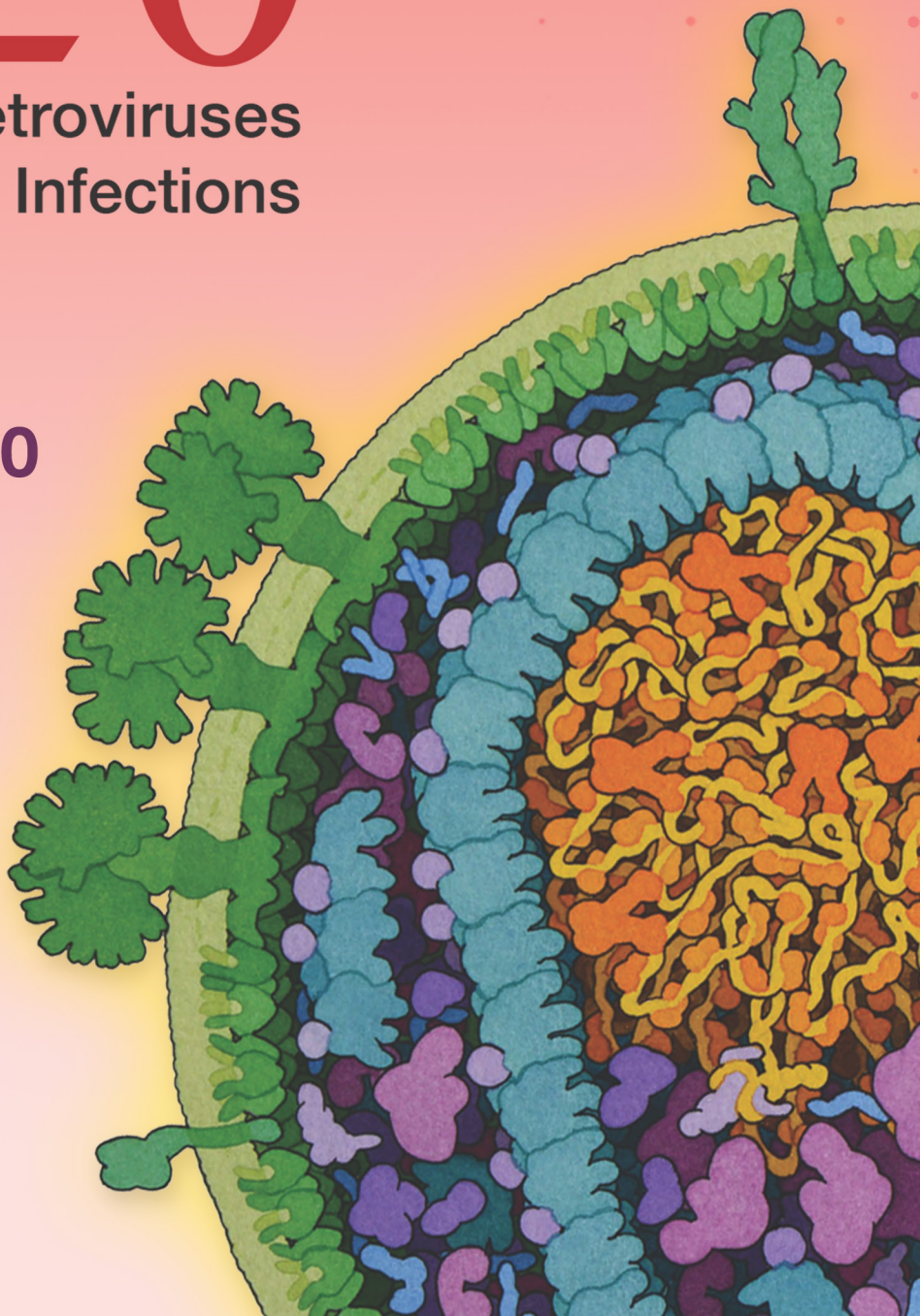
Abstract eBook

CROI 2020

Conference on Retroviruses and Opportunistic Infections

Boston
March 8-11, 2020



IAS–USA
International Antiviral Society–USA

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ABSTRACT PROCESS

Scientific Categories

A. Virology
B. Pathogenesis: Human Studies and Animal Models
C. HIV-Associated Tumor Viruses
D. Host Immune Responses to Infection, Vaccines, and Immunotherapy
E. HIV Reservoirs, Latency, and All Curative Strategies Including Therapeutic Vaccines and Gene Therapy
F. Neuropathogenesis and Neurologic Complications

G. Clinical Pharmacology
H. Antiretroviral Therapy: Pre-Clinical Data, Randomized Trials, Efficacy and Effectiveness Studies
I. HIV Drug Resistance
J. Hepatitis Viruses and Liver Complications
K. AIDS-Related Malignancies
L. Cardiovascular Complications of HIV Infection and Antiretroviral Therapy
M. Other Complications of HIV Infection and Antiretroviral Therapy
N. Tuberculosis and Other Opportunistic Infections
O. Maternal and Fetal HIV
P. Pediatrics and Adolescents

Q. Epidemiology
R. Testing
S. Prevention Interventions
T. Contraception, Sexually Transmitted Infections, and Reproductive Health
U. Implementation and Scale-Up of Treatment and Care

Abstract Content

Author names, institutions, titles, and abstracts in the CROI Program and Information Guide, Abstract eBook, Mobile App, and other materials are presented largely as submitted by the submitting author. The submitting author is responsible for ensuring that all coauthors have reviewed and approved the abstract before submission and for providing the complete and accurate contact information for all authors, including email address. **THE SUBMITTING AUTHOR MUST ENSURE THAT THE EMAIL ADDRESSES OF ALL LISTED AUTHORS IN THEIR SUBMISSION ARE CORRECT** in order for authors to receive important information regarding dispositions, presentation details, registration and housing information, and other CROI-related announcements.

Special Notes on Abstract Content

Presentations from randomized trials and cohorts should follow the International Committee of Medical Journal Editors (ICMJE) guidelines, including reporting of study designs, (eg, prospective, observational, randomized, double-blind, STROBE, CONSORT, or others), statistical methods, and outcomes by demographic variables.

Appropriate information and correct terminology should be used with regard to **sex and gender**. For human clinical or epidemiologic studies, sex-stratified results should be provided or who was included if the study includes only a single population. Appropriate terminology such as cisgender (people whose gender match the sex assigned at birth) or transgender (people whose gender does not match the sex assigned at birth) should be used. Both sex and gender data should be provided in the presentation. Presentations of preclinical data including use of cell lines and animal studies should include the sex of the animals or the sex of the source of the cell lines. If data are not available on sex and gender, this should be identified as a limitation in your presentation.

Out of respect for their contributions to our scientific advances, avoid calling study volunteers "subjects." The **preferred terms** are study "participants" or "volunteers."

Presenting Author Responsibilities

The presenting author is responsible for presenting the abstract at the conference and must be present at the poster during the entire session. **Submitting authors are responsible for ensuring that all coauthors have reviewed and approved the abstract contents before submission.**

Embargo Policies and Social Media

All research presented at CROI 2020 is embargoed until the conclusion of the study's presentation at the conference. For example, if a study is presented from 2:15 PM to 2:30 PM, as part of a session that begins at 2:00 PM and ends at 3:00 PM, the embargo on that study lifts at 2:30 PM. Embargoes on poster presentations lift at the beginning of the session in which the poster is presented.

If a study to be presented at CROI 2020 is included in an official CROI press conference that takes place before the scheduled presentation of the study, the embargo on that study lifts at the conclusion of the press conference panel in which the study is featured.

No public dissemination of research information from the conference is permitted prior to the lifting of the conference embargo. CROI embargo policies apply to any public dissemination of research information presented at the conference, including electronic publications (eg, blogs) or social media (eg, Twitter, Instagram, Facebook). Individuals or organizations that violate the conference embargo policy may have their conference credentials revoked and may forfeit the opportunity to participate in future conferences.

Abstract Review Process

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

Abstracts were reviewed for the quality and originality of the work and were scored 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 for each abstract were averaged and the standard deviation was calculated to assess variability. If variability was high, outlier scores were discussed. 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 (distinct from a late submission, as they must meet a high threshold of scientific merit).

Common Reasons for Abstract Rejection

- Subject matter is not appropriate for CROI
- All coauthors did not approve the abstract prior to submission
- Information is not novel (new enough)
- Abstract is duplicative of other submissions
- Format does not follow guidelines (eg, data missing, more than 1 table or figure submitted)
- Submission is poorly written and difficult to understand
- Background does not summarize the hypothesis
- Methodology is inadequate or insufficient to support conclusions
- Controls are absent or inadequate
- Statistical evaluation is inadequate or absent
- Summary of essential results is inadequate or absent
- Data are not included or offer inadequate or insufficient support for conclusions
- Submission reports clinical trial data from unplanned analyses or incomplete or ongoing studies

Statistics for Abstracts

General abstract submitted	1852
General abstracts accepted	1035
General oral abstracts	85
General poster abstracts	878
Late-breaking abstracts submitted	188
Late-breaking abstracts accepted	46
Late-breaking oral abstracts	17
Late-breaking poster abstracts	29
Total abstracts submitted	**2040**
Total abstract accepted	**1081**

All Presenting Authors on Accepted Abstracts

Region	N	Percent
Africa	84	9%
Asia	17	2%
Australia	19	2%
Europe	10	1%
Central and South America	206	23%
North America	570	63%

Abstracts Related to Study Populations

1. Adolescents	52
2. Men who have sex with men (MSM)	118
3. People who inject drugs (PWID)	38
4. Transgender men or women	19
5. Women	114

Authors have noted specific populations as the focus of their study, if applicable. Indexes that list abstracts that relate to specific populations are on the CROI Mobile App and Abstract eBook on the CROI website. These indexes are developed for attendees with an interest in these areas.

ORAL ABSTRACTS

1 SESSION OVERVIEW: PROGRAM COMMITTEE WORKSHOP FOR NEW INVESTIGATORS AND TRAINEES

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

Over the past four decades, remarkable progress has been made in understanding HIV epidemiology, pathogenesis, treatment, and prevention from the combined efforts of community members, clinicians, investigators, and funding agencies worldwide. Yet more work and new approaches are needed to achieve the ambitious goal of ending the epidemic and ensuring optimal quality of life for those living with HIV. To encourage and stimulate the next generation of investigators, the CROI Program Committee organizes an annual Workshop for New Investigators and Trainees comprised of expert and comprehensible talks to cover current knowledge and controversies in basic, clinical and public health investigation into HIV and related infections, and to highlight relevant work to be presented over the ensuing days at CROI. This year's Workshop will begin with Dr. Wes Sundquist who will review aspects of HIV-1 replication and innate immunity, in particular recent developments in our understanding of mechanisms of virus sensing, early steps in the viral replication cycle, and virus-host arms races. Dr. Richard Koup will cover recent preclinical HIV vaccine advances, concentrating on efforts to induce either broad neutralizing antibody responses or protective CD8 T cells, and discuss the latest data on the development and use of broadly neutralizing antibodies in prevention and treatment of HIV. Dr. Hermione Lyall will review ongoing challenges in prevention of vertical HIV transmission during pregnancy and breastfeeding, short and long term challenges of getting infants on to treatment, and approaches to sustaining health and supporting 'undetectable=untransmittable' in youth with HIV. Dr. Susan Buchbinder will describe the current status of new infections globally, and discuss recent advances in biomedical HIV-1 prevention including treatment as prevention, pre-exposure prophylaxis, topical preventive agents, HIV vaccines, and combination approaches to HIV prevention. Finally, Dr. Nicolas Chomont will review the mechanisms that contribute to HIV persistence during ART, highlight the role of cell proliferation in that process and present recent therapeutic approaches aimed at curing HIV infection. The Workshop serves as the initial opportunity for Trainees and New Investigators to interact with Program Committee members. Such interactions will continue during new morning sessions organized to provide support and guidance for emerging investigators at this year's CROI.

2 SHIFTING FROM ACUTE TO CHRONIC, AGING, LONGEVITY, AND LIVED EXPERIENCE

Jim Pickett[1], Martha Tholanah[2], Gabriel Maldonado[3], Celeste Watkins-Hayes[4]
[1]AIDS Foundation of Chicago, Chicago, IL, USA, [2]Advocate, Harare, Zimbabwe, [3]TruEvolution, Riverside, CA, USA, [4]Northwestern University, Chicago, IL, USA

Globally, there were 5.7 million [4.7 million– 6.6 million] people living with HIV (PLHIV) 50 years of age and older (50+) in 2016. Although the proportion of PLHIV50+ was greater in high-income countries, low-and-middle-income countries have higher numbers of PLHIV50+ that are expected to continue to increase by 2020. The proportion of PLHIV50+ across the world increased substantially from 8% in 2000 to 16% in 2016 and is expected to increase to 21% by 2020*. In the United States, it is estimated that more than 70% of PLHIV will be 50 or older in 2020.

Thirty-nine years into the epidemic, we've seen a remarkable shift in the trajectory of HIV. No longer is an HIV diagnosis simply a death sentence, individuals with HIV are living longer than ever before. Issues related to aging, long ignored due largely to irrelevance, are coming to the fore. What does it mean to age with HIV across the lifespan? How do co-morbidities, polypharmacy, long-term adherence to medications, mental health, neurocognitive impairment, stigma, discrimination, and fatigue factor into long-term survival? How do resilience and other mechanisms shift the narrative from surviving to thriving? What factors must be considered beyond viral suppression when assessing the quality of life? Each panelist will share their distinctive perspectives and experiences and will then open up the discussion to include audience members.

* Global and regional trends of people living with HIV aged 50 and over: Estimates and projections for 2000–2020, PLoS One. 2018; 13(11): e0207005.

