of 1% and $45, respectively). Probabilistic sensitivity analyses confirmed the base-case analysis.

Conclusion: This modeling study indicates that repeat HIV testing is likely cost-effective and results in fewer infant HIV infections. In the "test and treat era," in which immediate ART is recommended for all HIV infected persons, retesting for HIV in pregnant women not only improves maternal health outcomes but may also contribute to the elimination of perinatal HIV transmission in Kenya.



1148 PREFERENCES AND WILLINGNESS-TO-PAY FOR BLOOD AND ORAL-FLUID HIV SELF-TESTS IN KENYA

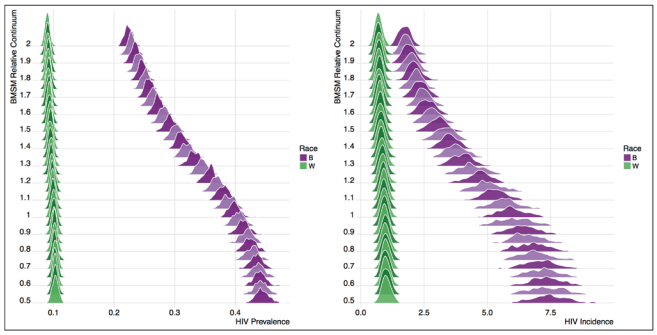
Kristen Little[1], Nicholas L. Wilson[2], Patrick Alyward[1], Hildah Essendi[3]

[1]Population Services International, Washington, DC, USA, [2]Reed College, Portland, OR, USA, [3]Population Services International, Nairobi, Kenya

Corrected data and updated results for this study, as presented at CROI 2018, are available in the electronic poster for abstract 1148 at http://www.croiconference.org/abstracts/search-abstracts.

Results: In the reference scenario, the disparity ratio of BMSM to WMSM incidence rates was 4.71. In the second, "as-observed" scenario, 8.4% of BMSM and 23.4% of WMSM were predicted to be on PrEP. Compared to no PrEP, incidence at year 10 was lower for both BMSM (HR = 0.77) and WMSM (HR = 0.56), with 14.1% and 33.1% of cumulative infections averted respectively. This stronger benefit for WMSM increased the disparity ratio to 6.31. In the third, equal parameters scenario, the disparity ratio (4.74) returned towards the reference scenario value, with slightly higher infections averted for WMSM (35.6% vs 29.6%) as a function of their higher levels of PrEP indications. With BMSM continuum parameters set to 120% of WMSM values, the hazard ratio for BMSM was stronger than for WMSM (0.40 vs 0.50), with the disparity ratio below the reference scenario (2.91).
Conclusion: Poorer levels of PrEP awareness, access, prescription, and adherence could limit the population-level prevention effects of HIV PrEP for BMSM, leading to higher than current disparities albeit at lower incidence rates for both races. Reducing HIV disparities with PrEP will require addressing race-specific gaps along the PrEP continuum to improve rates of PrEP initiation, adherence, and retention for BMSM in the United States.

Figure. Empirical distribution of model simulations (n = 250 in each scenario) for HIV prevalence and HIV incidence (per 100 person-years at risk) for BMSM and WMSM across relative values of the combined BMSM PrEP continuum (awareness, access, prescription, adherence, and retention). Relative value 1.0 is the observed BMSM continuum values, 0.5 is half of those observed, and 2.0 is twice of those observed.



1149 THE PrEP CARE CONTINUUM AND HIV RACIAL DISPARITIES AMONG MEN WHO HAVE SEX WITH MEN

Samuel Jenness[1], Kevin Maloney[1], Dawn K. Smith[2], Karen W. Hoover[2], Steven M. Goodreau[3], Kevin Weiss[1], Eli Rosenberg[1], Patrick S. Sullivan[1]
[1]Emory University, Atlanta, GA, USA, [2]CDC, Atlanta, GA, USA, [3]University of Washington, Seattle, WA, USA

Background: HIV preexposure prophylaxis (PrEP) could reduce the racial disparities in HIV incidence among black men who have sex with men (BMSM), particularly in the Southeast US where the disparities are greatest. Achieving this goal will depend on race-specific rates of movement through the PrEP continuum of care from awareness to adherence and retention.
Methods: We expanded our mathematical model of HIV transmission for MSM, which simulates PrEP based on the bio-behavioral indications of CDC's clinical practice guidelines, to include race-stratified transitions through the PrEP continuum from awareness to access to prescription to adherence to retention. Continuum parameters - consistently equal to or poorer for BMSM compared to white MSM (WMSM) - were estimated based on our Atlanta-based HIV incidence cohorts and published PrEP open-label studies. Models were calibrated to race-specific prevalence in these cohorts. We simulated four scenarios over a ten-year period: 1) no-PrEP (reference); 2) PrEP with the observed race-specific continuum parameters; 3) PrEP with BMSM parameters set to WMSM values; and 4) PrEP with BMSM parameters set to 20% higher than WMSM values.

1150 IMPROVING STATEWIDE PRE-EXPOSURE PROPHYLAXIS IMPLEMENTATION AMONG MSM

Jason Gantenberg[1], Maximilian King[1], Madeline C. Montgomery[2], Omar Galarraga[1], Mattia Prosperi[3], Brandon D. Marshall[1], Philip A. Chan[2]
[1]Brown University, Providence, RI, USA, [2]The Miriam Hospital, Providence, RI, USA, [3]University of Florida, Gainesville, FL, USA

Background: Daily oral PrEP is effective in reducing HIV transmission, yet uptake among men who have sex with men (MSM) has been slow in the United States. In this study, we sought to identify strategies that would yield the highest reduction in HIV incidence among MSM to help guide a statewide implementation effort and achieve the National HIV/AIDS Strategy goal of reducing new diagnoses by 25% over 10 years.
Methods: We used a discrete-time, stochastic agent-based model representing all MSM aged 15–74 in Rhode Island ($N = 25{,}000$), a state with approximately 4–5% HIV prevalence among MSM. We simulated the following scenarios in which different populations of MSM were engaged for PrEP uptake: 1) *Current Patient Population* - selection based on distributions of age and partner degree among actual patients in a PrEP program implemented according to CDC guidelines; 2) *Random* - random allocation, all HIV-negative MSM eligible; 3) *Partner Number (PN)* - Annual partner number greater than 5 or 10. The model was calibrated to reproduce statewide prevalence from 2009 through 2014. For each simulation, PrEP was implemented after this 6-year lead-in period and maintained at a fixed coverage level for the next 10 years. Scenarios were simulated 1,000 times each, with 5–30% PrEP coverage of the HIV-negative population.
Results: From 2015–2025, a median of 826 new HIV infections were predicted across the entire population in the absence of PrEP. At 15% PrEP coverage of HIV-negative MSM, 3 of the 4 scenarios achieved a greater than 25% reduction in cumulative incidence, exceeding the National HIV/AIDS Strategy goal in this timeframe (Table). A 25% reduction in the median cumulative incidence, relative to the scenario without PrEP, was apparent after 9.1, 6.8, and 3.4 years in the Current Patient Population, PN > 5, and PN > 10 scenarios, respectively. The only scenario to approach the goal at lower PrEP coverage was the PN > 10

scenario, which achieved a 23.5% (95% simulation interval: 10.9, 34.3) reduction in new infections at 10% population coverage over 10 years.

Conclusion: Under most of the scenarios tested, PrEP coverage of 15% was sufficient to reduce cumulative incidence by 25% over 10 years. Focused implementation efforts on MSM who have larger numbers of partners may maximize PrEP's impact and possibly its cost-effectiveness at lower levels of population coverage.

Table. Measures of HIV infection and PrEP impact among MSM in Rhode Island over 10 years, 0% vs. 15% PrEP coverage

Scenario	HIV (%)	New Infections	Incidence Rate	Infections Averted (#)	Infections Averted (%)	PrEP Years per Averted Infection
No PrEP	7.4 (6.7, 8.1)	826 (711, 955)	3.51 (3.00, 4.08)	-	-	-
Current Patient Population	6.5 (5.9, 7.2)	612 (523, 709)	2.59 (2.21, 3.02)	218 (121, 307)	26.2 (14.5, 37.0)	161 (115, 289)
Random	6.7 (6.0, 7.4)	654 (546, 756)	2.77 (2.31, 3.22)	176 (74, 284)	21.2 (8.9, 34.2)	199 (124, 474)
PN > 5	6.5 (5.8, 7.1)	595 (499, 691)	2.52 (2.11, 2.94)	235 (139, 331)	28.3 (16.7, 39.9)	150 (107, 252)
PN > 10	6.3 (5.7, 6.9)	555 (478, 639)	2.35 (2.01, 2.71)	275 (191, 352)	33.1 (23.0, 42.4)	128 (100, 184)

Medians and 95% simulation intervals are presented, the latter defined as the 2.5% and 97.5% quantiles of the model output distributions. Incidence rates are calculated per 1000 person-years at risk during the 10-year simulation window. Within each PrEP scenario, the infections averted distribution was created by subtracting each of 1000 cumulative incidence estimates from the mean cumulative incidence under No PrEP.
Abbreviations: PN, annual partner number; PrEP years, person-years on pre-exposure prophylaxis

1151 POTENTIAL EFFECTIVENESS OF LONG-ACTING INJECTABLE PrEP IN MSM: A MODELING STUDY

Brandon D. Marshall[1], William C. Goedel[1], Maximilian King[1], David P. Durham[2], **Philip A. Chan**[1], Jeffrey P. Townsend[2], Alison P. Galvani[2]
[1]Brown University, Providence, RI, USA, [2]Yale University, New Haven, CT, USA

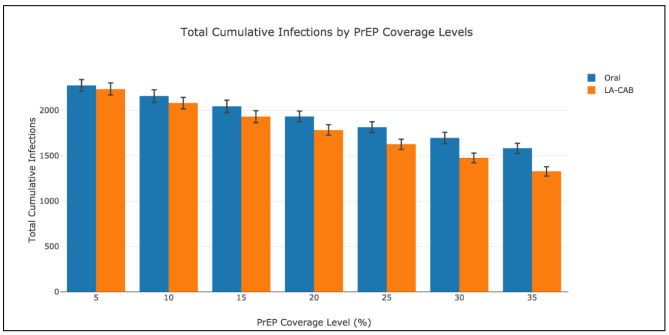
Background: Oral pre-exposure prophylaxis (PrEP) is highly effective for HIV prevention in men who have sex with men (MSM). To address challenges associated with daily pill adherence, injectable formulations are being tested in phase III trials. Long-acting cabotegravir (LA-CAB), an integrase strand transfer inhibitor, was demonstrated to have a strong protective effect in animal models. We used an agent-based model (ABM) to estimate the effectiveness of LA-CAB compared to oral PrEP on HIV incidence among MSM.