3 SHAPING VACCINES WITH DNA ORIGAMI

Mark Bathe, *MIT, Cambridge, MA, USA*

Viral-like structured DNA and RNA assemblies, also known as DNA and RNA origami, offer the ability to co-formulate gene-length single-stranded DNA or mRNA with CRISPR-RNPs, siRNAs, or ASOs, with the integration of active cellular targeting, stimulation, and uptake moieties including peptides, sugars, and small molecules. Biological stability and immunostimulation can additionally be programmed selectively through the use of chemical modifications. Scaleable bacterial production of custom length and sequence single-stranded DNA offers a low-cost path towards clinical-scale production. Here, I will present our lab's formulation and preclinical work in the context of the field, to produce pre-clinical scale, endotoxin-free structured DNA and RNA assemblies for targeted delivery of nucleic acid gene therapeutics and vaccines, including a case study of viral-like DNA assemblies applied to an HIV vaccine candidate.

4 CONCEPTS IN RESERVOIR MEASUREMENTS

Janet M. Siliciano, *Johns Hopkins University School of Medicine, Baltimore, MD, USA*

A stable latent reservoir for HIV-1 in resting CD4+ T cells precludes cure. Curative strategies targeting the reservoir are being tested and require accurate, scalable reservoir assays. The reservoir was originally defined with a quantitative viral outgrowth assays (QVOA) for cells releasing infectious virus following one round of T cell activation. This assay requires growing virus from individual latently infected cells and is costly and time consuming. Therefore, many studies have used DNA PCR to detect HIV-1 proviruses in infected cells or RT-PCR to detect the induction of viral RNA production from latently infected cells. However, two fundamental findings have altered how we view reservoir measurements. The first is that the vast majority of HIV-1 proviruses are defective due to the presence of large deletions and/or APOBEC-mediated hypermutation, as revealed by near-full genome proviral sequencing. These defective proviruses cannot contribute to viral rebound and should not be considered part of the latent reservoir. Most PCR assays fail to distinguish intact and defective proviruses. Therefore, they dramatically overestimate reservoir size and should not be used. The second important finding is that not all intact proviruses are induced by a single round of in vitro T cells activation. Therefore, induction assays that measure viral outgrowth or viral RNA production after a single round of T cell activation will underestimate reservoir size. A conceptually novel approach to measuring the latent reservoir is to count all of the intact proviruses regardless of their transcriptional status at any particular time. This can be done with the intact proviral DNA assay (IPDA). More recently identified conceptual issues in reservoir measurement include the problem of clonal expansion. The reservoir is dominated by large clones of infected cells that wax and wane over time, and current measurements do not capture dynamic changes in reservoir composition. In addition, the relationship between the viruses that cause rebound following interruption of antiretroviral therapy and the viruses detected in various reservoir assays needs to be clarified. This talk will discuss these issues and summarize the current state of reservoir measurements.

5 CHARTING GENOME-WIDE INTEGRATION

Mary F. Kearney, *National Cancer Institute, Frederick, MD, USA*

The HIV replication cycle includes integration of the reverse-transcribed viral genome into the host cell DNA where the provirus is retained for the life of the cell. Cellular machinery is used for proviral genetic expression, however, by means that are not fully understood, some HIV proviruses can maintain a latent, or transcriptionally-silent, state. It is thought that cells expressing HIV are susceptible to cell killing by cytopathic effects or immune responses. It stands

to reason, therefore, that long-lived latently-infected cells may accumulate over the course of HIV infection and persist after ART is initiated. Indeed, many studies have demonstrated the persistence of latently-infected cells during ART and, it is believed that such cells carrying replication-competent proviruses, when activated, are the source of viral rebound when ART is interrupted. It was recently discovered that HIV infected T-cells can persist in vivo through cellular proliferation, which occurs both prior to and during ART. Several cases, thus far, have described highly expanded infected CD4+ T cell clones that were shown to be the source of persistent infectious viremia during ART. This talk will summarize emerging data from studies investigating HIV infected CD4+ T cell clones including their sites of HIV integration in blood and tissues both prior to and during ART, the fraction of HIV expressing cells within cell clones, including those carrying replication-competent proviruses, and explore new technologies for investigating HIV integration landscape and full-length proviral structures. Understanding the integration site landscape in cell clones that persist during ART will lead to a better understanding of the HIV reservoir, the nature of latency, and the sources of rebound viremia when ART is interrupted.

6 SINGLE-CELL EPIGENETICS: COLORING IMMUNE CELLS WITH A RICH PALETTE OF HISTONE MARKS

Alex J. Kuo, *Stanford University, Stanford, CA, USA*

Chromatin-based epigenetic mechanisms govern diverse cellular and organismal phenotypes without DNA base alterations. Post-translational modifications of histone proteins, often referred to as histone marks, directly modulate chromatin dynamics and genome organization, adding additional complexity and plasticity to the relatively static genetic code. The harmonious orchestration of chromatin regulators is essential for hematopoiesis and immune system development, effective immune responses against foreign substances and pathogens, and immune tolerance to prevent damage to host tissues. Previously, we have leveraged highly multiplexed single-cell mass cytometry to characterize global histone modification profiles of various immune cells in the human immune system. This powerful analytic platform, which we term "Epigenetic landscape profiling using cytometry by Time-Of-Flight (EpiTOF)", facilitates the discovery of histone marks preferentially enriched in selected immune cells. We identify immune cell subtype- and hematopoietic lineage-specific epigenetic patterns, which predict immune cell identity. Differential analysis between younger and older adults reveals increased epigenetic variation between individuals, and elevated cell-to-cell epigenetic variability between single cells with age. Analysis of a twin cohort further shows that these aging-related epigenetic alterations are driven predominantly by non-heritable influences. Recently, we have demonstrated how EpiTOF can be integrated with genomic methods to investigate chromatin dynamics (i.e. ChIP-seq, ATAC-seq), and combined with transcriptomic and functional analyses to gain a comprehensive understanding of how the immune system is regulated by chromatin-based mechanisms. Using this "systems epigenetics" approach, we have extensively characterized the biological significance of a histone mark involving histone H3 proteolytic cleavage in monocyte-to-macrophage differentiation. Our findings have marked implications for cellular fate determination, trained immunity, and human diseases with prominent monocyte and/or macrophage involvements. Together, EpiTOF provides a unique opportunity to interrogate epigenetic regulation of the immune system. We propose that a systems epigenetics approach will i) reveal how acute and chronic viral infection alters the host chromatin landscape; ii) uncover chromatin-based mechanisms by which host immune cells develop an effective defense against viruses, and iii) provide insights into the variability of anti-viral response between single cells and between individuals.

7 PUTTING ANALYSIS INTO ANALYTICAL TREATMENT INTERRUPTIONS

Lu (Summer) Zheng, *Harvard T.H. Chan School of Public Health, Boston, MA, USA*

Analytic treatment interruption (ATI) is an essential component for HIV clinical trials assessing efficacy of interventions aimed at achieving HIV remission or virological control in the absence of antiretroviral or other treatments. With recent experiences of evaluating a variety of novel therapeutic interventions, including latency-reversing agents, therapeutic vaccines, and broadly neutralizing antibodies utilizing ATI, the design of treatment interruption studies has evolved towards shorter durations with more frequent monitoring and time to viral rebound as primary outcome measure. This talk will review and discuss the current practices of ATI studies on analytical approaches, design features related to the mechanism of action of the agents being evaluated, including the selection of study outcomes, ART re-initiation criteria, using historical controls vs. placebo-controlled design, as well as ethical considerations.

8 ADVANCING FROM PHASE II TO PHASE III: NAVIGATING THE LAND OF EXPECTATIONS

Patrick Phillips, *University of California San Francisco, San Francisco, CA, USA*

Mycobacteria tuberculosis kills more people every year than any other single pathogen, yet the first-line treatment regimen used globally has remained largely unchanged for 40 years. Shorter, safer, and more effective regimens are urgently needed to halt the epidemic. Clinical trials for new drugs to treat HIV depend on changes in HIV viral load as an established marker of infection and treatment response. In contrast, while several new TB drugs are in clinical development, the absence of a reliable surrogate endpoint hampers decisions about whether and when a new TB regimen is ready for confirmatory phase III evaluation. Further challenges include the necessity of determining the optimal combination and duration of therapy during phase II development alongside the limited funding for TB drug development and the allure of accelerated approval. In this workshop, I will talk about the burden of expectations and the latest developments in designing phase II trials to identify the best regimens to advance to phase III. I will talk about platform and other adaptive treatment-selection trial designs, the novel phase IIC design, designs to identify the optimal duration of therapy and the role of an internal control. I will also touch on challenges in TB prevention trials in the absence of a true marker of infection.

9 NONINFERIORITY COMPLEX

Jeffrey Murray, *FDA, Silver Spring, MD, USA*

In general, active-controlled noninferiority (NI) trials are considered when superiority trials, to an active control or placebo, are not possible due to ethical or other considerations. NI trials share some of the same biases as historically controlled trials because they rely on information external to the clinical trial. Food and Drug Administration (FDA) guidance states that NI designs are credible and appropriate only in situations in which the active control has shown a consistent effect (generally compared to placebo) in prior superiority trials conducted in a patient population similar to the population in the clinical investigation being planned. This is called the constancy assumption and allows for assay sensitivity in an NI trial. NI is met if the new intervention is 'not unacceptably worse' than the active control by a specified amount, the NI margin. The NI margin should be no larger than the effect the active control had in previous trials. Unless a placebo group is also included, NI trials depend on the assumption that the active control had its expected effect in the trial. From a regulatory perspective knowing the active control had its expected effect is necessary to ensure that a trial that concludes NI has identified a treatment that is superior to placebo. HIV treatment trials have successfully used NI trials for antiretroviral (ARV) drug development for many years; however, quantifying the treatment effect of each component of an ARV regimen has been challenging as drug regimens evolve, which can have consequences when designing an NI trial. HIV prevention research also illustrates the limitations of NI trial designs. Although collective data show that emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) can be highly efficacious at preventing HIV infection when taken as prescribed in uninfected individuals, the prophylactic effect has been highly variable over time and by population. Two trials that included FTC/TDF arms in cisgender women in Africa showed a lack of pre-exposure prophylaxis (PrEP) efficacy due to poor adherence. The lack of a consistent PrEP effect across trials in all populations invalidates a constancy assumption of FTC/TDF as an active control in an NI trial for some populations. Other types of trial designs using external controls might be more credible and appropriate than NI trials and are currently being explored.

10 INCLUSION OF DIVERSE POPULATIONS IN TRIALS

Mark Harrington, *Treatment Action Group, New York, NY, USA*

The unprecedented nature of AIDS as a syndrome and a pandemic created unprecedented demands on clinical trials investigators and networks to creatively and meaningfully address the syndromic nature of AIDS, the complex etiology and pathogenesis of HIV infection, its associated opportunistic infections, coinfections, and malignant, end-organ, and neurologic sequelae, in diverse affected populations including men who have sex with men, drug users, sex workers, young people, infants, children, adolescents, pregnant women, and people grappling with multiple syndemics (opioids, viral hepatitis, sexually

transmitted infections), social and structural barriers to research, prevention, treatment, access, care, and support. Traditional models of infectious disease clinical research needed to be adapted to the complex disease settings and diverse populations which made studying HIV and its complications more challenging than studies of a single drug for a single infectious agent. In this talk I will review 1) contributions made by activists, people living with HIV, and their communities to restructure and reform clinical trial designs to make them more relevant, ethical and efficient in the early days of clinical HIV research, including by expanding eligible trial populations and changing trial designs to make them more flexible, inclusive, and adapted to the real needs of people living with HIV; 2) the impact of broadened inclusion criteria and community priorities on HIV clinical research in the discovery of highly effective combination therapy (cART), pre-exposure prophylaxis (PrEP), and defining the optimal time to begin cART in all people living with HIV; and 3) current challenges and opportunities facing trial designers and networks in selected key high priority populations including those co-infected with HIV and Mycobacterium tuberculosis and those at risk for those infections in current and upcoming multi-modality prevention and treatment trials in selected diverse populations. I will close with some observations about the impact of diverse community engagement and participation in all aspects of the clinical trial process.

11 WHEN AT THIRD YOU DON'T SUCCEED

David L. Wyles, *Denver Health and Hospital Authority, Denver, CO, USA*

Current HCV direct acting antiviral (DAA) regimens are highly efficacious; including in populations previously recognized to have poor responses to interferon-based therapies (e.g. HIV co-infection, cirrhosis etc.). However, as DAAs are used in a greater number of patients in clinical practice, scenarios which have not been adequately addressed in clinical trials, or are impractical to study, will invariably arise. The approach to management of HCV treatment interruptions of varying durations at different times during therapy and re-treatment for multiple DAA regimens failures are examples of such scenarios. In this interactive session, cases will be used to highlight clinical conundrums focusing on:

- Determination or HCV relapse versus reinfection
- Multiple DAA regimens failure retreatment
- Approach to treatment interruptions during DAA therapy

While FDA approved options for retreatment exist for initial DAA regimen failure, robust data are lacking for patients failing multiple DAA regimens and retreatment approaches are not standardized. Inferences from studies in other HCV scenarios can provide insight into reasonable re-treatment approaches which generally rely on extension of therapy with addition of other drug classes and ribavirin when possible. In situations where no data exists- such as evidence based approaches for dealing with treatment interruptions, expert opinion and audience input will be used to offer management options.

12 "A" CASE TO REMEMBER: HEPATITIS A - MANAGING AN OLD VIRUS IN NEW POPULATIONS AT RISK

Darcy Wooten, *University of California San Diego, San Diego, CA, USA*

This session will use a case-based approach with audience response questions to review important updates in epidemiological risk factors for hepatitis A virus (HAV) infection, unusual presentations and complications that occur with HAV, and strategies for prevention.