Methods: The ABM simulated HIV transmission in a dynamic sexual network of 11,000 MSM in Atlanta, Georgia over a 10-year time period (2015-2025). The model was calibrated to reproduce current HIV prevalence and incidence among MSM in Atlanta (30.3% and 3.9 per 100 person-years). We assumed agents received bimonthly LA-CAB bimonthly injections, with retention rates based on phase II trial data. The theoretical efficacy of LA-CAB was estimated from published macaque data using logistic regression, with waning protection up to 12 months following a final injection. LA-CAB concentrations over time were estimated from human pharmacokinetic data. The impact of LA-CAB on HIV incidence compared to oral PrEP was investigated across different PrEP target coverage levels. Sensitivity analyses investigated varied efficacies, retention rates, and half-lifes of LA-CAB.

Results: We estimated a theoretical efficacy of >99% among agents receiving bimonthly LA-CAB injections. Over the 10-year simulation period, HIV incidence was reduced in scenarios in which agents received LA-CAB compared to scenarios in which all received oral PrEP, at every coverage level (Figure). For example, a scenario in which 35% of HIV-uninfected agents receive LA-CAB averted an additional 255 infections over the next decade compared to a scenario in which 35% receive oral PrEP. The relative benefit of LA-CAB was sensitive to the maximum efficacy of bi-monthly LA-CAB injections and the terminal half-life after a final injection. For any given coverage level, decreasing the LA-CAB retention rate increased relative the benefit of the injectable formulation, due to a greater pool of agents with partial protection.

Conclusion: Long-acting PrEP may be more effective than oral PrEP for preventing HIV acquisition in MSM. However, the population impact and relative benefit of LA-PrEP will depend on the efficacy observed in ongoing phase III trials, as well as the extent and duration of protection among persons who drop out of LA-PrEP care.

Figure. Total cumulative number of new HIV infections over a 10-year time period (2015-2025) observed in an agent-based model representing MSM in the City of Atlanta, assuming all agents on PrEP receive LA-CAB (orange bars) vs. oral therapy (blue bars) for various PrEP coverage levels.



LA-CAB = long-acting cabotegravir; PrEP = preexposure prophylaxis
Note: Oral PrEP adherence was assumed to be 92% with 6-month retention in care set to 60%, based on previously published data. In the LA-CAB scenarios, 15% dropped out of care after 3-months, based on phase II trial data.

1152 QUANTIFYING INDIRECT BENEFITS OF PrEP: MODELING ANALYSIS OF ORAL PrEP IN ZIMBABWE

Zindoga Mukandavire[1], Daniel J. Klein[2], Graham F. Medley[1], Anna Bershteyn[2], Katharine Kripke[3], Delivette Castor[4], Definate Nhamo[5], Joseph Murungu[5], Taurai Bhatasara[6], Lawrance Nyazema[6], Kudakwashe Takarinda[6], Kristine Torjesen[7]
[1]London School of Hygiene & Tropical Medicine, London, UK, [2]Institute for Disease Modeling, Bellevue, WA, USA, [3]Avenir Health, Washington, DC, USA, [4]United States Agency for International Development, Washington, DC, USA, [5]Pangaea Zimbabwe Aids Trust, Harare, Zimbabwe, [6]Zimbabwe Ministry of Health and Child Care, Harare, Zimbabwe, [7]FHI 360, Durham, NC, USA

Background: HIV incidence remains high among adolescent girls and young women (AGYW) in Zimbabwe. Tenofovir-based oral pre-exposure prophylaxis (PrEP) can prevent individual infection, but population level impact and disaggregation of the direct (primary) and indirect (secondary/onward) preventive effects remain unexplored for this population. We assessed potential population-level benefits of oral PrEP use among female sex workers (FSW) and AGYW, and parse direct from indirect effects.

Methods: An individual-based HIV network model, EMOD-HIV v2.5, was parameterized for Zimbabwe to simulate provincial-level epidemics. The model was fit to age/gender/province-specific data on HIV prevalence and treatment coverage from DHS and Zimbabwe MoHCC reports. In the simulation, oral PrEP was provided to FSW and/or AGYW (18-24 years) with multiple partners at 40% coverage beginning in 2017 with a 5-year regimen of 73% effectiveness, which represents 90% efficacy with 81% adherence. Direct and indirect infections averted by oral PrEP were estimated by simulating a randomized trial (RT) in which 40% of the target population received oral PrEP and 40% received placebo drug. Direct prevention was computed from the incidence rate ratio between the two arms. Indirect prevention was computed as the difference between the number of HIV infections in the RT simulation and the number of HIV infections in a separate PrEP-free counterfactual simulation.

Results: For every infection directly averted by providing oral PrEP to FSW, 1.3 additional infections were indirectly averted in the community over 5 years and 1.7 additional infections were prevented in 20 years. The ratios were 1 and 1.7 when targeting only AGYW with multiple partners over the same horizons. Total numbers of indirect infections averted by oral PrEP increased in all ten provinces when providing PrEP to both FSW and AGYW, compared to the scenario of providing oral PrEP to FSW alone. In this scenario, the ratio of indirect to direct infections averted was 0.9 over 5 years and 1.8 over 20 years.

Conclusion: Results suggest that community benefit of oral PrEP can outweigh direct individual-level benefit. Indirect benefits of PrEP should be considered when prioritizing populations for PrEP service provision.

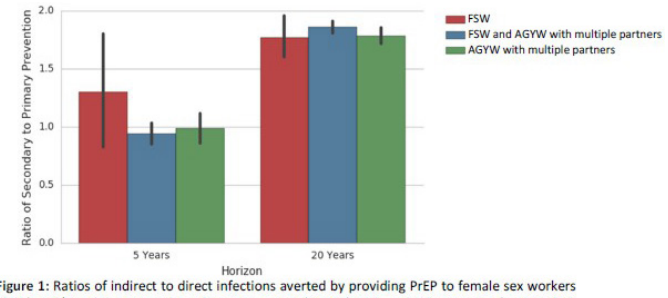


Figure 1: Ratios of indirect to direct infections averted by providing PrEP to female sex workers (FSW) and/or adolescent girls and young women (AGYW) with multiple partners for 5 and 20 years.

1153 DESIGNING HIV VACCINE DELIVERY STRATEGIES IN SOUTH AFRICA: A POLICY ANALYSIS

Blythe J. Adamson[1], Simon de Montigny[2], Benoît R. Mâsse[2], Louis Garrison[1], James G. Kublin[3], Peter Gilbert[3], Dobromir Dimitrov[3]
[1]University of Washington, Seattle, WA, USA, [2]Université de Montréal, Montreal, QC, Canada, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: Promising multi-dose HIV vaccine regimens are being tested in trials in South Africa. Efficient delivery will be a crucial component of future HIV immunization policies. To inform policy design, we estimate the epidemiological and economic impact of HIV vaccine campaigns compared to continuous clinic-based delivery, assuming efficacy is transient and dependent on immune response.

Methods: We used a dynamic mathematical model of HIV transmission calibrated to 2012 epidemiological data to simulate vaccination with anticipated antiretroviral treatment scale-up in South Africa. The model estimates new HIV infections, quality-adjusted life years (QALYs), and healthcare costs from a government perspective discounted 5% annually. We assume a price of $75 per 5-dose regimen in the base case and a range of prices in the sensitivity analysis. Vaccine delivery policy is simulated following three strategies: standard care with no HIV vaccine, continuous clinic-based delivery, and a mass campaign every two years. We compared costs and health outcomes across strategies, including the maximum vaccine price that remains cost-effective in South Africa. We explore outcome sensitivity in a range of scenarios.

Results: We estimate that biennial vaccination with a 70% efficacious vaccine reaching 20% coverage of the sexually active population could prevent 0.48-0.65 million HIV infections (13.8%-15.3% of the projected infections under standard care) over 10 years. Implementation with this campaign delivery dominated clinic-based delivery due to lower costs and increase in QALYs gained. The campaign strategy had an incremental cost-effectiveness ratio of $13,746 per QALY compared to no vaccine. Using a willingness-to-pay threshold of 3xGDP per capita, we find vaccination to be cost-effective if the price remains less than $29 per dose for the 5-dose series. Increasing vaccination coverage to 50% is expected to prevent more HIV infections but is less likely to be cost-effective. Mass campaign vaccination is consistently more effective and less costly than continuous clinic-based vaccination achieving the same biennial coverage across scenarios.

Conclusion: Our analysis suggests that a partially effective HIV vaccine will have substantial impact on the HIV epidemic in South Africa and will offer good value if priced less than $145 per five-dose series. Vaccination campaigns every two years may offer greater value for money than continuous vaccination reaching the same coverage level.

Table 1. Results from the policy analysis

Model Outcome	Standard Care (No Vaccine)	Continuous Clinic-Based	Mass Campaign
Vaccinated Adults (Millions)	-	24.72	24.45
Total Cost (Millions $)	11.70	14,744	14,728
Total QALYs (Millions)	269.3	269.4	269.5
AIDS Deaths (Millions)	2.86	2.82	2.81
Incremental Cost (Millions $)	-	3,090	3,074
per person vaccinated ($)		124.99	125.74
Incremental QALYs, total	-	165,856	223,624
per person vaccinated		0.0067	0.0091
AIDS Deaths Avoided	-	32,388	44,480
ICER ($/QALY)		Dominated	13,746

Scenario assuming 70% vaccine efficacy, 20% coverage of the adult population, vaccine price of $15 per dose. *Abbreviations: QALY, quality adjusted life-year; ICER, incremental cost-effectiveness ratio*

1154 FINE TUNING SPATIAL RESOLUTION OF HIV EPIDEMIOLOGIC DATA WHILE PROTECTING PRIVACY

Marta M. Jankowska, Tommi O. Gaines, Susan J. Little, Sanjay R. Mehta, **Antoine Chaillon**
University of California San Diego, La Jolla, CA, USA

Background: Privacy is a major concern with HIV-associated data. These data are often aggregated into larger spatial units to preserve privacy. However, the absence of HIV data at finer geographic scales limits the utility of spatial analyses to optimally target HIV interventions. Dasymetric mapping (DASY) is an areal interpolation method where the target polygons are zones of relative homogeneity with the purpose of best portraying the underlying statistical surface of the data being mapped. Here, we developed a cartographic DASY approach coupled with probabilistic reweighting to identify clusters of new HIV infections in San Diego County.