13 Hepatocellular Carcinoma

Susanna Naggie, *Duke University, Durham, NC, USA*

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death globally. Viral hepatitis, specifically hepatitis B and hepatitis C infections are a major cause of HCC. Antiviral therapies for both HBV and HCV infection can decrease the risk of HCC. This presentation will focus on the contribution of HCC to global liver-related mortality and the impact of antiviral therapies on the incidence of HCC. This presentation will discuss the emerging data on the impact of direct-acting antivirals (DAA) on HCC incidence and recurrence and on the role of DAA therapies in patients diagnosed with HCC. In particular, the presentation will discuss in detail (1) the evidence supporting the safety of DAA therapies in patients with cirrhosis as it relates to risk of HCC development, (2) the optimal timing for initiating DAA therapy in patients who have been diagnosed with HCC and will discuss the impact, if any, of HCC diagnosis on response to DAA therapy, and (3) the impact of SVR on HCC incidence. Lastly, the presentation will discuss monitoring for HCC after SVR in patients with HCC and will highlight emerging non-invasive biomarkers that may be utilized after DAA HCV cure to improve risk stratification. When possible the presentation will discuss differences in HCC presentation and outcome in people with HIV and viral hepatitis.

14 NONALCOHOLIC STEATOHEPATITIS

Kathleen E. Corey, *Massachusetts General Hospital, Boston, MA, USA*

Non-alcoholic fatty liver disease (NAFLD) impacts affecting 25% of adults worldwide. NAFLD is a spectrum of pathology including steatosis and non-alcoholic steatohepatitis (NASH), the progressive form of NASH which can lead to fibrosis development, cirrhosis, end-stage liver disease, and hepatocellular carcinoma. NASH cirrhosis is the second leading indication for liver transplantation in the United States. In addition, NAFLD is strongly associated with the metabolic syndrome and obesity and is an independent risk factor for cardiovascular disease (CVD) and CVD-related death. In persons with HIV (PWH) liver disease is a significant cause of mortality. With the high prevalence of diabetes and metabolic disease in PLWH, NAFLD and NASH are being increasingly diagnosed. This talk will present strategies for the risk factors for and diagnosis and management of NAFLD in PWH.

15 THE ANCIENT AND MODERN ORIGINS OF HIV

Michael Emerman, *Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

How did HIV-1 become a human pathogen? In this talk, I will trace the origins of HIV-1 through the cross-species transmissions and viral adaptations that preceded its emergence in humans. The immediate precursor of HIV-1 is a virus that infects chimpanzees, Simian Immunodeficiency Virus of Chimpanzees (SIVcpz). SIVcpz is itself derived from other SIV lineages that infect old world monkeys. Cross-species transmission events require mutations to the viral genome that allow adaption to replicate in a new host. Much of this adaptation involves gaining the ability to counteract or evade a repertoire of antiviral genes, called restriction factors. The selective pressure between host restriction factors and the viral proteins that antagonize these factors sets up an "arms-race" that can be read out in the rapid evolution of the two proteins. The example of such restriction factors and viral antagonists that I will describe in the most detail is that of the primate APOBEC3 proteins that hypermutate viral genomes and the lentiviral Vif proteins that antagonize APOBEC3 activity. Study of the functional and evolutionary relationships between APOBEC3 proteins in primates and Vif proteins in primate lentiviruses allow us to make inferences about how long lentiviruses have been present in primates and about the steps that occurred for a lentivirus in monkeys to adapt to replicate first in chimpanzees, and then in humans. This talk will also highlight the role that basic science can play in ending the current HIV-1 pandemic.

16 TRANSLATING HIV SCIENCE INTO POPULATION IMPACT: A REALITY CHECK FROM THE FRONTLINE

Alex G. Coutinho, *Partners in Health, Kigali, Rwanda*

Over the past 20 years, tremendous strides have been achieved in the response to HIV/AIDS, especially in the incredible scale-up of life-saving ART to over 25 million people globally, most of them in Africa. This heroic achievement has resulted in an estimated 56% reduction in mortality since 2004 and as a consequence led to an increasing life expectancy and a marked drop in HIV/AIDS orphans – all of which are significant population impacts. However, the expected reductions in new infections have only been achieved modestly with an estimated reduction of HIV incidence of 16% in the 10 years since 2010. This is in part due to the challenge of translating scientifically proven HIV prevention interventions like ART, PMTCT, and VMMC and PreP into an environment that has many obstacles and challenges that include funding constraints, struggling health systems, disempowered communities and structural barriers. In particular, HIV prevention faces the challenge of promoting approaches like condoms that often face opposition from some politicians, cultural leaders, and religious leaders. Other approaches like VMMC and PreP face both opposition and skepticism, on the grounds that there are fears that individuals using these partially effective approaches will exhibit a rebound increase in risky sexual behaviors that will lead to new HIV infections. In addition, many of the target populations that are at greatest risk for HIV infection are also the groups that are the hardest to reach because they are considered illegal, are harassed and discriminated and often live and operate underground to avoid scrutiny. However, there are several excellent examples of effective scale-up of scientifically proven interventions and population impact, as well as a few examples of large scale combination HIV treatment/prevention interventions

that have reduced HIV incidence at a population level. These examples provide hope and a template to use when planning to scale up new technologies like PreP, as well as scaling up the use of older technologies like condoms. However for this to be successful at the frontline it will require scientists and politicians and communities and frontline implementers to sit down together, listen to each other, understand the science AND the realities of people's lives and the systems that support them, and come up with scientifically sound and pragmatic approaches to scale up services, impact populations and measure progress. The history of HIV has many lessons for us as we look into the future. Science, even brilliant science, will not end the HIV epidemic without collaboration and synergy with a wide range of other actors, strategies and full involvement of infected and affected communities.

17 HIV CURE FROM BENCH TO BEDSIDE

Sharon R. Lewin, *University of Melbourne, Melbourne, Australia*

Despite the great success of antiviral therapy (ART), treatment is life long for the majority of people living with HIV (PLWH). Antiviral treatment is simple and relatively cheap and close to 60% of PLWH have access to treatment. However, ART is still not available or secure for many, drug resistance is common globally and there are emerging toxicities from some of the most potent antivirals. Modelling studies of the cost and impact of a cure have identified that the need for frequent follow up and viral load testing after cessation of ART, unpredictable viral rebound and lack of protection from re-infection will all reduce the impact of a cure at a population level. Therefore there is now an increasing focus in the field to achieve a true cure and not HIV remission. Understanding where and how virus persists is key to the development of novel interventions to achieve a cure. Recent work has identified the significant contribution of proliferation of infected cells to HIV persistence on ART. Understanding the drivers of proliferation and clonal expansion remains a key unanswered question. In addition, multiple factors including the site of integration can influence the transcriptional activity of a virus and a deeper state of latency may reduce the chance of viral rebound off ART. Finally, the majority of viruses that persist on ART are defective and unable to replicate. A cure may therefore occur with loss of intact virus but persistence of only defective forms. New high throughput assays can now quantify intact and defective viruses more accurately and positive emission tomography and imaging can potentially identify tissue reservoirs of virus persistence. Multiple strategies to achieve a cure are being evaluated in both animal models and human clinical trials including combination immunotherapy to reduce the viral burden and enhance immune clearance. Results from recent clinical trials of newer latency reversing agents, immune checkpoint blockade and other immune adjuvants, broadly neutralising antibodies and gene therapy will be discussed. It is likely that in the next few years long acting and implantable antiretrovirals will be available and these newer modalities may address many of the current challenges of ART. Therefore, ongoing consultation is needed with PLWH and all other stakeholders to develop an acceptable target product profile for a cure that will have the greatest personal and population impact and can be implemented at scale.

18 UNIVERSAL TEST AND TREAT (UTT): LESSONS FROM THE PAST AND FOR THE FUTURE

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This presentation discusses the four recently completed community randomized trials of "Universal Test and Treat" (UTT) in East and southern Africa and their implications. Three themes developed in parallel and led to these ambitious implementation studies: recognition of the centrality of viral load for HIV pathogenesis and HIV transmission; studies showing >90% effectiveness of "treatment for prevention"; and evolution of antiretroviral treatment guidelines that since 2015 recommend immediate treatment of all persons living with HIV. Mathematical modeling in 2008 suggested UTT, with repeated and regular HIV testing, could eliminate HIV in an epidemic of South African severity (Granich et al, Lancet, 2009). Political advocacy highlighted the concept of "Ending AIDS" while scientific debate culminated in four community randomized trials aiming to assess UTT with HIV incidence as the primary outcome in Botswana (BCPP); Kenya and Uganda (SEARCH); South Africa (TASP); and South Africa and Zambia (PopART), from 2012-2018. Primary results of the four trials were published in Lancet HIV (TASP, 2018) and NEJM (2019) and additional analyses, including on cost-effectiveness, are underway. All four trials achieved >90% knowledge of HIV serostatus but TASP yielded low linkage to treatment. The other three trials met the UNAIDS 90:90:90 targets, achieving 74-88% population-level viral suppression. Treatment guidelines changed over the studies' course, resulting in some erosion of differences between intervention and control communities. BCCP and one of PopART's two intervention arms showed 30% reduction in HIV incidence compared to control communities, while no significant differences were found in the other studies. Despite the successful achievement of 90:90:90 targets, HIV incidence in intervention communities (6-22.3/1000/year) remained well above an arbitrary definition of HIV elimination of <1/1000/year. Knowledge of HIV serostatus and early treatment are essential for individual and the public health, but UTT alone will not lead to HIV elimination. Priorities include expansion in scale and scope of HIV testing to reduce the diagnostic and treatment gap in generalized epidemic settings, addressing needs of key and underserved populations (including youth and men), and scale-up of highly effective interventions such as voluntary medical male circumcision and PrEP. Greater focus on measuring HIV incidence and mortality is required to better understand epidemic trends in the face of combinations of preventive interventions.

19 MECHANISMS OF PSGL-1 AND CD43 RESTRICTION OF HIV INFECTION OF CD4 T CELLS

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Background: PSGL-1 (P-selectin glycoprotein ligand-1) and CD43 are surface glycoproteins that are expressed on blood CD4 T cells to bind to selectins for T cell tethering, rolling, and migration into inflamed tissues. PSGL-1 is primarily expressed on the surface of lymphoid and myeloid cells and is up-regulated during inflammation to mediate leukocyte tethering and rolling on the surface of the endothelium for migration into inflamed tissues. Recently, PSGL-1 has also been identified as an INF-γ-regulated anti-HIV-1 restriction factor that inactivates virion infectivity. However, the mechanisms of PSGL-1-mediated anti-HIV activity remain to be elucidated.

Methods: We studied PSGL-1 and CD43 restriction of HIV-1 virion infectivity by co-expression of PSGL-1 or CD43 DNA with HIV-1 DNA in virion producer cells, and then quantified virion infectivity in an HIV Rev-dependent GFP indicator cell. We also studied virion incorporation of PSGL-1 by gradient ultracentrifugation and western blot detection of PSGL-1 in virion particels. In addition, we examined virion proteins of PSGL-1 imprinted particles. We also performed mapping studies to identify functional domains of PSGL-1 necessary for blocking virion infectivity. Furthermore, we performed HIV-1 entry and attachment assays to study the interaction of PSGL-1 imprinted virion particles with target cells.

Results: We found that the expression of PSGL-1 in virus-producing cells inhibits virion infectivity by inhibiting virion attachment to target cells. Mapping studies show that the extracellular, N-terminal domain of PSGL-1 is necessary for its anti-HIV-1 activity, and the PSGL-1 cytoplasmic tail contributes to inhibition. In addition, we demonstrate that the PSGL-1 related monomeric E-selectin binding glycoprotein CD43 also effectively blocks HIV-1 infectivity. HIV-1 infection, or expression of either Vpu or Nef, downregulates PSGL-1 from the cell surface; expression of Vpu appears to be primarily responsible for enabling the virus to partially escape PSGL-1-mediated restriction. Finally, we found that PSGL-1 inhibits the infectivity of other viruses such as murine leukemia virus and influenza A virus.

Conclusion: These findings demonstrate that PSGL-1 is a broad-spectrum antiviral host factor with a novel mechanism of action. Further elucidation of PSGL-1 and CD43 interaction with HIV-1 and other viruses may offer new therapeutic strategies for targeting viral infections.

20 STRUCTURAL ANALYSES OF A BOUND ANTI-CD4 ADNECTIN INHIBITOR OF HIV-1

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Background: GSK3732394 is a multi-specific biologic inhibitor of HIV entry currently under clinical evaluation. A key component of this molecule is an

Adnectin that binds to CD4 and inhibits downstream actions of gp160. Studies were performed to help elucidate the binding site of the Adnectin on CD4 and understand the mechanism of inhibition.
Methods:
Hydrogen-deuterium exchange mass spectrometry (HDX) was used to examine comparative deuteration rates of amide backbone protons of CD4, either in the absence or presence of saturating amounts of Adnectin. In addition, crystal structures of CD4 bound to both the Adnectin and a Fab subunit of ibalizumab were solved at a 3.7Å resolution. Cryo-EM studies of Adnectin bound to soluble CD4 were also generated. Finally, mutagenic analyses on CD4 were performed to confirm and extend these findings.
Results: Using HDX, CD4 peptides at the N-terminus of D2 and in D3 showed differential rates of deuteration (both enhanced and slowed) in the presence of the Adnectin that mapped predominantly to the D2-D3 interface. The structure of the ibalizumab Fab/CD4 D1-D4/Adnectin complex revealed an extensive interface between the Adnectin and residues on CD4 domains D2-D4 that stabilize a novel T-shaped CD4 conformation. A cryo-EM map of the gp140/CD4/combinectin complex clearly shows the bent conformation for CD4 while bound to gp140. Mutagenic analyses on CD4 confirmed that amino acid F202 forms a key interaction with the Adnectin. In addition, amino acid L151 was shown to be a critical determinant of the specificity for binding to human CD4 protein over related primate CD4 molecules. Mutation of L151 to R (the residue present in cynomolgus monkey CD4) abrogated Adnectin binding to human CD4, while the reverse mutation (R151L) restored binding to cynomolgus monkey CD4.
Conclusion: The significant conformational change of CD4 upon Adnectin binding brings the D1 domain of CD4 in proximity to the host cell membrane surface and provides a potential explanation for the ability of the CD4-bound Adnectin to inhibit HIV-1 infection. In addition, mutations of D2-D3-interface residues, specifically F202 and L151, dramatically impacted Adnectin binding to human and primate CD4, providing a rationale for the observed species specificity of the Adnectin.

21LB SERINC3/5 PERTURB HIV MEMBRANE FUSION POST-HEMIFUSION AT FUSION-PORE DILATION STEPS

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Background: Serinc3 and Serinc5 are recently described host restriction factors that in the absence of Nef, can block HIV infection by incorporating into budding viral particles and decreasing their ability to infect subsequent cells. Serincs are thought to block the very earliest stages of infection, membrane fusion and cell entry, by an incompletely understood mechanism.
Methods: We used giant plasma membrane vesicles (blebs) as model target membranes to study "wildtype" and Serinc-disrupted HIV membrane fusion at a single-particle level with cryoElectron Tomography and Total Internal Reflection Fluorescence (TIRF) microscopy.
Results: Using fluorescent reporters of membrane and content mixing, we observed that Serinc3 and Serinc5 do not cause a defect in mixing of the outer lipid leaflets (hemifusion), but a pronounced defect in fusion pore opening. Additionally, cryo-electron tomography of HIV pseudoviruses mixed with blebs showed rearrangements of viral and target membranes and proteins at multiple intermediates steps of HIV membrane fusion. We found that Serinc3 and Serinc5 increased the number of hemifusion and early fusion product events and that many of the fusion products are cinched between former virus and bleb.
Conclusion: These results suggest that Serinc3 and Serinc5 create bottlenecks in the process of membrane fusion; a first bottleneck after hemifusion and an additional bottleneck that prevents full fusion pore dilation such that the viral capsid cannot pass into the cytosol. Understanding how Serincs disrupt HIV membrane fusion will clarify the requirements for normal HIV membrane fusion and potentially identify new viral weaknesses that could become drug targets.

22 CRISPR-INDUCED MUTAGENESIS POINTS TOWARD A ROLE OF TRN-SR2 IN HIV NUCLEAR IMPORT

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Background: In order to infect non-dividing cells, HIV needs to cross the nuclear envelop. In 2010 we reported the identification of the importin TRN-SR2 (TNPO3) as the determining host factor for nuclear import. While the importance of TRN-SR2 for HIV nuclear import is generally accepted, the detailed mechanism and role of TRN-SR2 remains under debate. According to one model the direct interaction of TRN-SR2 with HIV integrase drives nuclear import of the pre-integration complex (PIC), alternatively TRN-SR2 may play an indirect role linked to uncoating of the PIC and the protein CPSF6.
Methods: We have designed CRISPR-Cas9 guide RNAs targeting exon 2 and 8 of TNPO3 in HeLaP4 cells. After selection of clones with reduced TRN-SR2 expression on both mRNA (QPCR) and protein expression levels (western blotting), a detailed analysis of HIV replication and PIC nuclear import was performed.
Results: CRISPR-Cas9 induced DNA breaks in TNPO3 using guide 2 and 8 failed to generate complete knockout clones but instead allowed for selection of 2 HeLaP4 clones with a single allelic KO, resulting in 2-fold reduced TRN-SR2 levels (clone #20 and #25). Nevertheless, HIV single round and multiple round replication was severely hampered in clone #20 and #25. Interestingly genome sequencing of TNPO3 revealed that the remaining allele showed small in-frame deletions resulting in deletion of Aa (V103 and 373LHAL376). We then analyzed the PIC nuclear import in the respective cell lines by QPCR and fluorescent imaging of eGFP-IN labeled PICs. Both techniques evidenced a strong defect in nuclear import. Recombinant TRN-SR2 deletion mutants demonstrated an impairment of the molecular interaction with HIV-integrase.
Conclusion: CRISPR-Cas9 targeting two different exons of TNPO3 failed to generate KO cell lines indicating that a full KO of TRN-SR2 might be toxic for HeLaP4. Yet, CRISPR-Cas9 unexpectedly led to mutagenesis. The resulting clones were fully viable but failed to support HIV replication. The block of replication was pinpointed to nuclear import and the corresponding recombinant mutant TRN-SR2 was impaired for interaction with HIV-IN. The presented data support the notion that TRN-SR2 is a genuine co-factor of HIV replication and interacts differently with HIV-IN than with its cellular cargoes.

23 NUCLEAR UNCOATING OF HIV-1 OCCURS NEAR SITES OF INTEGRATION

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Background: A critical step in HIV-1 replication is the disassembly (uncoating) of the viral core. Remarkably, the timing and intracellular location of HIV-1 uncoating remain unknown. Studies of HIV-1 uncoating have been hampered by an inability to accurately quantify capsid protein (CA) loss from the viral complexes and by an inability to identify rare infectious viral complexes (~1/50) in infected cells.
Methods: We developed methods to label CA with GFP (GFP-CA) in infectious viral complexes and to identify transcriptionally-active proviruses in live-cell imaging assays. We analyzed the dynamics of viral complex association with nuclear envelope and nuclear uncoating, and identified rare viral complexes that integrate to form transcriptionally active proviruses.
Results: Using live-cell imaging, we observed >110 GFP-CA-labeled infectious viral complexes that integrated and expressed HIV-1 RNA and the gfp reporter gene. The infectious viral complexes maintained steady GFP-CA fluorescence signals for several hours after nuclear import followed by abrupt (<20 min) GFP-CA loss ~10.5 hours after infection, signifying nuclear uncoating. HIV-1 transcription sites appeared near the sites of nuclear uncoating, indicating that uncoating occurs at or very close to the site of integration. Similar GFP-CA fluorescence intensities of nuclear viral complexes and viral cores in vitro suggest that viral cores in the nucleus retain >90% of the CA and that nuclear uncoating is the major uncoating event. The nuclear GFP-CA-labeled viral complexes rapidly disassembled after treatment of the infected cells with capsid inhibitor PF74 indicating that the nuclear viral complexes retained CA hexamers. Time-of-addition assays with PF74, nevirapine, and raltegravir indicate that nuclear uncoating occurs ~3 hrs after the completion of reverse transcription and ~1 hr before integration. We probed the potential mechanism by which viral cores enter the nucleus and found that cleavage and polyadenylation specificity factor 6 (CPSF6), a host nuclear protein that binds to CA, influences the intracellular location of uncoating and facilitates the nuclear import of intact or nearly intact viral cores.
Conclusion: Intact or nearly intact viral cores of infectious viral complexes that retain >90% of their CA enter the nucleus and uncoat near their genomic integration sites just before integration.

24LB RECONSTITUTION OF HIV-1 CAPSID-DEPENDENT REPLICATION AND INTEGRATION IN VITRO

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Background: To initiate an infection, the HIV-1 genome must be reverse transcribed and integrated into the DNA of the host cell. Despite progress in characterizing and inhibiting these viral processes, detailed mechanistic and structural studies remain challenging because they are executed by individual preintegration complexes deep within cells.
Methods: To address these limitations, we have reconstituted the early stages of HIV-1 replication in a cell-free system. Starting with purified virions, membrane permeabilization, capsid stabilization, and dNTPs were used to release viral cores and initiate the process of reverse transcription. Cell-free extracts were used to facilitate efficient integration into a target plasmid. Quantitative PCR (qPCR) was used to monitor three different stages of reverse transcription (Strong Stop, First Strand Transfer, and Late RT). Integration was assayed using three different approaches: 1) a two-step PCR system designed to amplify HIV-1 integration sites coupled with qPCR, 2) deep sequencing of PCR-amplified integration sites, and 3) cloning and sequencing of target plasmids to test for concerted HIV-1 integration.
Results: HIV-1 core particles released from permeabilized virions supported highly efficient, capsid-dependent endogenous reverse transcription to produce ~0.8 double-stranded DNA genomes/core. Concerted integration of the transcribed viral genome into a target plasmid then proceeded in a cell extract-dependent reaction. Controls established that, as expected, reverse transcription and integration required active RT and IN enzymes. Efficient viral replication required a stable capsid as assayed by CA mutagenesis and small molecule CA inhibitors. Sequence analyses revealed integration site preferences, and demonstrated that concerted integration occurred with the expected 5 bp target site duplication.
Conclusion: Starting with purified HIV-1 virions, we have reconstituted the first half of the HIV-1 life cycle in a cell-free system. This system highlights the key role of the viral capsid and should facilitate dissection of the mechanisms and host factor contributions to HIV-1 replication.

25 STRUCTURAL BASIS OF SECOND-GENERATION HIV INTEGRASE INHIBITOR ACTION AND VIRUS ESCAPE

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Background: During integration, a multimer of integrase (IN) assembles on viral DNA ends, forming a highly stable nucleoprotein complex termed the intasome. The HIV IN strand transfer inhibitors (INSTIs) specifically target the IN active site engaged with the viral DNA end, in the context of the intasome. Previously, we adopted the intasome from the prototype foamy virus (PFV), which is amenable to X-ray crystallography, to study INSTI binding. However, scarce amino sequence identity with HIV-1 IN outside of the active site greatly limits the use of this highly tractable system in studies of drug resistance. For the same reason, the PFV structures are not ideal templates for optimization of the clinical INSTIs.
Methods: To derive a robust model suited to informing INSTI development, we characterized IN proteins from a wide range of simian immunodeficiency viruses (SIVs). We discovered that IN from SIVrcm, which shares a recent common ancestor and 75% amino acid IN sequence identity with HIV-1, readily forms functional nucleoprotein complexes with viral DNA in vitro. Moreover, virus resurrected from the available sequence information was highly susceptible to the first and second-generation INSTIs. We used single-particle cryo-electron microscopy to visualize at near atomic resolution the advanced clinical INSTIs dolutegravir and bictegravir bound to the SIVrcm intasome.
Results: We show that the expanded second-generation INSTI scaffolds span the active site, making critical stabilizing contacts with its boundary defined by the IN β4-α2 connector element. The Q148H/G140S mutations that pervade clinical INSTI failure perturb optimal magnesium ion coordination in the integrase active site. The expanded chemical scaffolds of the second-generation drugs mediate novel interactions with the protein backbone, which are critical for antagonising Q148H/G140S mutant virus.
Conclusion: Our results reveal that binding to magnesium ions underpins a fundamental weakness of the INSTI pharmacophore that is exploited by the virus and provide structural framework for the development of this important class of anti-HIV/AIDS therapeutics.

26 THE CHROMATIN LANDSCAPE AT THE HIV-1 INTEGRATION SITE DETERMINES VIRAL EXPRESSION

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Background: Since the HIV provirus persists lifelong in memory cells of the immune system but rebounds upon treatment interruption, the latent reservoir is the main target for HIV cure. One of the less studied determinants of latency is the impact of integration site selection on HIV expression. HIV integration is catalyzed by integrase that uses the host chromatin reader LEDGF/p75 to target integration to active genes. We previously showed that inhibition of the LEDGF/p75-IN interaction by LEDGINs retargets residual integration out of active genes. Moreover, these proviruses were more often in a latent state and refractory to reactivation. These results suggested a direct link between HIV-1 integration and transcription.
Methods: We now studied the underlying mechanism with two advanced technologies. (1) Barcoded HIV (B-HIVE) tags the HIV genome with a unique barcode that allows to determine insert-specific HIV-1 expression by simultaneously tracking the barcode in the DNA and RNA of infected cells. (2) Branched DNA (bDNA) imaging was used to visualize the effect of LEDGINs at the single cell level. bDNA is a signal amplification method for Fluorescent In Situ Hybridization (FISH) that enables simultaneous detection of viral DNA and mRNA.
Results: B-HIVE confirmed that LEDGIN treatment retargets integration out of gene-dense regions. LEDGINs increased the distance to H3K36me3 (recognized by LEDGF/p75). Viral RNA expression per DNA barcode was reduced while the proportion of silent proviruses increased. Yet, at high concentrations of LEDGINs some rare residual proviruses with high RNA expression were detected. The silent proviruses after LEDGIN treatment were located further away from epigenetic marks associated with active transcription. Interestingly, while the distance to H3K36me3 changed after treatment, proximity to (super)enhancers stimulated transcription independently of LEDGF/p75. bDNA imaging of SupT1 cells infected with HIV-1 in the presence of LEDGINs showed a dose-dependent reduction in both DNA spots and RNA expression. The DNA spots obtained after treatment with LEDGINs were located at increased distance from the nuclear rim. Finally, LEDGINs hampered reactivation upon stimulation with TNFα 10 days post infection.
Conclusion: Our studies reveal how the direct link between integration site selection and transcriptional status of the provirus is mediated by the epigenetic landscape surrounding the integration site. The results support block-and-lock strategies to cure HIV infection.

27 SINGLE-CELL GENOMIC ANALYSIS OF BLOOD AND CSF T CELLS IN HIV+ AND HIV− ADULTS

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Background: The biology driving central nervous system T cell dysregulation in people with HIV (PWH) during antiretroviral therapy (ART) remain incompletely understood. Single cell RNAseq allows high resolution characterization of immune cells, including T cells contained in cerebrospinal fluid (CSF) and blood. We applied distinct approaches to the computational analysis of scRNAseq of T cells to identify genes distinguishing treated-HIV from the HIV-negative state.
Methods: scRNA seq was performed on CSF cells and peripheral blood mononuclear cells (PBMC) from PWH on ART (plasma HIV RNA <20 cps/mL for > 1 yr, n=5) and HIV- individuals (n=4). Within each fluid, to compare T cell transcripts differentiating ART-suppressed HIV from the HIV- state we applied: 1. Standard differential expression, using the Seurat FindMarkers function, based on the Wilcoxon rank sum test; and 2. Feature selection, using logistic least absolute shrinkage (LASSO), a machine learning approach to identify genes whose variable expression is most predictive of disease state.