Methods: Age, sex, and ethnicity were collected for 657 HIV individuals enrolled in the San Diego Primary Resource Consortium (SDPIRC) across 6 SD Health and Human Services Agency (HHSA) regions. Transforming the data from HHSA region to a high resolution grid involved the following steps (Fig.): Generation of a background 500x500m grid surface combined with residential use data (step 1); DASY to interpolate data on residential land use, U.S. Census demographic data, and HIV prevalence data from Health Department into a 500x500m grid (step 2); finally, probabilistic reweighting was applied to the SDPRIC data to redistribute HIV new infection from HHSA regions to the 500x500m grid (step 3). Constraining variables (data from the SDPIRC cohort and grid cell map) were used to infer which grid cells HIV+ individuals were most likely to reside. A map was generated for each individual, and then aggregated for the full cohort to generate a final grid-based model of the distribution of the SDPIRC cohort.

Results: The resolved grid map shows considerably more details of where clusters of new infections reside throughout the county compared to the map divided into the 6 HHSA regions. While the expected cluster of infection in central San Diego remains, two hot spots that are not visible at the HHSA region level map emerge in north SD County, and in east SD County (Fig., circled in blue). Furthermore, the final grid model shows increased resolution of hotspots of HIV new infections in central and south-central SD.

Conclusion: The ability to identify and predict the spread of transmissible diseases, including HIV, is crucial to optimally target treatment and prevention programs. Downscaling health data without violating privacy and confidentiality restrictions can help to reveal spatial patterns at the local level that are not apparent in aggregated data sets.

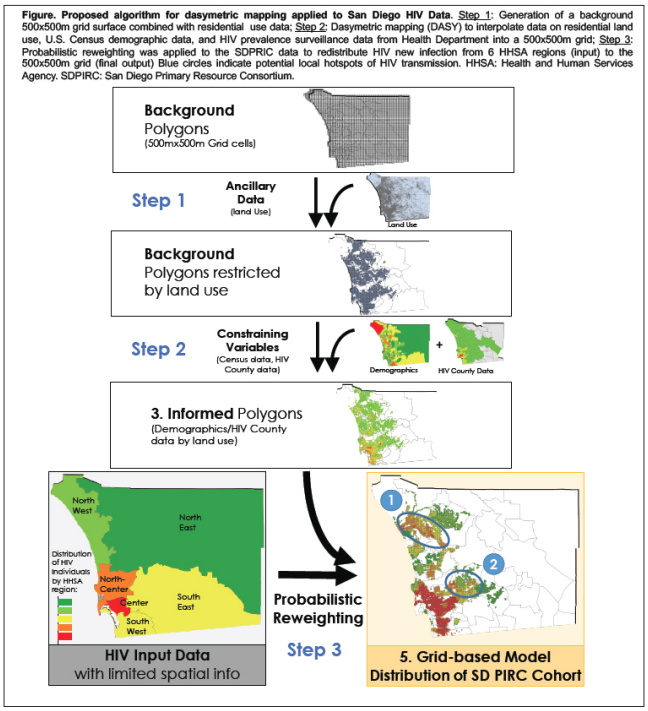


Figure. Proposed algorithm for dasymetric mapping applied to San Diego HIV Data. Step 1: Generation of a background 500x500m grid surface combined with residential use data; Step 2: Dasymetric mapping (DASY) to interpolate data on residential land use, U.S. Census demographic data, and HIV prevalence surveillance data from Health Department into a 500x500m grid; Step 3: Probabilistic reweighting was applied to the SDPRIC data to redistribute HIV new infection from 6 HHSA regions (input) to the 500x500m grid (final output) Blue circles indicate potential local hotspots of HIV transmission. HHSA: Health and Human Services Agency. SDPIRC: San Diego Primary Resource Consortium.

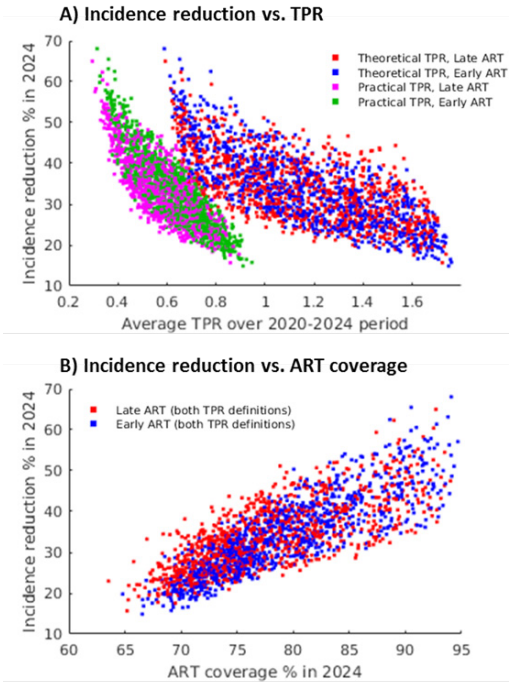


Figure 1. Results of 1000 simulations. Incidence reduction is relative to the base-case simulations calibrated to 2012 epidemiological data. Two definitions of TPR (theoretical and practical) and two ART access strategies (early ART and late ART priority) are shown.

1155 ASSESSING THE UTILITY OF THE TIPPING POINT RATIO FOR MONITORING ART PROGRAM SUCCESS

Simon de Montigny[1], Marie-Claude Boily[2], Benoît R. Mâsse[1], Kate M. Mitchell[2], Dobromir Dimitrov[3]
[1]Université de Montréal, Montreal, QC, Canada, [2]Imperial College London, London, UK, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, USA

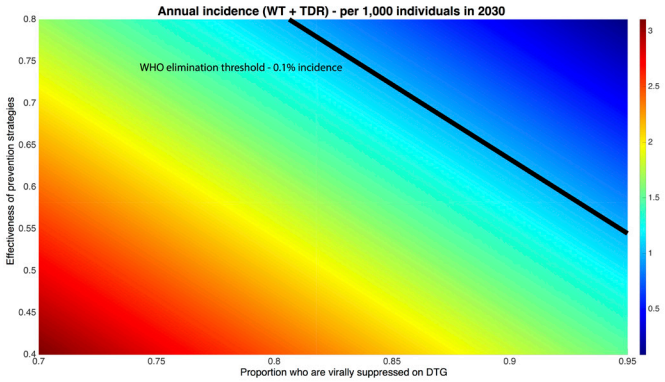
Background: The tipping point ratio (i.e. theoretical TPR), defined as the yearly ratio of new HIV infections to the net increase in HIV+ individuals on antiretroviral therapy (ART), has been used to compare ART scale-up efforts across countries and measure their progress toward HIV elimination. However, in the literature, estimates of TPR are often based on a definition, using new ART initiations as the denominator (i.e. practical TPR), which is easier to estimate. We analyze the utility of TPR, theoretical and practical, to evaluate the progress of ART rollout using different definitions under various epidemic conditions.
Methods: We developed a compartmental model of HIV transmission and ART rollout in South Africa, calibrated to 2012 epidemic data and reflecting expansion to universal treatment in 2017. We used Monte Carlo filtering to select 1000 simulations which represented uncertainty in base-case epidemic conditions. We simulated scenarios in which the theoretical TPR is targeting a fixed value between 0.6 and 1.8 over 2020-2024 using compensation for losses of individuals on ART over time (due to deaths and interrupted ART) and different ART access strategies by stage of HIV progression (late or early ART initiation). We compared the reduction in HIV incidence relative to the base-case epidemic in 2024 as function of the practical or theoretical TPR (averaged over 2020-2024) and ART coverage in 2024.
Results: Results show that the same HIV incidence reduction (35%) can be achieved with a wide range of TPR (theoretical TPRs 0.68-1.58; practical TPRs 0.42-0.72). Practical TPR which counts ART compensation as new initiations yields lower incidence reduction for the same value as theoretical TPR, e.g. TPR = 0.8 has 19-30% incidence reduction under practical definition and 29-54% under theoretical definition (Fig A). Simulated ART coverage achieved in 2024 (Fig B) is a better predictor of HIV incidence reduction (with Pearson's r = 0.85) than theoretical TPR (Pearson's r = -0.79). The difference between early and late ART initiation is small due to ART compensation.
Conclusion: Our analysis suggests some confusion when TPR is used in the literature. The practical TPR likely overestimates the progress of ART programs and often produces TPR values below 1. Although a more reasonable indicator, the theoretical TPR is technically more difficult to estimate and should be supplemented with ART coverage data to judge the progress of ART programs.

1156 PREDICTING THE PROBABILITY AND TREATMENT COSTS OF ELIMINATING HIV IN BOTSWANA

Katie Sharp, Sally Blower
University of California Los Angeles, Los Angeles, CA, USA

Background: Botswana has one of the most severe HIV epidemics worldwide, where ~24% of adults are infected with HIV. In 2002, Botswana was the first African country to roll out anti-retroviral treatment. Dolutegravir was introduced into first-line regimens in 2016 and all individuals became treatment eligible, regardless of CD4 cell count. We use modeling to reconstruct the epidemiological impact of treatment from 2002 to 2016. We then predict whether treatment, coupled with preventative interventions, will enable Botswana to reach the WHO elimination threshold of 1 new HIV infection per 1,000 individuals/year, and both UNAIDS's treatment targets, by 2030. We also estimate cumulative drug costs.
Methods: We use a transmission model, calibrated and parameterized with data from Botswana. We model both first and second-line therapies; including acquired and transmitted drug resistance. We conduct an uncertainty analysis and a multivariate sensitivity analysis based on response hypersurface modeling. We investigate the effect of treatment rates, viral suppression rates (VSR) (reflecting both efficacy and adherence), and the effectiveness (reflecting both efficacy and coverage) of interventions.
Results: We find the WHO elimination threshold will only be reached by 2030 if very stringent conditions are met: the effectiveness of interventions is > 55%, and the VSR for first-line regimens is > 95%. UNAIDS 90-90-90 goals will be reached if the VSR for second-line regimens is > 95%. The number of individuals needing treatment will increase steeply to ~2021, then stabilize and remain approximately constant to 2030. However, the proportion needing first-line regimens will decrease, and the proportion needing second-line regimens will increase; by 2030, ~25% of patients may need second-line regimens. Total cumulative drug costs for second-line regimens will be determined by the VSR to first-line regimens. If this is extremely high (95%), cumulative costs for second-line drugs will be ~70 million; if the VSR is only moderate (70%), costs will be approximately double.
Conclusion: Botswana will only be able to eliminate HIV by 2030 if adherence to first-line regimens is extremely high, and extremely effective interventions are also implemented. A high level of adherence is the key determinant in

minimizing cumulative drug costs. The number on treatment will not decrease by 2030, even if the elimination threshold is reached.



1157 COST-EFFECTIVENESS OF MEDICAL CARE COORDINATION FOR HIGH-RISK PWH IN LA COUNTY

Moses J. Flash[1], Wendy H. Garland[2], Bruce R. Schackman[3], Sona Oksuzyan[2], Justine A. Scott[1], Philip J. Jeng[3], Emily B. Martey[1], Marisol Mejia[2], Elena Losina[4], Emily P. Hyle[1], Sonali P. Kulkarni[2], Kenneth Freedberg[1]
[1]Massachusetts General Hospital, Boston, MA, USA, [2]Los Angeles County Department of Public Health, Los Angeles, CA, USA, [3]Weill Cornell Medicine, New York, NY, USA, [4]Brigham and Women's Hospital, Boston, MA, USA

Background: Many people with HIV (PWH) face psychosocial needs that impact their health status but are not typically addressed through routine HIV clinical care. The Los Angeles County (LAC) Division of HIV and STD Programs developed a comprehensive medical care coordination (MCC) program to improve HIV treatment access, retention, and adherence for PWH facing multiple psychosocial co-morbidities, including homelessness and substance use disorder.
Methods: We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-US model to project the lifetime clinical and economic outcomes for these high-risk PWH under two strategies: 1) usual care (*no MCC*), and 2) a 2-year *MCC* program. Model inputs were based on data from a cohort of high-risk PWH who started the LAC-MCC program in 2013 and were followed for 24 months. The baseline cohort included: mean age 40yr (SD 11yr), 87% male, 33% virologic suppression, and mean CD4 count 429/µL (SD 293/µL). High-risk characteristics included: 65% drug/alcohol use in past 6m, 51% current mental health diagnosis, 38% previously incarcerated, and 22% homeless in past 6m. Two-year virologic suppression was projected at 37% with *no MCC* and was 57% with *MCC*. *MCC* cost an additional $2,700/person annually (2017 USD), which included a mean of 17.3 service hours/person/year. For the *MCC* strategy, we applied program efficacy and costs for two years, assuming that individuals revert to their pre-program adherence after two years. The primary outcome was the incremental cost-effectiveness ratio (ICER, Δcost/Δquality-adjusted life year (QALY)). In sensitivity analyses, we examined the impact of varying the MCC program efficacy, program costs, and other parameters on the overall results.
Results: *MCC* increased quality-adjusted life expectancy from 9.99 to 10.63 QALYs; lifetime HIV-related medical costs increased from $381,570 to $402,840, resulting in an ICER of $33,100/QALY for *MCC* (Table 1). *MCC* had an ICER <$50,000/QALY gained if 2-year virologic suppression was at least 41%, annual program costs were below $8,100/person, or if there was moderate virologic suppression (47%) and annual costs were below $5,400.
Conclusion: Based on virologic suppression during the first two years of implementation, the LA County MCC program will improve survival and is cost-effective for high-risk PWH. Similar programs should be implemented in other settings to improve HIV outcomes among PWH with complex co-morbidities.

Table 1. Projected clinical outcomes and cost-effectiveness of Medical Care Coordination (MCC) in Los Angeles County (LAC)

(Base case in white; selected 1-way sensitivity analyses in gray)

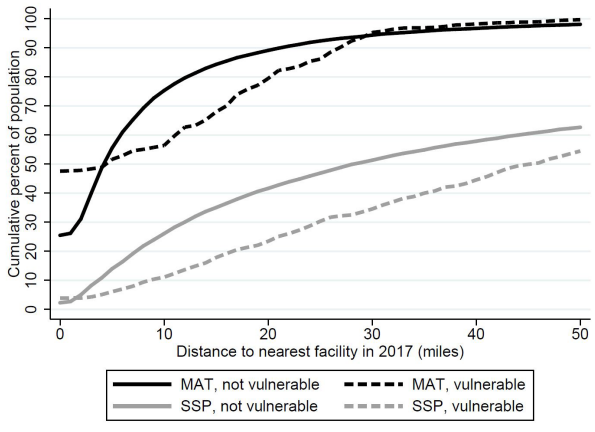
	Model input parameters (n=1,204)		Model output		
Strategy	Annual MCC program costs (2017 $)	2-yr overall virologic suppression	Quality-adjusted life years (QALY)	Cost (2017 $)	ICER ($/QALY)
No MCC	--	37%	9.99	381,570	--
MCC	2,700	57%	10.63	402,840	33,100
MCC 2-yr efficacy					
Low	2,700	41%	10.11	387,440	47,500
High	2,700	80%	11.32	424,440	32,200
MCC costs					
0.5X	1,350	57%	10.63	400,600	29,600
2X	5,400	57%	10.63	409,010	42,700

yr: year. **QALY:** quality-adjusted life-year. **ICER:** incremental cost-effectiveness ratio. **MCC:** medical care coordination.

1158 220 VULNERABLE COUNTIES: ONE YEAR LATER

Alana Sharp, Brian Honermann, Austin Jones, Gregorio A. Millett
amfAR, New York, NY, USA

Background: In 2016, the Centers for Disease Control and Prevention (CDC) published an assessment of county-level vulnerability to an HIV or hepatitis C (HCV) outbreak among injection drug users, finding 220 counties at high risk. Preventing outbreaks will require the delivery of preventive services including addiction treatment and syringe services programs (SSPs) to prevent HIV and HCV transmission. Twelve months after the publication of this analysis, we assess the status of access to healthcare services to prevent such an outbreak.
Methods: We compiled the number of outpatient facilities providing at least one form of medication-assisted treatment (MAT) from the National Survey of Substance Abuse Treatment (N-SSATS). The location of SSPs are taken from the North American Syringe Exchange Network (NASEN) database, current and archived from 2014. Minimum distance to a MAT-offering program or an SSP is calculated as the distance between the coordinates of each ZIP code tabulation area (ZCTA) in a vulnerable county and the nearest ZCTA containing a treatment program. ZCTA population is from the 2010 Census.
Results: Of the 220 vulnerable counties, 29.7% contained a treatment program providing MAT in 2014; by 2017, 36.4% of counties had a MAT program. Of all other counties, 34.5% contained a MAT facility in 2014 and 39.9% did in 2017. Of vulnerable counties, 1.4% contained an SSP in 2014 and 7.3% did in 2017; in all other counties, the percent rose from 4.6% in 2014 to 6.2% in 2017. In 2017, 56.4% of the population in vulnerable counties lived in or within 10 miles of a ZCTA containing a MAT program and 11.1% live within 10 miles of an SSP. In the rest of the country, 75.3% lived within 10 miles of a MAT program and 26.1% lived within 10 miles of an SSP. While the proportion of counties with treatment program and SSPs increased by 22.6% and 433.3%, respectively from 2014 to 2017, a significant proportion of the population continues to experience geographic barriers to care.
Conclusion: Many clients do not access SSPs unless they are within a ten minute walk from their home. As such, the finding that more than one-third of people in vulnerable counties are more than 10 miles away from MAT, and nine in ten are more than 10 miles from an SSP, suggests that geographic and capacity barriers persist. This analysis does not account for program capacity or insurance policies; as such, the availability of treatment and prevention services may be lower still.



DISCLOSURE OF FINANCIAL RELATIONSHIPS WITH COMMERCIAL CONCERNS

Disclosure information is presented generally as submitted by the corresponding presenting abstract author, invited speaker, session moderator, or member of the CROI Program Committee. The individuals below provided their relevant disclosures of financial relationships with commercial entities for themselves and their spouses or partners, as well as funding provided to their institutions.

Aboud, Michael
Self: Employee of ViiV Healthcare

Abrams, Elaine J.
Self: Relationship with ViiV and Merck

Adimora, Adaora
Self: Other relationship with Merck; research grant recipient from Gilead

Alland, David
Self: Recipient of research grant(s) and royalty holder Cepheid
Spouse or Partner: Stockholder of AstraZeneca; relationship with Tarveda Therapeutics

Alter, Galit
To self, paid to my institution: Recipient of research grant(s) from BioProtection Systems/New Link Genetics, Gilead Sciences, Bill and Melinda Gates Foundation, and Merck; contracted researcher for Sanofi, Curevac, and Janssen

Althoff, Keri N.
Self: Consultant for TrioHealth

Andreatta, Kristen
Self: Employee of Gilead Sciences, Inc

Andrieux-Meyer, Isabelle
Self: Cipla is the developer of LPV/R pellets

Baeten, Jared
To self, paid to my institution: Study medication, International Partnership for Microbicides; study medication donation and advisory committee for Gilead Sciences

Barouch, Dan
To self, paid to my institution: Recipient of research grant(s) from Gilead

Baxter, John D.
Self: Consultant for Quest Diagnostics

Becker, James T.
Self: Recipient of research grant(s) from National Institutes of Health
Spouse or Partner: Recipient of research grant(s) from National Institutes of Health

Bedimo, Roger
To self, paid to my institution: Recipient of research grant(s) from Merck and Bristol Myers Squibb; consultant for Merck, Theratechnologies, and ViiV Healthcare

Bekker, Linda-Gail
Self: Receive donations of PrEP for demonstration projects from Gilead

Benson, Constance A.
To self, paid to my institution: Recipient of research grant(s) from AbbVie, Gilead Sciences, ViiV Healthcare; consultant, data and safety monitoring board for GlaxoSmithKline/ViiV Healthcare.
Spouse or Partner: Consultant for CytoDyn, Antiva Biosciences; stockholder of Antiva Biosciences, CytoDyn; Scientific Advisory Board Member (honoraria remitted to the University of California) for Gilead Sciences, Inc, and LabCorps.