Results: Single cell transcriptomes were analyzed from 31,175 CSF cells and 35,694 PBMC. CSF cells were comprised of T cells (93%), B cells (0.5%), Monocytes (3%), Dendritic cells (1.9%), and NK cells (1.7%); CSF cell subset frequencies did not differ between PWH and HIV-.
Differential expression analysis identified 64 and 128 genes that were differentially expressed between PWH and HIV-, in CSF and blood T cells, respectively, with 33 genes that were differentially expressed in both blood and CSF T cells based on HIV infection (log fold change >0.1; FDR< 0.01). We next trained two logistic LASSO PBMC-based and CSF-based models to differentiate between T-cells from a HIV- or a PWH and tested them in a leave-one-out cross validation (LOOCV) approach. Expression of ~200 genes differentiated a T cell from a PWH versus a HIV- at accuracy of >0.8. 62 and 54 genes were stably selected in all LOOCV iterations for the CSF and PBMC models, respectively. Out of the 62 genes selected in the CSF model, 41 were common to the PBMC model. Ingenuity pathway analysis revealed a significant association between HIV status and signaling downstream of the pro-inflammatory cytokine IL-15 in both blood and CSF.
Conclusion: By using a multimodal analysis including machine-learning of single cell gene expression data in T cells, we identified potential regulators of immune dysfunction during ART-suppressed HIV infection, including IL-15 pathways.

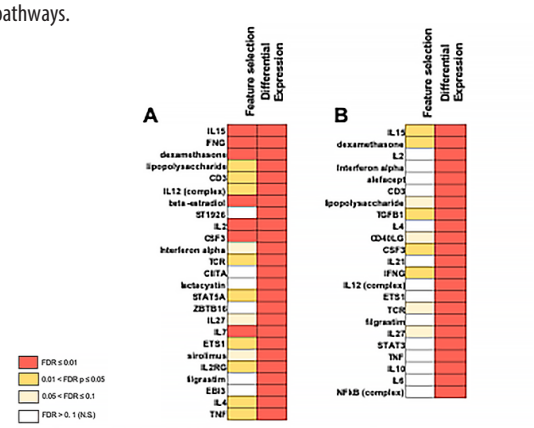


Figure 1. Top upstream transcriptional regulators that differentiate CSF (panel A) and Blood (panel B) immune cells from HIV versus uninfected individuals, using two computational approaches: Feature Selection and Differential Expression. FDR = False Discovery Rate. *N.S.* = not significant.

28 GREATER BURDEN OF INTRACRANIAL ARTERIAL-WALL ENHANCEMENT IN PERSONS LIVING WITH HIV

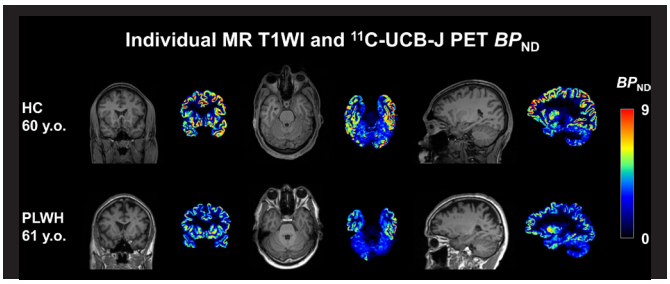
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Background: Persons living with HIV (PWH) are at higher risk of stroke compared with age-matched persons without HIV. However, the mechanisms underlying increased cerebrovascular risk in PWH are unclear. In particular, the contribution of intracranial arterial disease to HIV-associated stroke remains poorly defined. We compared intracranial vessel wall magnetic resonance imaging (VW-MRI), which can demonstrate atherosclerotic disease even when conventional angiography is normal, in treated, virologically suppressed PWH and persons without HIV.
Methods: All participants were >40 years of age with a history of cardiovascular (CV) disease or at least one CV risk factor. PWH were on antiretroviral therapy with undetectable plasma viral load. Demographics-matched persons without HIV were friends and family of PWH or recruited through flyers. Participants underwent a time-of-flight (TOF) MR angiogram (MRA) and 3D high resolution variable flip angle black blood post-contrast VW-MRI (CUBE) on a GE 3T Discovery scanner. The primary outcome was the number of visualized arterial segments with abnormal wall enhancement. Poisson models were used to compare the mean number of enhancing segments by HIV status.
Results: Of 31 participants (mean age 58 years, 97% men), 19 were PWH (median CD4 count 492 cells/mm$_3$). There were no significant differences in age, sex, race, or CV risk factors between PWH and persons without HIV. A greater proportion of PWH were on a statin (84% versus 42%, p=0.021). The mean number of enhancing arterial segments for PWH was 1.8 (SD 1.3) versus 0.4 (SD 0.9) for persons without HIV (p=0.003). The majority (80%) of enhancement was eccentric, which did not differ by HIV status. Over half (53%) of PWH with abnormal wall enhancement did not have associated luminal narrowing on TOF MRA. The greater mean number of enhancing arterial segments in PWH remained statistically significant after adjusting for demographics and CV risk factors. In a model adjusted for age, sex, race, and statin use, PWH had an average 4.58 times as many enhancing arterial segments as persons without HIV (95% CI 1.51-13.83, p=0.007).
Conclusion: PWH had a greater burden of primarily eccentric arterial wall enhancement compared with persons without HIV. Furthermore, luminal imaging with TOF MRA underestimated the burden of arterial disease in more than half of PWH. Future studies should investigate the association of arterial wall enhancement with indices of immune activation and radiologic markers of cerebrovascular disease.

29 PET IMAGING OF SYNAPTIC DENSITY IN HIV: PRELIMINARY FINDINGS FROM A PILOT STUDY

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Background: Synaptic injury, which is potentially reversible, is a pathological hallmark of HIV associated neurocognitive disorder (HAND) in people living with HIV (PLWH) on antiretroviral therapy (ART), but it has only been assessed in post-mortem studies in humans. Here we report initial results from a pilot positron emission tomography (PET) study employing the novel ligand 11C-UCB-J for synaptic vesicle protein 2A (SV2A) to measure synaptic density in virologically suppressed PLWH and healthy controls (HC).
Methods: Six male PLWH and seven age-matched HC underwent 3T magnetic resonance imaging (MRI) and high-resolution PET scanning with 11C-UCB-J combined with arterial blood sampling. Distribution volume (VT, mL/cm$_3$) and binding potential (BPND), a measure of SV2A binding, were assessed in 28 regions of interest (ROIs) using the centrum semiovale as a reference region. Partial volume correction using Freesurfer was performed to correct for atrophy. Differences in VT and BPND between the groups were analyzed using a Student's t-test.
Results: There were no significant differences in age (HC: mean [SD], 59 [8]; PLWH: 61 [5]; p=0.53), race, or body mass index between the groups. PLWH were well-suppressed on ART (mean [SD], CD4 T cells 703 [194] cells/mL, duration of ART 21 [8] years), and all participants had CSF and plasma HIV RNA <20 copies/mL. VT values of the reference region were similar in both groups (HC: 4.08 [0.70]; PLWH: 4.37 [1.01]; p=0.57). PLWH had significantly lower SV2A specific binding (BPND) in eight cortical ROIs compared with HC (p<0.05), illustrated by representative cases (Figure 1). Four of these ROIs, including the precuneus (HC: 6.13 [0.87]; PLWH: 4.89 [0.85]; p=0.03) and superior parietal lobule (HC: 6.04 [0.65]; PLWH: 4.71 [1.07]; p=0.03), are within the parietal lobe, which as a whole trended toward significance (HC: 6.19 [0.88]; PLWH: 5.07 [1.04]; p=0.07). There were no significant differences in VT, though lower values in PLWH were noted in the eight cortical ROIs with significantly decreased BPND.
Conclusion: This preliminary analysis of an ongoing pilot study demonstrates the potential utility of SV2A PET imaging in identifying regions of reduced synaptic density in suppressed PLWH. A larger sample is needed to draw conclusions on which ROIs are most affected, and to explore associations between synaptic density and lab and clinical parameters including neuropsychological performance. SV2A imaging may be a promising outcome measure for interventional trials of HAND.



30 HIV-INFECTED MACROPHAGES EVADE NK CELL-MEDIATED KILLING WHILE DRIVING INFLAMMATION

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Background: The primary targets for HIV infection are CD4+ T cells, however macrophages also become infected and persist despite antiretroviral therapy, suggesting evasion of immune responses. Our previous work shows that while HIV-infected macrophages are recognized by cytolytic CD8+ T lymphocytes (CTL), killing is inefficient due to resistance to CTL-derived granzymes. This poor killing delays CTL detachment from its target, causing hypersecretion of CTL-derived cytokines that propagate inflammation, emphasizing the need for rapid killing and release of effector-target contacts to limit inflammation. Thus, we hypothesized that cells with greater cytolytic potential compared to CTL, such as NK cells, would be able to rapidly kill HIV-infected macrophages while limiting excessive inflammation.

Methods: To test this hypothesis, innate interactions between NK cells and autologous HIV-infected macrophages or CD4+ T cells were assessed via flow cytometry-based recognition and killing assays. To characterize the potential for antibody-dependent cellular cytotoxicity (ADCC), HIV envelope expression on macrophages was characterized by flow cytometry, imaging flow cytometry, and confocal microscopy using HIV-specific antibodies, and HIV-specific CAR T cells were used to confirm envelope accessibility on target cells. Finally, ADCC responses against infected CD4+ T cells and macrophages were assessed via flow cytometry.

Results: Despite similar levels of total recognition of HIV-infected CD4+ T cells and macrophages (degranulation and TNF-α production), NK responses to macrophages were significantly skewed towards non-cytolytic, cytokine production ($p<0.0001$), which was associated with poor elimination ($p<0.0001$). HIV antibody-based detection confirmed that envelope was transiently expressed on the macrophage cell surface, and recognition of infected macrophages by HIV-specific CAR T cells was comparable to that of CD4+ T cells, suggesting that HIV envelope is equally accessible on both cell types. ADCC enhanced NK cell responses to both cell types, however, total responses to macrophages were significantly lower compared to that of CD4+ T cells ($p<0.001$ for 3BNC117 and $p<0.05$ for PGT121).

Conclusion: Together, these data suggest HIV-infected macrophages employ a unique mechanism to evade cytolytic recognition by NK cells while preserving pro-inflammatory cytokine responses, emphasizing the need to develop alternative strategies to eliminate infected macrophages.

31 HIV DNA DETECTED IN IMMUNE CELL SUBSETS IN CSF DURING ART

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Background: HIV-infected cells persist in the central nervous system (CNS) in at least half of people with HIV (PWH) on antiretroviral therapy (ART). We previously reported on a novel population of myeloid lineage microglia-like cells in cerebrospinal fluid (CSF) from PWH on ART; however the identity of CNS cells containing proviruses remains unknown.

Methods: Fresh CSF and blood were collected from PWH (median 20yrs on ART, range 4-24yrs). Single cell CITE-seq was performed to validate CD204 as a marker for CSF microglia-like cells. CSF cells and peripheral blood mononuclear cells (PBMCs) were separated using fluorescence activated cell sorting into three subsets based on expression of: CD3+CD4+, CD3+CD8+, and CD3-CD20-CD204+. HIV DNA levels were determined in each subset using a sensitive qPCR assay targeting HIV integrase (iCAD). HIV DNA measurements were normalized for cell equivalents determined by CCR5 qPCR.

Results: Six donors had plasma HIV RNA levels <20 copies/mL; one had 748 copies/mL. Two donors had HIV RNA detected in CSF despite plasma viral suppression, with 95 and 163 copies/mL HIV RNA detected in CSF. The median number of CSF cells obtained per donors was 35,327 (range 13,000-85,000) in 25mL of CSF. HIV DNA was detected in blood CD4+ T cells from 6/7 donors, and not detected in blood CD4+ T cells in one donor. In CSF, HIV DNA was detected in CD4+ T cells in 6/7 donors (of which 5 donors also had HIV DNA detected in blood CD4+ T cells). HIV DNA copies per 1 million cell equivalents was higher (median 7.1 fold, range 0.3-132) in CSF CD4+ T cells than in blood CD4+ T cells in 5/6 donors. No donor had HIV DNA detected in CSF CD8+ T cells.

We isolated genomic DNA from CD204+ CSF cells in three participants and observed that one participant had HIV DNA detected in CD204+ CSF cells. This donor had plasma HIV RNA 748 copies/mL and CSF HIV RNA 87 copies/mL. HIV DNA levels in this participant were 4368 copies per 1 million CD204+ CSF cells, 2769 copies per 1 million in CSF CD4+ T cells, and 401 copies per 1 million blood CD4+ T cells.

Conclusion: We detected HIV DNA in CD4+T and myeloid cells in CSF in a limited sample of PWH on ART. Normalized HIV DNA in CD4+ T cells from CSF was higher than in blood in most donors. Larger studies should assess whether the HIV DNA detected is in replication-competent proviruses, and whether other CNS immune cell types are HIV-infected.

32 EFFECTS OF HIV AND AGING ON RESTING-STATE NETWORKS

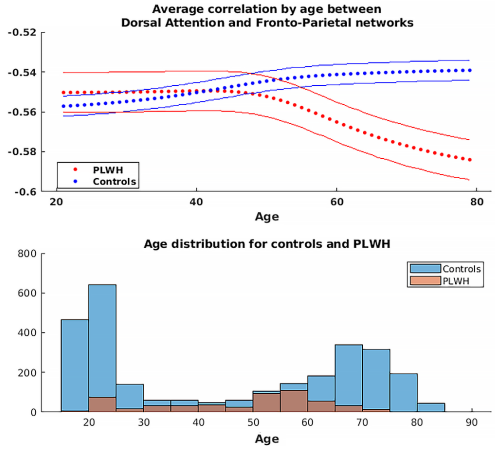
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Background: Despite the use of combination antiretroviral therapy, many HIV associated conditions, such as HIV associated neurocognitive disorders and frailty still exist in people living with HIV (PLWH). A potential biomarker reflective of these conditions is resting state functional connectivity (rsFC). Changes in rsFC strength have been hypothesized to reflect a compensatory reaction due to damage caused by persistent inflammation and chronic immune activation. Within a large cohort of PLWH and HIV- controls we identified networks most affected over the life span of HIV infection using machine learning methods.

Methods: A total of 538 rsFC scans from 318 PLWH (mean age 47.2y, 77% male, 31% Caucasian, mean duration of infection 12.8y +/-9.4, 84% viral load <200) collected from studies at Washington University School of Medicine (WUSM) and 2791 scans from 2133 HIV- controls (mean age 44.4y, 42% male, 69% Caucasian) collected from studies at WUSM and other sources were analyzed. Ages ranged from 20 to 70 years old (figure 1b). Ten rsFC networks were evaluated, and preprocessing was performed using in house methods. Correlation matrices were generated for all participants, and an average correlation matrix was computed for each year of age for both groups. A Relief feature selection algorithm was used to identify the strongest predictive networks of HIV status. We then evaluated which networks showed significantly different trajectories with respect to aging among PLWH and controls.