Betts, Michael R.
Self Recipient of research grant(s) from Merck

Bhattacharya, Debika
To self, paid to my institution: Recipient of research grant(s) paid to the University of California Los Angeles from AbbVie, Bristol-Myers Squibb, and Merck

Billings, Erik
Self: Employee of and contracted researcher for The Henry M. Jackson Foundation

Boesecke, Christoph
Self: Consultant and speaker's bureau for AbbVie, Gilead, Janssen, MSD, ViiV

Boettiger, David C.
Self: Recipient of research grant(s) from Gilead Sciences

Boffito, Marta
To self, paid to my institution: Recipient of research grant(s) from Gilead, BMS, ViiV, Janssen, Mylan, Teva, MSD; consultant and speaker's Bureau for Gilead, BMS, ViiV, Janssen, Clpla, Teva, MSD

Braun, Dominique L.
To self, paid to my institution: Recipient of research grant(s) from Merck Sharp & Dohme, recipient of research grant(s) Swiss HIV Cohort Study, and University of Zurich's Clinical Research Priority Programm Viral Infectious Diseases Zurich Primary HIV Infection Study

Brown, Todd T.
Self: Consultant for Gilead, Merck, and Theratechnologies

Buchbinder, Susan P.
Self: Relationship with Gilead Sciences

Bukusi, Elizabeth A.
To self, paid to my institution: Recipient of research grant(s) from National Institutes of Health, BMF, US Centers for Disease Control and Prevention, and European & Developing Countries Clinical Trials Partnership

Busch, Michael P.
To self, paid to my institution: Recipient of research grant(s) from Consultant Hologic, Inc

Cahn, Pedro
Self: Fundacion Huesped received a research grant from Richmond Argentina and Ministry of Science for this study

Callebaut, Christian
Self: Employee of and stockholder in Gilead Sciences Inc.

Campbell, Thomas
Self: Consultant for ViiV, Gilead Sciences, and Theralogic

Carr, Andrew
Self: Recipient of research grant(s) from and consultant for Gilead Sciences, MSD, and ViiV Healthcare; speaker's bureau for MSD and Gilead Sciences

Carrico, Adam W.
To self, paid to my institution: Recipient of research grant(s) from National Institutes of Health

Cespedes, Michelle S.
Self: Consultant for Gilead Sciences

Chaisson, Richard E.
Self: Consultant for Otsuka
Spouse or Partner: stockholder in Merck

Chamie, Gabriel
To self, paid to my institution: Recipient of research grant(s) from National Institutes of Health

Charpentier, Charlotte
Self: Recipient of research grant(s) from and consultant for Janssen-Cilag, MSD, Gilead, ViiV Healthcare

Chen, Janet
To self, paid to my institution: Recipient of research grant(s) from Eunice Kennedy Shriver National Institute of Child Health and Human Development with pass-through funding from Harvard School of Public Health, National Heart, Lung, and Blood Institute, and Gliead Sciences

Chomont, Nicolas
To self, paid to my institution: Recipient of research grant(s) from Merck & Co, Abivax, and Serono

Clutter, Dana S.
Self: Recipient of research grant(s) from Bristol-Myers Squibb

Coffin, John M.
Self: Consultant and Stockholder for Tocagen, Inc.

Colombo, Massimo G.
Self: Consultant for Merck, Roche, Novartis, Bayer, BMS, Gilead Sciences, Tibotec, Vertex, Janssen Cilag, Achillion, Lundbeck, GSK, GenSpera, AbbVie, Alfa Wasserman, and Intercept; speaker's bureau for Tibotec, Roche, Novartis, Bayer, BMS, Gilead Sciences, Vertex, Merck, Janssen, AbbVie

Costagliola, Dominique
To self, paid to my institution: Recipient of research grant(s) from Janssen and MSD; speaker's bureau for Janssen and MSD

Costiniuk, Cecilia
To self, paid to my institution: Recipient of research grant(s) from Gilead and Merck

Cotte, Laurent
Self: Consultant for AbbVie, Gilead Sciences, Janssen-Cilag

Currier, Judith S.
Self: Recipient of research grant(s) from Theratechnologies

Cu-Uvin, Susan
To self, paid to my institution: Recipient of research grant(s) from National Institutes of Health

Cysique, Lucette A.
To self, paid to my institution: Recipient of research grant(s) from NHMRC, and Gilead Sciences Award

Dadabhai, Sufia
To self, paid to my institution: Research grant and funding support from National Institutes of Health: R21HD085874; study participants and their families; institutional review boards and community stakeholders; study staff; Blantyre District Health Office and all health facility in-charges

Deguit, Christian Deo T.
To self, paid to my institution: Recipient of research grant(s) from Philippines Department of Science & Technology

Del Amo, Julia
Self: Recipient of research grant(s) from, and other relationships with, ViiV Health Care, Gilead, and MSD

del Rio, Carlos
Self: Consultant for ViiV

Di Perri, Giovanni
Self: Recipient of research grant(s) from and consultant or speaker's bureau for AbbVie, BMS, GSK, MSD, Janssen, ViiV, Basilea, Astellas, Angelini, and Pfizer

Dixon Diallo, Dázon
Self: Consultant and Speaker's bureau for Gilead Sciences (Advisory Board, Speaker) Merck & Co (Advisory Board, Speaker) ViiV Healthcare (Advisory Board, Speaker)

Dombrowski, Julia C.
To self, paid to my institution: Recipient of research grant(s) from Hologic, Quidel, Curatek; speaker in CME sponsored by Gilead

Domínguez-Domínguez L.
Self: Relationship with ViiV Healthcare, MSD, and Janssen

Dooley, Kelly
Self: Relationship with ViiV Healthcare

Dryden-Peterson, Scott
Self: Royalty holder for UpToDate, Inc

Durand, Christine
Self: Relationship with Gilead Sciences; consultant for Merck Pharmaceuticals; recipient of research grant(s) from Merck Pharmaceuticals and GlaxoSmithKline

Eckard, Allison R.
To self, paid to my institution: Consultant for Gilead Sciences

Elinav, Hila
Self Recipient of research grant(s) from Israel Science Foundation

Erlandson, Kristine, M.
Self: Recipient of research grant(s) from and consultant for Gilead and consultant for Theratechnologies

Eron, Joseph, J.
To self, paid to my institution: Recipient of research grant(s) from and consultant for Janssen, Gilead Sciences, ViiV Healthcare; consultant for Merck

Esser, Stefan
To self, paid to my institution: Recipient of research grant(s) from and consultant for ViiV Healthcare, Gilead Sciences, MSD, Janssen

Evans, Ceri
To self, paid to my institution: Recipient of research grant(s) from Wellcome Trust, National Institute for Health Research, UK

Falcó, Vicenç
Spouse or partner, paid to institution: Recipient of research grant(s) from ViiV; relationship with Gilead; **Self:** relationship with Janssen-Cylag

Feaster, Daniel
To self, paid to my institution: Recipient of research grant(s) from National Institute on Drug Abuse

Feld, Jordan J.
To self, paid to my institution: Recipient of research grant(s) from and consultant for AbbVie, Gilead Sciences Inc; recipient of research grant(s) from Janssen, Merck

Finocchario Kessler, Sarah
Self: Recipient of research grant(s) from University of Kansas Medical Center

Fishbein, Dawn
To self, paid to my institution: Recipient of research grant(s) from Gilead; stockholder in AbbVie, Merck

Fletcher, Courtney V.
To self, paid to my institution: Recipient of research grant(s) from National Institutes of Health

Flynn, Patricia M.
Self: Royalty holder for UpToDate; consultant for Merck & Co

Force, Gilles
To self, paid to my institution: Recipient of research grant(s) from AbbVie France for the Neuro+3 study; consultant for AbbVie

Franco, Ricardo A.
Self: Recipient of research grant(s) from and consultant for Gilead; contracted researcher for Merck and Janssen

Furrer, Hansjakob
To self, paid to my institution: Recipient of research grant(s) from ViiV Healthcare, Gilead Sciences, Inc, MSD, Abbott, Janssen

Gaiha, Gaurav D.
Spouse or Partner: Employee of Gilead Sciences

Gantenberg, Jason
To self, paid to my institution: Recipient of research grant(s) from National Institutes of Health (R21 MH109360-01, Co-PIs: Brandon D.L. Marshall, Philip A. Chan)

Gaur, Aditya
To self, paid to my institution: Recipient of research grant(s) from Gilead

Gianotti, Nicola
Self: Recipient of research grant(s) from, consultant and speaker's bureau for Gilead Sciences, ViiV, Bristol-Myers Squibb, Merck Sharp and Dohme, Roche, AbbVie, Boehringer Ingelheim, and Janssen-Cilag

Girardi, Enrico
Self: Consultant for Otsuka Novel Products, Janssen; speaker's bureau for Angelini. Gilead Sciences
To self, paid to my institution: Recipient of research grant(s) from Mylan

Golden, Matthew R.
To self, paid to my institution: Recipient of research grant(s) from Hologic, GlaxoSmithKlein

Gorman, Daniel
Self: Employee of and stockholder in Merck

Graham, Susan M.
Spouse or Partner: Recipient of intellectual property rights from University Health Network, Toronto, Ontario

Gross, Robert
Self: Data and safety monitoring board for, and other relationship with, Pfizer, Inc

Grulich, Andrew
To self, paid to my institution: Recipient of research grant(s) from ViiV Healthcare, Gilead Sciences, Inc, Sequirus
Self: Consultant for ViiV Healthcare; speaker's bureau for Merck

Günthard, Huldrych F.
Self: Recipient of travel support and research and other grant(s) from, consultant for, and served on data and safety monitoring board for Gilead Sciences, Inc; data and safety monitoring board for Merck

Gupta, Phalguni
Self: Recipient of research grant(s) from University of Pittsburgh

Haas, David
To self, paid to my institution: Recipient of research grant(s) from Vanderbilt University Medical Center

Haberer, Jessica E.
Self: Stockholder in Natera

Hallett, Timothy B.
To self, paid to my institution: Recipient of research grant(s) from Gilead

Hammer, Scott M.
Self: Consultant for CytoDyn

Hamzah, Lisa
To self, paid to my institution: Recipient of research grant(s) (institution) from, and other relationship (self only) with, Gilead

Handoko, Ryan C.
Self: Recipient of research grant(s) from National Heart, Lung and Blood Institute of the National Institutes of Health. HIVMA Medical Student Award

Harrison, Thomas S.
To self, paid to my institution: Recipient of research grant(s) from Gilead Sciences, Inc
Self: Speaker's bureau for Pfizer, Gilead; consultant for Viamet

Hendrix, Craig W.
To self, paid to my institution: Recipient of research grant(s) from National Institutes of Health, Bill & Melinda Gates Foundation
Self: Consultant for ViiV/GSK, UCLA, RTI, Inc; scientific advisory board for Population Council

Henrich, Timothy J.
Self: Recipient of research grant(s) from National Institutes of Health/National Institute of Allergy and Infectious Diseases, amFAR

Hileman, Corrilynn O.
Self: Consultant for Gilead Sciences, Inc

Hillier, Sharon L.
Self: Consultant for Merck, Lupin, Hennepin Life Sciences, Biofire Diagnostics
To self, paid to my institution: Recipient of research grant(s) from Cepheid, Becton Dickinson

Ho, Ya-Chi
Self: Recipient of research grant(s) from Gilead Sciences

Hodder, Sally L.
To self, paid to my institution: Consultant for Gilead, Janssen, ViiV, and Merck; recipient of research grant(s) from Gilead Sciences

Holland, David P.
Self: Consultant for Gilead Sciences

Hoornenborg, Elske
To self, paid to my institution: Recipient of research grant(s) from Gilead Sciences Inc (only PrEP medication)

Horberg, Michael A.
Self: Employee of Kaiser Permanente

Howell, Bonnie J.
Self: Employee of Merck

Hsieh, Yu-Hsiang
To self, paid to my institution: Recipient of research grant(s) from Gilead HIV Focus Program

Hsue, Priscilla
Self: Recipient of research grant(s) from Pfizer; honoraria from Gilead

Hudson, Parker
Self: Consultant for Best Doctors

Huhn, Gregory D.
Self: Recipient of research grant(s) from and consultant for Gilead, ViiV, Janssen; recipient of research grant(s) from Proteus, National Institutes of Health; consultant for Theratechnologies, CSL

Hunt, Peter W.
To self, paid to my institution: Recipient of research grant(s) from Gilead Sciences, Inc
Self: Consultant for Viiv, Seres Therapeutics

Imaz, Arkaitz
To self, paid to my institution: Recipient of research grant(s) from Gilead Sciences, Inc, ViiV Healthcare
Self: Relationships with Gilead Sciences, MSD, Janssen, AbbVie

Jain, Mamta K.
Self: Recipient of research grant(s) from Gilead Sciences, Merck, Janssen

Jani, Ilesh V.
To self, paid to my institution: Recipient of research grant(s) from Janssen Vaccines

Jhaveri, Ravi
To self, paid to my institution: Recipient of research grant(s) from AbbVie, Gilead, Merck

Kant, Sanket
Self: Relationship with The Research Institute of the McGill University Health Centre, McGill University

Katlama, Christine
Self: Relationship with InnaVirVax

Kattakuzhy, Sarah
Self: Recipient of research grant(s) from Gilead Sciences

Kaur, Jasmine
Self: Employee of Gilead Sciences

Keating, Sheila M.
Self: Employee of Blood Systems Research Institute

Keiser, Olivia
To self, paid to my institution: Recipient of research grant(s) from Gilead

Keller, Marla J.
To self, paid to my institution: Recipient of research grant(s) from National Institutes of Health

Kelley, Colleen F.
Self: Recipient of research grant(s) from and consultant for Gilead Sciences; consultant for Medscape

Khalili, Kamel
Self: Recipient of intellectual property rights from, consultant for, and stockholder in Excision Biotherapeutics

Khoo, Saye
To self, paid to my institution: Recipient of research grant(s) from ViiV Healthcare

Kiser, Jennifer J.
To self, paid to my institution: Recipient of research grant(s) from Gilead, Janssen

Klatt, Nichole
Self: Consultant for Seres Therapeutics, Takeda Pharmaceutics

Kostman, Jay
To self, paid to my institution: Recipient of research grant(s) from and consultant for Gilead, Merck

Koup, Richard A.
To self, paid to my institution: Recipient of research grant(s) from Bill & Melinda Gates Foundation

Krakower, Douglas
To self, paid to my institution: Recipient of research grant(s) from Gilead Sciences

Krogstad, Paul
Self: Relationship with Merck

Kuritzkes, Daniel R.
Self: Recipient of research grant(s) from and consultant for Gilead, Merck, ViiV; consultant for CytoDyn; relationship with Sanofi

Kwarisiima, Dalsone
To self, paid to my institution: Recipient of research grant(s) from National Institutes of Health

Kwiek, Jesse
Self: Recipient of intellectual property rights from The Ohio State University

Kwon, Douglas
Self: Co-founder of and consultant for Day Zero Diagnostics

Lacombe, Karine
Self: Consultant for Gilead. MSD, AbbVie

Leal, Lorna
Self: Relationship with Gilead

Lee, Sulggi
Self: Recipient of research grant(s) from Viiv Healthcare, Gilead Sciences, Inc

Li, Jonathan Z.
Self Recipient of research grant(s) from and consultant for Gilead and Merck

Lin, Nina
Self: Recipient of research grant(s) from Gilead and Merck

Little, Susan J.
To self, paid to my institution: Recipient of research grant(s) from Gilead Sciences, Inc
Self: Consultant for GlaxoSmithKline

Lu, Wei
To self, paid to my institution: Recipient of research grant(s) from Peking Union Medical College Hospital

Ma, Qing
Self: Recipient of research grant(s) from Gilead, National Institute of Mental Health

Maartens, Gary
Self: Consultant for Johnson & Johnson

Mallon, Patrick W.G.
To self, paid to my institution: Recipient of research grant(s) from and consultant and speaker's bureau for Gilead Sciences, BMS, ViiV Healthcare (consultant, grant), MSD (consultant), AbbVie (grant)

Margot, Nicolas A.
Self: Employee of and stockholder in Gilead Sciences Inc.

Markowitz, Martin
Self: Recipient of research grant(s) from and consultant for Merck, GlaxoSmithKline. Speaker's bureau for Gilead Sciences, Inc

Marks, Kristen M.
To self, paid to my institution: Recipient of research grant(s) from BMS, Gilead, Merck

Marra, Christina
Self: Royalty holder for UpToDate, Wolters Kluwer

Martinelli, Elena
Self: Recipient of research grant(s) from National Institutes of Health

Martinson, Neil A.
To self, paid to my institution: Recipient of research grant(s) from Roche, Pfizer

Matsushita, Shuzo
Self: Consultant for Janssen Pharmaceutical KK, Japan Tobacco Inc, CURED Co, Ltd; relationships with Bayer Yakuhin, Ltd, MSD KK, Torii Pharmaceutical Co, Ltd, Shire Japan KK, Bioverativ Japan KK, Novo Nordisk Pharma Co

Matthews, Gail
To self, paid to my institution: Recipient of research grant(s) from AbbVie, Gilead
Self: Recipient of research grant(s) from BMS; speaker's bureau for Gilead

Matthews, Randolph P.
Self: Employee of Merck

Mayer, Kenneth H.
Self: Recipient of research grant(s) from Gilead Sciences and ViiV Healthcare

McComsey, Grace A.
Self: Consultant for Gilead, ViiV, and Merck
To self, paid to my institution: Research support from Gilead, BMS, ViiV, Merck, Astellas, and Roche.

McFall, Allison M.
To self, paid to my institution: Recipient of research grant(s) from The Johns Hopkins University

McIntyre, James A.
Self: Consultant for Novavax

Meissner, Eric G.
To self, paid to my institution: Recipient of research grant(s) from Gilead Sciences

Mellors, John W.
To self, paid to my institution: Recipient of research grant(s) from National Institutes of Health; grant support from Janssen Pharmaceuticals and Gilead Sciences
Self: Scientific Advisory Board Member for Gilead Sciences; owns share options, value unknown, in Co-Crystal PHarma, Inc.; Patent #: 8,815,829 issued

Mena, Leandro A.
Self Consultant for Gilead Sciences, Inc (also speaker's bureau), ViiV Healthcare, Thera Technologies
To self, paid to my institution: Contracted researcher for Bioclinical, Inc, Roche Diagnostic

Metsch, Lisa
To self, paid to my institution: Recipient of research grant(s) from National Institute on Drug Abuse

Mills, Anthony
Self: Recipient of research grant(s) from, and other relationships with, Gilead, ViiV, Merck; recipient of research grant(s) from Janssen, Sangamo, Medrio, Eisai

Mitchell, Charles D.
To self, paid to my institution: Recipient of research grant(s) from National Institute of Allergy and Infectious Diseases, National Institutes of Health

Molina, Jean-Michel
To self, paid to my institution: Recipient of research grant(s) from, speaker's bureau for, and other relationship with Gilead
Self: Relationships with Merck and ViiV

Morrocchi, Elena
Self: Relationship with ViiV Healthcare

Mugavero, Michael J.
Self: Consultant for Gilead Sciences; scientific review committee for the Gilead Sciences Research Scholars Program in HIV

Mukandavire, Zindoga
To self, paid to my institution: Recipient of research grant(s) from the US President's Emergency Plan for AIDS Relief (PEPFAR) with the US Agency for International Development (USAID) under the Optimizing Prevention Technology Introduction On Schedule (OPTIONS) Cooperative Agreement

Mulka, Larissa V.
Self: Recipient of research grant(s) from The British HIV Association

Myer, Landon
Self: Consultant for Pfizer

Neary, Megan
Self: Employee of University of Liverpool

Negredo, Eugènia
Self: Recipient of research grant(s) from and consultant and speaker's bureau for Janssen, MSD, ViiV, Gilead, BMS

Nel, Annalene
Self: Employee of International Partnership for Microbicides

Nijhawan, Ank E.
Self: Recipient of research grant(s) from Gilead sciences

Orkin, Chloe
Self: Recipient of research grant(s) from and consultant and speaker's bureau for MSD, ViiV, Janssen, Gilead
To self, paid to my institution: NHS/MSD/Viiv/Janssen/Gilead

Owen, Andrew
Self: Consultant for Merck, ViiV
To self, paid to my institution: Recipient of research grant(s) from Janssen, ViIV, Merck, AstraZeneca

Parczewski, Milosz
To self, paid to my institution: Recipient of research grant(s) from AbbVie
Self: Consultant for Gilead Sciences, AbbVie, MSD, Janssen-Cilag; speaker's bureau for Gilead Sciences

Paredes, Roger
Self: Recipient of research grant(s) from Merck, ViiV Healthcare

Parkes-Ratanshi, Rosalind M.
To self, paid to my institution: Recipient of research grant(s) from Johnson and Johnson Corporate Citizenship Trust and Janssen Global Public Health

Pérez-Valero, Ignacio
Self: Consultant and speaker's bureau for Gilead, Janssen, ViiV, MSD

Pettifor, Audrey
Self: Recipient of research grant(s) from University of North Carolina at Chapel Hill

Peytavin, Gilles
Self: Consultant and speaker's bureau for AbbVie, Gilead Sciences, Janssen, Merck, ViiV Healthcare

Pohlmeyer, Christopher
Self: Employee of Gilead Sciences

Poteat, Tonia
Self: Contracted researcher for ViiV Healthcare

Ragonnet-Cronin, Manon
To self, paid to my institution: Recipient of research grant(s) from Gilead

Rashbaum, Bruce
Self: Speaker's bureau for and stockholder in Gilead, Johnson & Johnson (speaker only)

Reddy, Krishna P.
To self, paid to my institution: Recipient of research grant(s) from National Institutes of Health

Reiss, Peter
To self, paid to my institution: Recipient of research grant(s) from, and scientific advisory board participation for, Gilead Sciences, ViiV, Janssen (data safety monitoring board), Merck, Teva (grant only)

Richman, Douglas D.
Self: Consultant for Antiva Biosciences, Chimerix, Gilead Sciences, Inc, and Monogram Biosciences, Inc.