Results: The Relief algorithm identified the strongest predictors of HIV status as multiple connections between the somatomotor, cingulo-opercular, and dorsal attention networks. The strongest difference in average connectivity strength as a function of aging between PLWH and controls were between the dorsal attention and both the fronto-parietal (figure 1a) and cingulo-opercular networks ($R2 = -.82, -.52$, $P<.01$), as well as the ventral attention and somatomotor networks ($R2 = -.38$, $P<.01$).

Conclusion: Our data suggest changes in rsFC occurs as a result of HIV infection, and are primarily associated with motor, control, and attention. Further, changes exhibit specific temporal patterns between networks which is independent of reorganization that occurs due to normal aging, and these changes begin around midlife. These results will allow for a more tailored treatment approach for PLWH, and should be considered when conducting clinical trials.



33 MYELIN CONTENT IS ELEVATED IN VIROLOGICALLY UNSUPPRESSED PEOPLE LIVING WITH HIV

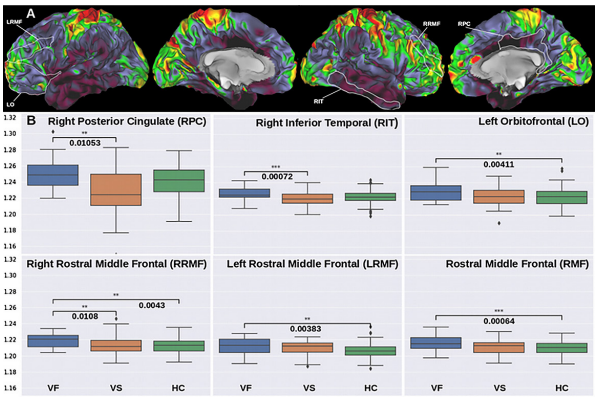
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Background: HIV adversely affects myelin and leads to white matter pallor. With a recently developed method, myelin content can be assessed by T1-weighted (T1w) and T2-weighted (T2w) MRI. The overall pattern in the myelin maps is affected by disease with increases in the T1w/T2w ratio seen in neurodegenerative conditions. We hypothesized that older (> 50 years old) persons living with HIV (PLWH) who had virological failure (VF) would have an increase in the T1w/T2w ratio compared to individuals with virological suppression (VS) or healthy controls (HC).

Methods: Structural T1w and T2w MRI scans were obtained from 424 participants including 206 HC, 140 PLWH with VS, and 78 PLWH with VF. T1w images were processed with FreeSurfer 6.0 to generate brain parcellations . Standard pipelines established for the Human Connectome Project (HCP) were used to derive myelin maps for each individual. Their myelin was estimated from the T1w to T2w ratio and assigned to the cortical surface of the brain. Individual brains were then registered to a common surface atlas. Average meylin for each FreeSurfer parcel was computed. Omnibus ANCOVA analysis with age as a covariate was used to identify the regions of interest (ROI) where myelin among VF, VS and HC groups was significantly different. Only ROI which survived corrected statistical threshold of 0.05 corrected for multiple comparisons, were then further assessed with pair-wise t-tests between each group. Spearman correlations were performed between viral load and myelin content in the VF group.

Results: Exemplar myelin content maps from a characteristic PLWH are presented in Figure 1A. Regions of interest (ROI) from the Desikan-Killiany cortical atlas exhibited significantly elevated T1w/T2w ratio for PLWH with VF compared to PLWH with VS and HC. Areas that were significantly different included the right posterior cingulate, right inferior temporal, left orbitofrontal, right and left rostral middle frontal. Within PLWH with VF there was no significant correlation between the T1w/T2w ratio and VL for any of the regions.

Conclusion: Our results suggest that PLWH who have VF have increases in myelin content compared to PLWH who have VS and HIV- controls. The observed increases in T1w/T2w ratio may reflect myelin damage or increases in inflammation and are similar to what has been observed in other neurodegenerative diseases. The T1w/T2w ratio does not measure virological failure.



34 CABOTEGRAVIR + RILPIVIRINE EVERY 2 MONTHS IS NONINFERIOR TO MONTHLY: ATLAS-2M STUDY

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Background: The 2-drug regimen of long-acting (LA) cabotegravir (CAB) and rilpivirine (RPV) dosed i.m. every 4 weeks (Q4W) was noninferior to daily oral 3-drug ART in Phase 3 studies. These results and supportive CAB+RPV LA pharmacokinetics enable regimen evaluation at a longer and potentially more convenient 8-week dosing interval (Q8W).

Methods: ATLAS-2M is a multicenter, open-label, Phase 3b noninferiority (NI) study of CAB+RPV LA maintenance therapy administered Q8W (600mg CAB + 900mg RPV) or Q4W (400mg CAB + 600mg RPV) to treatment-experienced, HIV-infected adults. Virologically suppressed individuals on CAB+RPV LA Q4W (ATLAS study rollover) or oral standard-of-care were randomized 1:1 to receive CAB+RPV LA Q8W or Q4W. The primary endpoint at Week 48 was the proportion with plasma HIV-1 RNA ≥50 c/mL (Snapshot, ITT-exposed [ITTe]) with an NI margin of 4%. The key secondary endpoint was the proportion with HIV-1 RNA <50 c/mL (Snapshot, ITTe) with an NI margin of -10%.

Results: 1045 participants were randomized and treated with CAB+RPV LA Q8W (n=522) or Q4W (n=523); 27% were female, 73% were white. Median age was 42 years (range 19–83); 63% were naïve to CAB+RPV LA while 37% transitioned from Q4W CAB+RPV LA in ATLAS. CAB+RPV LA Q8W was noninferior to Q4W dosing in both the primary (1.7% vs 1.0%) and secondary analysis (94.3% vs 93.5%; see Table). There were 8 and 2 confirmed virologic failures (CVFs; 2 sequential measures ≥200 c/mL) on Q8W and Q4W dosing, respectively; 5 and 0 CVFs, respectively, had archived resistance-associated mutations (RAMs) to RPV (E138A, Y188L, H221Y, Y181C) either alone (n=4) or with a CAB RAM (G140R, n=1) in baseline Peripheral blood mononuclear cells (PBMCs). On-treatment RAMs to RPV (K101E, E138K, M230L), CAB (N155H, Q148R, E138K), or both not present in baseline PBMCs were found in 5/8 Q8W CVFs and both Q4W CVFs. The safety profile was similar for Q4W and Q8W dosing (Table). Injection site reactions (ISRs) were mostly mild or moderate (98% overall) with a median duration of 3 days. Discontinuation for an adverse event occurred in 2% of patients (Q8W, n=12; Q4W, n=13), with 5 (1%) in each group due to ISRs. There was one death (Q8W; sepsis). Of those treated Q8W in ATLAS-2M after ≥48 weeks of Q4W dosing in ATLAS, 93% (115/124) expressed a preference for Q8W dosing.

Conclusion:
Q8W dosing of CAB+RPV LA was noninferior to Q4W dosing and well tolerated. These results support the therapeutic potential of CAB+RPV LA administered every 2 months.

Outcome, n (%), ITTe	Q8W (n=522)	Q4W (n=523)
Primary endpoint HIV-1 RNA ≥50 c/mL at Week 48	9 (1.7)	5 (1.0)
Adjusted difference (95% CI)[a]	0.8 (−0.6; 2.2)	
Data in window not <50 c/mL	3 (0.6)	2 (0.4)
Discontinued for lack of efficacy	6 (1.1)	2 (0.4)
Discontinued for other reasons while not <50 c/mL	0	1 (0.2)
No virologic data	21 (4.0)	29 (5.5)
Discontinued for AE or death	9 (1.7)	13 (2.5)
Discontinued for other reasons	12 (2.3)	16 (3.1)
Key secondary endpoint HIV-1 RNA <50 c/mL at Week 48	492 (94.3)	489 (93.5)
Adjusted difference (95% CI)[a]	0.8 (−2.1; 3.7)	
All AEs	473 (90.6)	482 (92.2)
Serious AEs	27 (5.2)	19 (3.6)
Grade 3–5 AEs	41 (7.9)[b]	49 (9.4)
Discontinued for AEs	12 (2.3)	13 (2.5)
Number of injections	8470	15,711
Number of ISR events	2507	3152
Grade 1 – mild	2010 (80.2)	2561 (81.3)
Grade 2 – moderate	454 (18.1)	543 (17.2)
Grade 3 – severe	43 (1.7)	48 (1.5)
Drug-related grade 3–5 AEs excluding ISRs	4 (0.8)	5 (1.0)
Discontinued for ISRs	5 (1.0)	5 (1.0)

[a]Cochran–Mantel–Haenszel analysis adjusting for prior exposure to CAB+RPV (0, 1–24, or >24 weeks)
[b]Includes 1 death from sepsis on Day 205.
AE, adverse event; CI, confidence interval; ISR, injection site reaction; ITT, intention-to-treat; ITT-e, ITT-exposed; Q4W, 4-week dosing interval; Q8W, 8-week dosing interval.

35 PROSPECTIVE ENHANCED MONITORING OF DOLUTEGRAVIR-BASED FIRST LINE IN MALAWI

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Background: In January 2019 the Ministry of Health of Malawi rolled-out tenofovir-lamivudine-dolutegravir (TLD) as national first-line antiretroviral therapy (ART). Transitioning of patients already on non-nucleoside-reverse-

transcriptase-inhibitor-(NNRTI) first line was without prior HIV-1 viral load (VL) testing. VL monitoring and drug resistance testing (DRT) are still in scale-up in Malawi. In parallel to the national ART policy change, a prospective enhanced monitoring is conducted in three health centres of the decentralized HIV-programme in rural Chiradzulu District. We present month 6 outcomes.
Methods: Inclusion criteria were age >20 years (male), ≥45 years (female) and eligible for TLD by Malawian guidelines. Plasma VL is assessed at 3, 6, 12- and 18-months post TLD-start. Baseline VL was assessed retrospectively from blood collected at inclusion. Virological suppression was defined as VL<50 copies/ml. Participants with VL>50 copies/ml during follow-up receive enhanced adherence counselling and a confirmatory VL test three months later. For virological failure (VF), VL>500 copies/ml at confirmatory test, resistance genotyping (dried blood spots) is done and plasma ARV concentration is measured. Serious adverse events, including treatment discontinuation, are reported.
Results: From January–May 2019, 1928 participants were included: 49.1% female, 98.2% TLD-transitioners, with a median 98.2 months (IQR: 50.9 - 135.5) on ART, and 35 ART-initiators. Baseline VL-suppression of transitioners was 94.5% (95%CI: 93.3 - 95.4), 3.3% had VL>1000 copies/ml. Among TLD-initiators, 54% had a CD4 count < 200 cells/μL and the median baseline VL was 5 $\log_{10}$ (IQR: 4.5 – 5.6). Overall VL suppression was 98% (95%CI: 97.3 - 98.6) at M3 and 98.3% (95%CI: 97.5 – 98.9) at M6 (among 1361 currently assessed). Six (0.4% of tested) transitioners had M6 VF. Among three with currently available DRT, two had DTG resistance (mutation R263K or G118R) in combination with resistance to TDF. Two treatment discontinuations occurred before M3, both due to severe neuropsychiatric events reported as related to dolutegravir.
Conclusion: In a cohort highly suppressed on NNRTI-first-line ART, VL-suppression was well maintained at 6 months post-transitioning to TLD, and VL-suppression was high among the few ART-initiators. Of concern are 2 cases of DTG resistance detected after 6 months on TLD, emphasizing the importance of further monitoring and resistance surveillance.

36 RANDOMIZED SWITCH TO B/F/TAF IN AFRICAN AMERICAN ADULTS WITH HIV

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Background: Black Americans have the highest rates of HIV/AIDS in the US but are under-represented in HIV medical research. The single-tablet regimen bictegravir, emtricitabine, tenofovir alafenamide (B/F/TAF) is a guidelines-recommended treatment for HIV. We evaluated the safety and efficacy of switching to B/F/TAF among Black adults.
Methods: In the Phase 3 BRAAVE 2020 study, adults with HIV who self-identified as Black or African American and were virologically suppressed on 2 NRTIs plus a 3rd agent were randomized (2:1) to switch to open-label B/F/TAF once daily or stay on their baseline regimen (SBR). Prior virologic failure was permitted with the exception of failure on an INSTI-based regimen. Prior resistance to NNRTIs, PIs and/or NRTIs was permitted except for K65R/E/N, ≥3 thymidine analogue mutations or T69-insertions; primary INSTI-resistance was excluded. Primary efficacy endpoint was the proportion with HIV-1 RNA ≥50 c/mL at Week (W) 24 (FDA snapshot); noninferiority was assessed through 95% confidence intervals (CI). Change from baseline in CD4 was a secondary endpoint. The HIV-Treatment Satisfaction Questionnaire (HIV-TSQ) was assessed at baseline, W4 and W24.
Results: 558 were screened, 495 randomized and treated (B/F/TAF n=330, SBR n=165): 32% cis women, 2% trans women, median age 49 yrs (range 18-79), median HIV treatment duration 10 yrs (IQR 6,17), 11% had M184V/I mutation, 62% lived in the US South. Baseline 3rd agents: INSTIs 61%, NNRTIs 31% and PIs 9%. At W24, 0.6% on B/F/TAF and 1.8% on SBR had HIV-1 RNA ≥50 c/mL (difference -1.2%; 95% CI -4.8% to 0.9%) demonstrating noninferiority of B/F/TAF. The proportion with HIV-1 RNA <50 c/mL was 96% B/F/TAF and 95% SBR. No participant had treatment emergent resistance to study drugs. The mean (SD) changes in CD4 were +13 (209) and +1 (171) (p=0.56), median changes in weight 0.9 and 0.2 kg for B/F/TAF and SBR respectively. Study drug related AEs occurred in 10% on B/F/TAF, most were grade 1. Drug related AEs led to discontinuation in 5 participants on B/F/TAF vs 0 on SBR. Participants on B/F/TAF had higher HIV-TSQ scores at W4 and W24 compared to SBR (p<0.001).
Conclusion: For Black Americans, switching to B/F/TAF was noninferior to continuing their regimen with high efficacy in both arms. The single-tablet regimen B/F/TAF was safe and effective for people switching from a variety of regimens, including those with pre-existing NRTI resistance, and was associated with greater treatment satisfaction.