Robertson, Kevin
Self: Consultant for ViiV

Rockstroh, Jürgen K.
Self: Consultant for, and other relationships with, Abbott, AbbVie, Gilead, Hexal (consultant only), Janssen, Merck, ViiV (cosultant only)

Rodgers, Mary
Self: Employee of and stockholder in Abbott Laboratories

Rosen, Sydney
Self: Recipient of research grant(s) from Bill & Melinda Gates Foundation

Rosenbloom, Daniel S.
Self: Employee of Merck; consultant for Accelevir Diagnostics

Ryan, Pablo
To self, paid to my institution: Recipient of research grant(s) from and speaker's bureau for Merck
Self: Speaker's bureau for Gilead, ViiV

Sabin, Caroline
Self: Consultant, speaker's bureau for and other relationships with Gilead Sciences, ViiV Healthcare (non speaker), Janssen-Cilag

Sacha, Jonah
Self: Consultant for Vir Biotechnology
To self, paid to my institution: Recipient of research grant(s) from Vir Biotechnology

Saravanan, Shanmugam
Self: Employee of YRG CARE

Schechter, Mauro
Self: Advisory board member for Gilead, GlaxoSmithKline, ViiV Healthcare, Janssen, and Merck

Schooley, Robert T.
Self: Consultant for and stockholder in CytoDyn, Antiva Biosciences (stockholder), VIR (consultant)
To self, paid to my institution: Consultant for Monogram Biosciences, Gilead Sciences

Sekhar, Rajagopal V.
Self: Recipient of research grant(s) from National Institutes of Health

Serrano-Villar, Sergio
To self, paid to my institution: Recipient of research grant(s) from MSD
Self: Speaker's bureau for ViiV, Gilead, MSD

Shan, Liang
Self: Employee of Washington University in St Louis

Shivakoti, Rupak
Self: Recipient of research grant(s) from Gilead Foundation

Sigel, Keith M.
Self: Recipient of research grant(s) from National Institutes of Health

Slyker, Jennife
Self: Recipient of research grant(s) from National Institutes of Health, grants HD094718, HD023412

Sohn, Annette H.
To self, paid to my institution: Recipient of research grant(s) from ViiV Healthcare

Springer, Sandra
Self: Recipient of research grant(s) from National Institute on Drug Abuse

Spudich, Serena S.
Self: Viiv Healthcare provides study medications for a clinical trial co-directed by Dr Spudich.

Stradling, Clare
Self: Recipient of research grant(s) from National Institute for Health Research (UK Dept of Health)

Svedhem-Johansson, Veronica
Self: Recipient of research grant(s) from Bristol-Myers Squibb and Swedish Society of Medicine

Taha, Taha E.
To self, paid to my institution: Recipient of research grant(s) from the National Institute of Allergy and Infectious Diseases under Award Numbers UM1, with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health

Takle, Jeff
Self: Employee of SystemOne

Tariq, Shema
Self: Consultant for Gilead Sciences

Thienemann, Friedrich
Self: Employee of and recipient of research grant(s) from University of Cape Town

Thomas, David L.
Self: Consultant for Merck

Thomas, Réjean
Self: Consultant for Gilead, Merck, ViiV Healthcare

Thudium, Rebekka F.
To self, paid to my institution: Recipient of research grant(s) from Gilead Sciences

Tolstrup, Martin
To self, paid to my institution: Recipient of research grant(s) from Bionor Pharma

Torres, Berta
To self, paid to my institution: Relationship with MSD

Torres, Thiago S.
Self: Recipient of research grant(s) from Gilead Sciences

Trkola, Alexandra
To self, paid to my institution: Recipient of research grant(s) from Gilead Sciences; cure grant recipient
Spouse or Partner: Recipient of research grant and travel support from, consultant for, and served on data and safety monitoring board for Gilead Sciences, Inc
Spouse or partner paid to institution: Served on data and safety monitoring board for Merck

Trypsteen, Wim
Self: Consultant for COMBiNATi

Tsibris, Athe
To self, paid to my institution: Recipient of research grant(s) from Merck
Self: Relationship with Gilead Sciences

Uldrick, Thomas S.
To self, paid to my institution: Recipient of research grant(s) from Celgene, Merck

Vareil, Marc
Self: Recipient of research grant(s) from MSD France

Velásquez, Gustavo E.
To self, paid to my institution: Recipient of research grant(s) from National Institutes of Health

Venter, Willem D.F.
Self: Investigator-initiated antiretroviral trials received drug donations from Gilead and ViiV; speaker's bureau for Gilead, ViiV, Aspen, Merck, Abbott, J&J, Mylan, Adcock Ingram

Wagner, Thor A.
To self, paid to my institution: Recipient of research grant(s) from Gilead; **r**ecipient of intellectual property rights from Seattle Children's Research Institute

Wang, Dan
Self: Employee of and recipient of research grant(s) from Georgetown University, National Heart, Lung, and Blood Institute

Weinberg, Adriana,
Self: Recipient of research grant(s) from Merck, GSK, Medimmune

Weinheimer, Steven
Self: Employee of TaiMed Biologics USA

Weiser, John
Self: Stockholder in Gilead

White, Kirsten L.
Self: Employee of and stockholder in Gilead Sciences, Inc.

Wijting, Ingeborg
Self: Relationship with Gilead Sciences

Wilkin, Timothy
To self, paid to my institution: Recipient of research grant(s) from and consultant for Bristol Myers-Squibb (grant only), GlaxoSmithKline/ViiV Healthcare
Spouse or Partner: Stockholder for Johnson&Johnson

Williams-Nguyen, Jessica
Spouse or Partner: Employee of Microsoft

Wyles, David L.
Self: Consultant for AbbVie, Gilead, Merck
To self, paid to my institution: Recipient of research grant(s) from AbbVie, Gilead, Merck

Yapa, H. Manisha. N
Self: Recipient of research grant(s) from Australian Government Research Training Programme scholarship

DISCLOSURE INDEX

The following have no relevant financial relationships to disclose. Any updates will be reflected in the mobile App.

Aamer, Hadega
Abdel-Mohsen, Mohame
Abdool Karim, Quarraisha
Abgrall, Sophie
Achwoka, Dunstan
Adamson, Blythe J.
Adu-Gyamfi, Clement G.
Aepfelbacher, Julia A.
Agnew-Brune, Christine
Aguirre, Alfredo
Ajaykumar, Abhinav
Ajibola, Gbolahan
Akapirat, Siriwat
Akiyama, Hisashi
Aldovini, Anna
Aldrete, Sol
Alvarez, Angeles
Alvarez, Jean-Claude
Alvi, Raza M.
Ambia, Julie
Ambrose, Zandrea
Amelio, Patrizia
Anderson, Elizabeth M.
Anderson, Motswedi
Antonio, Marilia B.
Apondi, Edith
Arikawa, Shino
Arinaminpathy, Nimalan
Armstrong, Abigail
Arpadi, Stephen M.
Arthos, James
Arts, Eric
Asmuth, David M.
Assoumou, Sabrina A.
Atindaana, Edmond A.
Atwine, Daniel W.
Audsley, Jennifer
Auld, Andrew F.
Avihingsanon, Anchale
Avila-Rios, Santiago
Avino, Mariano
Avoundjian, Tigran
Awadalla, Magid
Ayieko, James
Bachmann, Nadine
Bacon, Oliver
Badaro, Roberto
Badia, Roger
Baggaley, Rachel
Baiyegunhi, Omolara
Baker, Jason V.
Balogun, Kayode
Bandera, Alessandra
Bandi, Kiran
Banga, Riddhima
Bar, Katharine J.
Barlow-Mosha, Linda
Barrenas, Fredrik
Bassett, Ingrid V.
Batista, Cynthia Julia B.
Bauer, Anya
Bauer, Rebecca
Baugher, Amy R.
Baum, Marianna K.
Beard, Rachel S.
Bekker, Adrie
Benbow, Nanette
Benson, Eve-Marie A.
Berenguer, Juan
Bernal, Enrique
Bertagnolli, Lynn N.
Bieniasz, Paul
Billock, Rachael
Bismut, Gilad
Bjorkman, Pamela J.
Blanc, François-Xavier
Blanch-Lombarte, Oscar
Blumenthal, Jill
Boerekamps, Anne
Bohn, Jennifer
Boltz, Valerie F.
Bomsel, Morgane
Boon, Denali
Borges, Christine M.
Boritz, Eli A.
Boucau, Julie
Boudreau, Carolyn
Bourgi, Kassem
Box, Helen J.
Braunstein, Sarah L.
Brennan, Alana T.
Brenner, Bluma G.
Breton, Yann
Bridge, Sarah
Brocca-Cofano, Egidio
Browne, Edward P.
Browne, Sara H.
Bruner, Katherine
Buchacz, Kate
Bullo, Manuela
Buranapraditkun, Supranee
Burgener, Adam
Burgunder, Erin M.
Burnett, Janet C.
Buskin, Susan E.
Byambaa, Enkhmaa
Cachay, Edward R.
Cai, Haotian
Cai, Yanhui
Calkins, Keri
Cameron, Mark
Campos, Nicole G.
Cannizzo, Elvira S.
Carlander, Christina
Carney, Brandon W.
Caro-Vega, Yanink
Castel, Amanda D.
Castelnuovo, Barbara
Castillo-Mancilla, Jose R
Cavallari, Eugenio Nelson
Cedarbaum, Emily
Celani, Luigi
Celum, Connie L.
Cerrone, Maddalena
Chaillon, Antoine
Chaix Baudier, Marie-Laure
Chang, Linda
Chakalisa, Unoda A.
Chakrabarti, Lisa A.
Chan, Man
Chan, Philip A.
Chan, Phillip
Chang, Ming
Chaudhury, Chloe S.
Chaudron, Sandra E.
Chen, Bing
Chen, Bonnie
Cheng, Adam Z.
Cheng, Liang
Chernoff, Miriam
Cheru, Lediya
Chettimada, Sukrutha
Cheu, Ryan
Chi, Benjamin H.
Chiasson, Mary Ann
Chihana, Menard L.
Childs, Kathryn
Chow, Dominic
Chow, Felicia C.
Chowdhury, Fatema Z.
Chowdury, Pranesh P.
Christ, Frauke
Christensen-Quick, Aaron
Christopoulos, Katerina A.
Chung, Raymond T.
Clarridge, Katherine
Clayton, Kiera L.
Clemenzi-Allen, Angelo A.
Closson, Kalysha
Coelho, Lara
Cohn, Lillian B.
Cohen, Yehuda Z.
Colasanti, Jonathan
Colby, Donn
Collins, Intira J.
Colon-Rivera, Krystal
Coltart, Cordelia
Copelyn, Julie
Corbett, Elizabeth L.
Corey, Kathleen, E.
Corleis, Bjorn
Cortés-Rubio, César N.
Council, Olivia
Coutinho, Roel
Covino, Daniela Angela
Craig, Morgan L.
Crane, Heidi M.
Crawford, Sue
Cressey, Tim R.
Cuadros, Diego F.
Custodio, Joseph M.
Cuypers, Lize
Dabis, François
Dai, Weiwei
Darling, Katharine
Das, Jishnu
Dasgupta, Sharoda
Davis, Zachary
Davy-Mendez, Thibaut
de Almeida, Sergio M.
de Armas, Lesley R.
De Cock, Kevin M.
De Francesco, Davide
de Montigny, Simon
De Zan, Valentina
Del Prete, Gregory Q.
Delagreverie, Heloise M.
Deleage, Claire
Delelis, Olivier
Derby, Nina
Desir, Fidel A.
Desrosiers, Vincent
Dhummakupt, Adit
Di Mascio, Michele
Diez Fuertes, Francisco
Dillon, Stephanie
Dobard, Charles
Doblecki-Lewis, Susanne
Döring, Matthias
Doshi, Rupali K.
Drain, Paul K.
D'Souza, Gypsyamber
Dumchev, Kostyantyn
Dumond, Julie B.
Dzialowy Adams, Nicole
Eberhardt, Kirsten
Ebrahimi, Diako
Egan, James E.
Egger, Matthias
El-Far, Mohamed
Eller, Michael A.
Elliot, Emilie R.
El-Sadr, Wafaa M.
Emery, Ann
Enns, Eva A.
Esber, Allahna L.
Estes, Jacob D.
Evans, Emily
Evans, Mary
Fabrizio, Claudia
Fadrosh, Douglas
Fairlie, Lee
Falade-Nwulia, Oluwaseun
Fanjul, Francisco
Farhadian, Shelli
Fernández-Rodríguez, Amanda
Fichorova, Raina
Fiorillo, Suzanne P.
Fisher, Bridget
Fischinger, Stephanie
Flash, Moses J.E.
Flynn, Jacob
Flynn, JoAnne L.
Fogel, Jessica M.
Folkvord, Joy M.
Ford, Nathan
Fourman, Lindsay T.
France, Anne Marie
Frederix, Koen
Freeman, Michael L.
Freiberg, Matthew
Fujitnirun, Chris
Fukuda, Hirofumi
Fulcher, Jennifer A.
Gaeta, Giovanni B.
Gagliardini, Roberta
Gale, Michael
Gandhi, Monica
Gandhi, Neel R.
Ganesan, Anuradha
Gangcuangco, Louie M. A.
Gantner, Pierre
Gaolathe, Tendani
Garber, David A.
García, Federico
Garcia Broncano, Pilar
García-Álvarez, Mónica
Garcia-Fraile Fraile, Lucio Jesus

Pavlakis, George N.
Pegu, Amarendra
Peterson, Tess
Pett, Sarah
Pham, Hanh T.
Pham, Phuong
Phillips, Andrew N.
Phillips, Tamsin K.
Phuphuakrat, Angsana
Pierone, Gerald
Pierre, Samuel
Pinnetti, Carmela
Pino, Maria
Piselli, Pierluca
Piske, Micah
Podany, Anthony
Pollack, Todd
Pollard, Alex
Ponte, Rosalie
Poschman, Karalee
Post, Frank
Post, Wendy
Poveda, Eva
Prendergast, Andrew
Presti, Rachel,
Price, Joan T.
Proust, Alizé
Provost, Joel
Purdy, Julia
Puttkammer, Nancy
Pyra, Maria
Rabie, Helena
Rabkin, Miriam
Radix, Asa
Radtke, Kendra K.
Radwan, Daniel
Rahman, Mohammad Arif
Rajasingham, Radha
Rajoli, Rajith Kumar Reddy
Rallón, Norma
Ram, Daniel
Ramos Muniz, Cláudia Priscil
Rappocciolo, Giovanna
Rasmussen, Thomas A.
Ravimohan, Shruthi
Ready, Erin
Redd, Andrew D.
Registre, Ludy
Reid, William C.
Reidy, William J.
Reiff, Julie
Remien, Robert H.
Restar, Arjee J.
Revollo, Boris
Reynolds, Helen
Rhein, Joshua
Richter, Enrico
Risher, Kathryn A.
Ritchie, Anne M.
Rivero-Juárez, Antonio
Rocafort, Muntsa
Rodriguez-Garcia, Marta
Rojas, Sarah
Ronit, Andreas
Rosales Del Real, Ofelia M.
Rosen, Elias
Roy, Monika
Rubin, Leah H.
Rubio Garrido, Marina
Rusie, Laura
Rutishauser, Rachel L.
Ryom, Lene
Sachathep, Karampreet
Sacktor, Ned
Sadanand, Saheli
Sadder, Liane S.
Saeed, Sahar
Sailasuta, Napapon
Saito, Suzue
Salahuddin, Syim
Salazar-Austin, Nicole
Salazar-Vizcaya, Luisa
Salpini, Romina
Samboju, Vishal
Samaneka, Wadzanai
Samri, Assia
Sanford, Ryan
Sanmartí, Montserrat
Sarca, Anamaria D.
Saroli Palumbo, Chiara
Saunders, John
Scarsi, Kimberly K.
Schacker, Timothy
Scheer, Susan
Scherrer, Alexandra
Schillinger, Julia A.
Schleimann, Mariane H.
Schneider, Jennifer M.
Schreiber-Stainthorp, William T.
Schuetz, Alexandra
Schuster, Christopher
Sconza, Rebecca
Scott, Hyman
Scully, Eileen P.
Seaberg, Eric C.
Sengayi, Mazvita
Serra Peinado, Carla
Sette, Paola
Shah, Spandan
Shah, Swati
Shan, Zhilei
Shapiro, Adrienne E.
Shapiro, Roger L.
Sharaf, Radwa
Sharp, Alan
Sharp, Katie
Shava, Emily
Shen, Jing
Sheth, Anandi N.
Shiau, Stephanie
Shiels, Meredith S.
Short, Charlotte-Eve S.
Shover, Chelsea L.
Sibanda, Euphemia
Sibiude, Jeanne
Siegler, Aaron J.
Sikazwe, Izukanji
Sikombe, Kombatende
Silverman, Michael
Silvestri, Guido
Simon, Viviana A.
Simonetti, Francesco R.
Sinharay, Sanhita
Sivay, Mariya V.
Smith, Bryan
Smith, Dawn K.
Smith, James M.
Smith, Renee
Smith, Shayla
Solomon, Sunil S.
Soriano-Sarabia, Natalia
Sousa, Ana E.
Spector, Stephen A.
Spence, Amanda B.
Spinelli, Matthew A.
Spivak, Adam M.
Srinivas, Nithya
Srinivasa, Suman
Srinivasan, Sujatha
Ssebambulidde, Kenneth
Stafylis, Chrysovalantis
Starke, Carly Elizabeth C.
Stecher, Melanie
Stekler, Joanne
Stella-Ascariz, Natalia
Stephenson, Kathryn E.
Stone, Lauren
Stone, Mars
Strain, Jeremy
Strbo, Natasa
Streeck, Hendrik
Strongin, Zachary
Stumpf, Megan M.
Sudjaritruk, Tavitiya
Sun, Jing
Sundquist, Wesley I.
Swanstrom, Adrienne E.
Tadesse, Birkneh T.
Tan, Nicholas
Tang, Xiaoli
Tanner, Mary
Tatham, Lee M.
Tawakol, Ahmed
Taylor, Bryn C.
Taylor, Ian A.
Taylor, Jeff
Taylor, Kirk A.
Teasdale, Chloe A.
Telwatte, Sushama
Tembo, Taniya
Teran, Richard A.
Thao, Vu P.
Thiébaut, Rodolphe
Thielman, Nathan
Thin, Kyaw
Thindwa, Deus
Thirumurthy, Harsha
Thrift, Aaron P.
Tiraboschi, Juan M.
Tobin, Nicole
Tomezsko, Phillip
Torgersen, Jessie
Torian, Lucia V.
Toribio, Mabel
Touloumi, Giota
Trichavaroj, Rapee
Trunfio, Mattia
Truong, Hong-Ha M.
Tully, Damien C.
Turan, Janet M.
Ukpong, Morenike O.
Underwood, Jonathan
Urasa, Peris
van Bilsen, Ward P.H.
Van de Perre, Philippe
Van Duyne, Rachel
Van Hecke, Clarissa
van Lettow, Monique
Vandormael, Alain
Vargas, Benni S.
Vasan, Sandhya
Velloza, Jennifer
Vestad, Beate
Viani Puglisi, Elisabetta
Vibholm, Line K.
Vickerman, Peter
Villinger, Francois
Visseaux, Benoit
Vo, Quynh
Vos, Alinda
Votteler, Joerg
Vucicevic, Katarina
Waitt, Catriona
Walimbwa, Stephen I.
Walker-Sperling, Victoria E. K.
Wang, Qi
Wang, Ruibin
Wang, Zheng
Wang, Zheng
Watson, Meg
Webb, Nicholas E.
Weiss, Helen A.
Weiss, Kevin
Wertheim, Joel O.
Wesolowski, Laura
Wheeler, Darrell
White, Lisa Diane
Whitney, James
Wiche Salinas, Tomas Raul
Wiley, Dorothy J.
Williams, Darlisha A.
Winchester, Nicole E.
Winston, Jennifer
Wirtz, Andrea L.
Withers, Keenan
Wittner, Melanie
Wonderlich, Elizabeth R.
Wood, Robin
Wu, Helen
Yende-Zuma, Nonhlanhla
Youn, Christine
Yu, Wen-Han
Zaikos, Thomas D.
Zangerle, Robert
Zarwell, Meagan
Zash, Rebecca
Zhang, Peng
Zhang, Yinfeng
Zhao, Connie A
Zhong, Yaoyu
Zhou, Shuntai

AUTHOR INDEX

–C–

–D–

–H–

–I–

–J–

–K–

–L–

–M–

–N–

KEYWORD INDEX