Table: Switch to B/F/TAF vs stay on baseline regimen: Week 24

	B/F/TAF (n=328)[a]	SBR (n=165)
HIV-1 RNA <50 copies per mL	316 (96.3%)	156 (94.5%)
HIV-1 RNA ≥50 copies per mL	2 (0.6%)	3 (1.8%)
Difference in Percentages (95% CI) B/F/TAF – SBR	-1.2% (-4.8% to 0.9%)	
HIV-1 RNA ≥50 copies per mL	2 (0.6%)	3 (1.8%)
Discontinued Due to Lack of Efficacy	0	0
Discontinued Due to Other Reasons	0	0
No Virologic Data and Last Available HIV-1 RNA <50 copies per mL	10 3.0%)	6 (3.6%)
Discontinued Due to AE or Death[b]	6 (1.8%)	0
Discontinued Due to Other Reasons[c]	4 (1.2%)	1 (0.6%)
Missing data but on Study Drug	0	5 (3.0%)

a. 2 participants had primary INSTI mutations on historical genotype and were excluded from the primary analysis, both continued on study and had HIV-1 RNA below the limit of detection at Week 24.
b. AEs: headache (n=1); nightmare, diarrhea, migraine (n=1 each); diarrhea, dry mouth, psychomotor hyperactivity, agitation, anxiety, insomnia (n=1), acute kidney injury (n=1, not related to study drug). No deaths.
c. Other reasons: participant decision (n=2), lost to follow-up (n=3).

37 IMPACT OF ANTI-PD-1 AND ANTI-CTLA-4 ON THE HIV RESERVOIR IN VIVO: THE AMC-095 STUDY

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Background: Antibodies to PD-1 and CTLA-4 may perturb HIV persistence during antiretroviral therapy (ART) by reversing HIV-latency and/or boosting HIV-specific immunity. We tested this hypothesis in a prospective multi-center clinical trial of individuals on ART who had cancer and received single immune checkpoint blockade (ICB) with nivolumab (anti-PD-1) or combination therapy with nivolumab and ipilimumab (anti-CTLA-4).
Methods: This is a substudy of the AIDS Malignancy Consortium-095 Study. ART-suppressed HIV-infected participants with advanced malignancies were assigned to nivolumab (anti-PD-1) 240 mg every two weeks or nivolumab 240 mg every two weeks plus ipilimumab 1 mg/kg (anti-CTLA-4) every 6 weeks. In samples obtained at baseline, within 24 hours and 7 days after the first and fourth dose of ICB and at one late time point after multiple cycles, we quantified cell-associated unspliced (CA US) HIV-RNA and CA HIV-DNA. Plasma HIV-RNA was quantified during the first cycle of ICB using replicate testing using the Aptima HIV-1 Quant assay. Quantitative viral outgrowth assay to estimate the frequency of replication competent HIV was done at baseline and during ICB for a subset of participants. Changes from baseline, including the difference between those on single compared to dual ICB, were tested using non-parametric and parametric statistics (as appropriate) and repeated-measures analysis of variance.
Results: Forty participants were included, 36 males and 4 females. Of those, 33 received anti-PD-1 alone and 7 received anti-PD-1 plus anti-CTLA-4. At baseline, median age was 53.0 (IQR 47.0-58.5) and CD4 count was 315 (IQR 227-465). Whereas CA US HIV-RNA did not change from baseline in those receiving anti-PD-1 alone, we detected a median 1.44 fold-increase (IQR 1.16–1.89) within 24 hours of the first dose in participants on combination ICB (P=0.031). This increase was also significantly higher compared to the corresponding change from baseline in those on anti-PD-1 alone (P=0.025). There were no significant changes from baseline in plasma HIV RNA. We also detected no changes during ICB in the level of HIV DNA or the frequency of cells containing replication-competent HIV (n=10).
Conclusion: Dual ICB with anti-PD-1 and anti-CTLA-4 induced a larger increase in CA-US HIV RNA than anti-PD-1 alone with no effect on plasma HIV RNA or the latent HIV reservoir.

38 A RANDOMIZED TRIAL OF THE IMPACT OF 3BNC117 AND ROMIDEPSIN ON THE HIV-1 RESERVOIR

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Background: Broadly neutralizing antibodies (bNAbs) administered prior to reversal of latency may facilitate killing of HIV-1-infected CD4+ T cells and could be a component of an HIV-1 cure strategy. To clinically assess this concept in individuals on antiretroviral therapy (ART), we evaluated the impact of the bNAb 3BNC117 followed by latency reversal with romidepsin on measures of viral transcription, reservoir size, as well as time to viral rebound during analytical treatment interruption (ATI).

Methods: This randomized phase Ib/IIa trial enrolled 20 HIV-1-infected adults on long-term ART. Group A received 3BNC117 (30 mg/kg) 2 days prior to each romidepsin cycle, with romidepsin (5 mg/m$_2$) administered at weeks 0, 1, and 2 (cycle 1), and weeks 8, 9, and 10 (cycle 2). Group B received cycles 1 and 2 but no 3BNC117. This was followed by an ATI at week 24 when bNAb levels were expected to be low or undetectable. The primary endpoint was time to viral rebound (≥200 copies/mL) during ATI. Secondary endpoints were safety, changes in HIV-1 reservoir measures, as well as effects on HIV-1-specific immunity.

Results: Nineteen of 20 enrolled participants (3 females, 17 males, median age 44 years, median of 645 CD4+ cells/mm$_3$) completed all treatment cycles; 11 in Group A and 8 in Group B. Two participants (one in each group) opted out of the ATI. Seven participants (Group A = 4, Group B = 3) had detectable viral blips (21-144 copies/ml) after romidepsin infusions. Unspliced HIV-1 RNA increased in most individuals after the 2nd and 3rd infusions in each romidepsin cycle. Decline in total HIV-1 DNA was 90 vs 61 copies/106 CD4+ T cells for group A vs B (p=0.79). Median time from interrupting ART to plasma HIV-1 RNA ≥200 copies/ml during ATI was 2.5 weeks for Group A and 4.0 weeks for Group B. A total of 237 AEs were recorded (184 grade 1, 52 grade 2, and 1 grade 3), of which 64 (27.4%) were considered at least possibly related to study medications.

Conclusion: This is the first reported trial of the combination of a latency-reversing agent and potent bNAb designed to target the HIV-1 reservoir. While the combination was safe, it did not reduce the combined defective and intact proviral reservoir as measured by total HIV DNA, or delay viral rebound during ATI. These results may serve as a benchmark for further optimization of HIV-1 cure strategies under ART.

39 SAFETY & PHARMACOKINETICS OF GS-9722 IN HIV-NEGATIVE PARTICIPANTS AND PEOPLE WITH HIV

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Background: GS-9722 is an effector-enhanced, broadly neutralizing antibody (bNAb) targeting a V3 glycan motif of the HIV envelope protein which is being developed for use in a HIV cure regimen. GS-9722 is a derivative of the bNAb PGT121 which has demonstrated immune cell-mediated killing of HIV-infected cells in vitro and efficacy in SHIV-infected monkeys. The safety, tolerability and pharmacokinetics (PK) of GS-9722 administered intravenously (IV; 30′ infusion) were evaluated in a first-in-human study in HIV-negative participants (Study 1) and in virally suppressed people with HIV (VS-PWH; Study 2).

Methods: Two randomized, blinded, placebo-controlled, staggered dose escalation studies were conducted. In Study 1, HIV-negative participants received single dose (SD; 150, 500, or 1500 mg) or multiple doses (MD; 150, 500, or 1000 mg every other week [QOW] for three doses) of GS 9722 (n=6/cohort) or placebo (n=2/cohort). In Study 2, VS-PWH received SD or MD (QOW for five doses) GS-9722 150 or 500 mg (n=6/cohort) or placebo (n=2/cohort). Study 1 has completed; Study 2 is ongoing. Safety and PK are assessed throughout each study.

Results: In Studies 1 and 2, 45 of 49 and 32 of 32 participants completed treatment, respectively. In Study 1, dose-proportional increases in GS-9722 AUC and Cmax were observed (Table). GS-9722 $t_{1/2}$ was ~26 days, supportive of at least QOW dosing. Preliminary SD PK data in VS-PWH are similar to HIV-negative participants (Table); PK analysis in MD VS-PWH cohorts is ongoing.
Most AEs were grade 1 or 2. In Study 1, two participants discontinued study drug due to AEs (1000 mg; MD), both of which were considered related to study drug; one participant had a grade 3 SAE of thrombocytopenia and the other had a grade 2 AE of infusion related-reaction. In Study 2, one participant had a grade 3 unrelated SAE of small intestinal obstruction (150 mg; SD). No other SAEs or AEs leading to study drug discontinuation were reported to date.

Conclusion:
These studies demonstrate that GS-9722 is generally safe and well tolerated in HIV-negative participants and VS-PWH, with similar single dose PK in the two populations. These data support ongoing evaluation of GS-9722 as part of a combination therapy for HIV cure.

Table . GS-9722 Single and Multiple Dose PK in HIV-negative Participants and Preliminary Single Dose PK in Virally Suppressed PWH

PK Parameters	HIV-negative Participants (Study 1)			Virally Suppressed PWH (Study 2)	
Single dose GS-9722 PK Mean (%CV)	GS-9722 150 mg (N = 6)	GS-9722 500 mg (N = 6)	GS-9722 1500 mg (N = 6)	GS-9722 150 mg N=6	GS-9722 500 mg N=4
	Day 1	Day 1	Day 1	Day 1	Day 1
AUC_{inf} (h•µg/mL)	18,000 (15.0)	56,000 (11.5)	200,000 (14.7)	15,200 (21.0)	56,700 (6.90)
C_{max} (µg/mL)	49.7 (19.4)	164 (11.7)	553 (6.9)	41.9 (26.1)	152 (38.9)
$t_{1/2}$ (days)[a]	24.7 (23.4, 26.8)	26.4 (21.5, 26.8)	25.9 (22.4, 28.5)	28.4 (24.6, 32.9)	28.2 (26.8, 30.6)
Multiple dose (QOW) GS-9722 PK Mean (%CV)	GS-9722 150 mg N=6	GS-9722 500 mg N=6	GS-9722 1000 mg N=3	GS-9722 150 mg N=6	GS-9722 500 mg N=6
	Day 29; 3rd dose	Day 29; 3rd dose	Day 29; 3rd dose	Day 57; 5th dose	Day 57; 5th dose
$AUC_{0\text{-}168hr}$ (h•µg/mL)	12,600 (13.4)	48,600 (15.5)	106,000 (31.0)	P	P
C_{max} (µg/mL)	77.6 (12.8)	261 (12.8)	567 (35.2)	P	P
C_{168hr} (µg/mL)	25.8 (19.9)	108 (18.9)	221 (36.7)	P	P
$t_{1/2}$ (days)[a]	28.4 (26.0, 29.0)	23.4 (21.5, 42.0)	29.9 (23.3, 34.6)	P	P

PK parameters are presented to 3 significant figures as mean (%CV), except $t_{1/2}$ (median (Q1,Q3); multiple dose PK parameters represent exposure over 14 days ($AUC_{0\text{-}168hr}$) of the dosing interval (QOW); C_{168hr} = exposure at the end of the dosing interval; P: PK analysis is ongoing; PWH = people with HIV

40 SAFETY AND ANALYTIC TREATMENT INTERRUPTION OUTCOMES OF VESATOLIMOD IN HIV CONTROLLERS

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Background: Administration of a toll-like receptor (TLR) 7 agonist in combination with a therapeutic vaccine induces CD8+ T cell-mediated control of SIV in a non-human primate model. We hypothesized that among people living with HIV (PLH) who had evidence of a partially effective host response (viremic controllers), treatment with the investigational oral TLR7 agonist vesatolimod (VES; GS-9620) would lead to enhanced immune control post-ART.

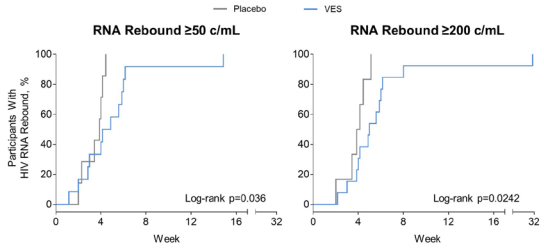
Methods: We conducted a phase 1b, randomized, double-blind, placebo-controlled study in virologically suppressed PLH with historical chronic pre-ART plasma HIV-1 RNA of 50 to ≤5,000 c/mL. Participants were randomized 2:1 to receive 10 biweekly doses of VES 4-8 mg or placebo while continuing ART, followed by carefully monitored analytical treatment interruption (ATI). Viral rebound and safety were evaluated through at least 24 weeks (w) of ATI.

Results: Twenty-five participants were randomized to VES (n=17) or placebo (n=8). The median age was 45 yrs (range 27-66 yrs) and 16% were women. The median pre-ART HIV-1 RNA 3.2 $\log_{10}$ c/mL (IQR 3, 3.3) and the median time on ART was 2.7 yrs (range 0.7-17.2 yrs). VES was well tolerated, with no drug-related discontinuations. Most common study-drug related AEs were lymphadenopathy, chills, and headache. Pharmacodynamic activity of VES was confirmed by increases in whole blood interferon stimulated gene mRNAs and plasma cytokine levels. During the ATI, the median (95% CI) times to viral rebound (>50 c/mL and >200 c/mL, respectively) were 4.1 w (2.9-5.9) and 5 w (3.9-6) for the VES group, and 3.9 w (2.0-4.1) and 4 w (2-4.4) for placebo (p=0.036; p=0.024; see Figure). Median (95% CI) plasma viral set-point change from pre-ART value was -0.34 (-0.60, 0.06) $\log_{10}$ c/mL for VES (p=0.035) and -0.28 (-0.75, 0.32) $\log_{10}$ c/mL for placebo (p=0.38). Four individuals in the VES group had no virologic rebound (>50 c/mL) for ≥6 w, with one participant rebounding at 15 w (and >200 c/mL at 31 w); this participant also had a 0.94 $\log_{10}$ c/mL decrease in viral set-point and completed the study after 48 w off ART with HIV-1 RNA 164-215 c/mL.

Conclusion: VES was well tolerated in HIV controllers at multiple doses up to 8 mg and was associated with a modest increase in time to viral rebound after ATI,

potentially due to an augmented antiviral immune response. Trials evaluating the efficacy of VES in combination with other agents such as CD8-inducing vaccines and monoclonal antibodies are warranted.

Figure.



41LB DURABLE HIV-1 ANTIBODY PRODUCTION IN HUMANS AFTER AAV8-MEDIATED GENE TRANSFER

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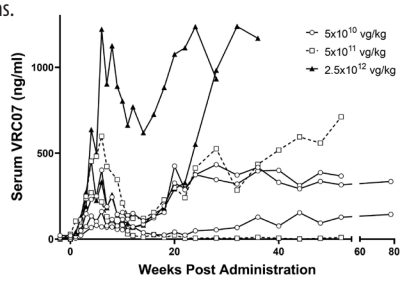
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Background: Gene transfer protocols offer an alternative to repeated injections of HIV broadly neutralizing antibodies (bNAb) as a means of maintaining effective immunoprophylaxis. VRC07 is a bNAb targeting the CD4 binding site of the HIV-1 envelope glycoprotein.

Methods: Seven HIV-infected volunteers on effective ARV therapy were enrolled in a phase I, open-label dose escalation trial of an AAV8 vector encoding the HIV bNAb VRC07 at doses of 5x1010 (N=3), 5x1011 (N=2), and 2.5x1012 (N=2) viral genomes per kilogram (vg/kg) by IM injection. Volunteers were between 30 to 60 yr. All volunteers in the 5x1010 and 5x1011 vg/kg doses were followed for 1yr or longer. Two volunteers in the 2.5x1012 dose group have been followed for between 7-9 mo.

Results: Product administration was well tolerated. Local reactogenicity was observed only in the 2.5x1012 vg/kg dose group where both volunteers reported mild pain and tenderness at the injection sites. One person in the intermediate dose group reported mild myalgia. All reactogenicities resolved within 1 week of product administration. No serious adverse events were attributed to product. Vector-based VRC07 production was found in all volunteers following injection. Peak VRC07 concentrations were 0.17-0.43 µg/ml in the 5x1010 dose group, 0.23-0.74 µg/ml in the 5x1011 dose group and 1.1-1.2 µg/ml in the 2.5x1012 dose group (Figure). The data suggest a pattern of antibody production defined by an early peak in VRC07 concentration 4-6 wks after product administration, a decrease in concentration 7-14 weeks after product administration and then a slow increase in concentration after 16 wks resulting in stable or continually increasing antibody concentration over the next 36 wks. In 3 of 5 individuals followed for one year or longer, antibody concentrations at 1 yr were higher than at the 4-6 wk peak. In the other 2 volunteers, one in the 5x1010, the other in the 5x1011 vg/kg dose group, anti-VRC07 antibodies were identified starting 6 and 14 wks after product administration. Anti-VRC07 antibodies were not detected in the other 5 volunteers.

Conclusion: These data suggest that adeno-associated viral vectors can safely be used to stably produce HIV-1 specific bNAbs in humans for over a 1-year period following a single administration of vector. AAV8 mediated gene transfer may offer a means to generate effective vectored immunoprophylaxis in humans.



42 INDEX FACTORS INCREASE PARTNER NOTIFICATION YIELD FOR KENYAN PEOPLE WHO INJECT DRUGS

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Background: Assisted partner notification services (aPNS) to find, test, and link to care partners of HIV+ individuals may aid in achieving HIV care cascade goals in key populations. Our ongoing evaluation of aPNS for people who inject drugs (PWID) in Kenya identifies characteristics of indexes associated with highest yield for this community.

Methods: Indexes were recruited from needle/syringe programs and methadone clinics in Nairobi and Kilifi County and offered enrollment if HIV+. Indexes provided contact information for injection and sexual partners (past 3 years). Community-embedded peer educators traced partners and referred them to study sites for HIV testing. aPNS efficiency was assessed by number of indexes needed to interview (NNTI) to find one additional HIV+ partner not on ART.

Results: 441 enrolled indexes named 1821 partners (70% injection partners, 18% sexual, and 11% sexual and injection). Indexes named a median of 4 partners (interquartile range [IQR] 3-5). aPNS was provided to 1565 (86%) partners, with a median of 4 partners (IQR 2-5) tested among female indexes and 3 (IQR 2-4) among males (p=0.002). aPNS yielded 470 HIV+ partners, of whom 116 (25%) were not on ART and 50 (11%) were unaware of their HIV status. One or more HIV+ partners were identified for 262 (59%) indexes, with a single HIV+ partner identified for 34% of indexes and ≥2 HIV+ identified for 25% of indexes. Overall, NNTI was 3.8 to identify one partner not on ART; aPNS in Nairobi was more likely than Kilifi Country to yield HIV+ partners not on ART (NNTI=3.3 vs 9.1; p<0.001). NNTI to identify partners not on ART was 2.5 for female indexes versus 7.1 for males (p<0.001). Adjusted for sex of the index, aPNS was more efficient for finding HIV+ not on ART among indexes not in a methadone program (NNTI=2.5 vs 4.1 for females; NNTI=4.9 vs 19.2 for males; p=0.003). After 6-months, 71% of partners not initially on ART had started treatment.

Conclusion: aPNS can improve the HIV care cascade for partners of PWID in Kenya, finding 1 HIV+ partner not on ART per 3.8 indexes. While most HIV+ partners were aware of their HIV status, 25% were not currently on ART, highlighting a need for improved care engagement. Focusing on index PWID most likely to yield HIV+ partners not fully engaged in care will maximize aPNS to achieve viral suppression. We found females, those not in methadone programs, and in Nairobi yielded the most partners not on ART.

43 COMMUNITY-BASED MULTIMONTH DISPENSING OF ART: A CLUSTER RANDOMISED TRIAL IN LESOTHO

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Background: Lesotho adopted the test and start strategy for HIV services in June 2016 with anticipated increase in patient load. Our study evaluated community-based differentiated models of multi-month dispensing (MMD) of ART among stable HIV-infected adults in Lesotho. We report 12 month outcomes of the study.

Methods: The cluster-randomised trial was conducted in 30 selected clusters, stratified into rural and urban geo-locations. The clusters were randomised to three differentiated model of care arms: (i) 3 monthly ART supply at facilities (3MF) as control, (ii) 3 monthly ART supply through community ART groups (3MC) as intervention; (iii) 6 monthly ART supply through community ART distribution points (6MCD) as intervention. The primary outcome was retention in care with virologic suppression as secondary outcome. Outcome analysis were by intention-to-treat. We compared risk differences between arms with binomial population and used Cox's proportional hazards regression to compare

arms, controlling for potential imbalances between arms and specifying for clustering.

Results: A total of 5336 participants were enrolled, 3MF (1898), 3MC (1558) and 6MCD (1880) arms. Retention in ART care was not different across the arms and achieved the noninferiority limit (-3.25%) with 3MC vs. 3MF 6MCD vs. 3MF (control) and 6MCD vs. 3MC, adjusted RD= -0.1% (95% CI: -1.6% to 1.5%), adjusted RD= -1.3% (95% CI: -3.0% to 0.5%), and adjusted RD= -1.2% (95% CI: -2.9% to 0.5%), respectively. Retention in the intervention arms for both 3MC and 6MCD arms did not differ vs. 3MF, adjusted RD=1.1% (95% CI: -0.6% to 2.8%) and adjusted RD= -0.6% (95% CI: -2.4% to 1.1%), respectively. However, there was a slight reduction in 6MCD vs 3MC, adjusted RD= -1.9% (95% CI: -3.6% to -0.2%). Amongst 1503, 1126 and 1285 participants with available viral load results after 12 months, 1482 (98.6%), 1104 (98.1%) and 1263 (98.3%) were virally suppressed in arms 3MF, 3MC and 6MCD, respectively. There were no differences in viral suppression between 3MC, or 6MCD vs. control, risk ratio (RR)=1.00 (95% CI: 0.98-1.01) and RR=1.00 (95% CI: 0.98-1.01), respectively.

Conclusion: There is no difference in retention in care or viral load suppression for stable patients receiving 3 or 6 month dispensing of ART within community-based differentiated models of care when compared to the standard 3 month facility dispensing model

44 AN MHEALTH CHW INTERVENTION TRIAL IN AN HIV HYPERENDEMIC COMMUNITY IN RAKAI, UGANDA

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Background: Effective strategies are needed to increase engagement in HIV services in HIV hyperendemic settings. We conducted a cluster-randomized trial in a fishing community on Lake Victoria (HIV prevalence ~41%) in Rakai, Uganda to assess the impact of a community health worker intervention called "Health Scouts" which used motivational interviewing strategies, a situated Information, Motivation, and Behavioral Skills framework, and mobile health (mHealth) counseling support tools to promote engagement in HIV treatment and prevention services.

Methods: From September 2015 to December 2018, the Health Scout intervention was deployed in the community which had been divided into 40 contiguous, similarly populated clusters (20 intervention; 20 control). Community-wide surveys of consenting 15-49 year-old residents with HIV viral load testing of HIV-positive participants were conducted at mid-study (~15 months) and end-of-study (~39 months) to assess self-reported antiretroviral therapy (ART) and male circumcision coverage and HIV viral load suppression (defined as <400 copies/mL). The primary analytic method was an as-treated analysis using generalized estimating equations models including participants from both surveys in a pragmatic analysis due to high participant mobility and contamination by study arm.

Results:2522 and 1891 community residents completed the mid-study and end-of-study surveys respectively. By end-of-study, 95.7% (1789/1891) of residents reported awareness of the Health Scouts; 31% (580/1891) of residents reported having been visited and counseled by a Health Scout (i.e. exposed); 2.2% (41/1311) reported being approached but refusing to be seen. Health Scout exposure was higher in intervention (38%) compared to control clusters (23%), among those living with HIV (39%) compared to those who were not (23%), and among women (32%) compared to men (26%). As shown in Table 1, residents who reported having received the intervention (exposed) were more likely to report being on ART and to be virologically suppressed compared to residents who reported not having received the intervention (unexposed); however, there were no differences in male circumcision coverage.

Conclusion: A novel community health worker intervention using motivational interviewing techniques and mHealth tools was associated with improved ART coverage and HIV virologic suppression. However, intervention uptake varied by subgroups and cluster contamination was substantial. This intervention may be a useful community-based component of a comprehensive HIV response.

Table 1: Study outcomes and prevalence risk ratios; *includes participants from both surveys.

	Mid-Study Survey			End-of-Study Survey				
Outcome	**n**	**Exposed**	**Unexposed**	**n**	**Exposed**	**Unexposed**	**Prevalence Risk Ratio (95% CI)***	**p value**
ART Coverage	972	91.1%	82.0%	773	97.0%	85.6%	1.13 (1.09-1.17)	<0.001
HIV Viral Suppression	963	78.4%	70.8%	760	80.7%	76.1%	1.09 (1.03-1.15)	0.003
Male Circumcision Coverage	1505	67.5%	65.0%	1166	68.4%	66.4%	1.07 (0.94-1.22)	0.30

45 IMPROVED TIME IN CARE AND VIRAL SUPPRESSION WITH STREAMLINED CARE IN THE SEARCH STUDY

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Background: HIV differentiated service delivery (DSD) models are being scaled up in resource-limited settings for stable patients; less is known about DSD outcomes for patients newly linked or re-linked to care. We evaluated the effect of the SEARCH streamlined care intervention by comparing care engagement and viral suppression (VS) between intervention and control arms among HIV+ persons ART eligible by country guidelines at study start who were already enrolled or who linked to care after universal HIV testing in the SEARCH trial (NCT:01864603).

Methods: Our analysis included HIV+ adults (age ≥15 yrs) at baseline (2013) who were country guideline ART eligible (prior ART experience or CD4≤350) and had ≥1 clinic visit for HIV care between 2013-2017 in SEARCH communities randomized to intervention (N=16) or control (N=16). We assessed the effect of streamlined care (patient-centered care, increased appointment spacing, improved clinic access, reminders, and tracking) on time in care (TIC) and viral suppression (VS) at 3 years. TIC was defined as the proportion of total follow up time that patients adhered to visit schedules. Analysis was stratified by baseline care status, namely: 1) ART-experienced with baseline VS, 2) ART-experienced with baseline viremia, or 3) ART-naïve with baseline CD4≤350. Comparisons between study arms used cluster-level TMLE.

Results: Among 4,391 HIV+ persons (35% men, 8% youth 15-24 yrs) in care and eligible for ART by country guidelines, 2,958 (67%) were ART-experienced with baseline VS, 568 (13%) were ART-experienced with baseline viremia, and 865 (20%) were ART-naïve with CD4≤350. Among ART-experienced patients with baseline viremia, streamlined care was associated with both higher TIC (RR 1.11, 95% CI 1.01-1.21) and VS (67% vs 47%, RR 1.41, 95% CI 1.04-1.92). Among ART-naïve persons, streamlined care was associated with higher TIC (RR 1.10, 95% CI 1.05-1.21) but VS was not significantly higher (83% vs 78%, RR 1.06, 95% CI 0.95 -1.19). Among ART-experienced persons with baseline VS, effects of streamlined care were observed on TIC (RR 1.07, 95% CI 1.01-1.13), although nearly all were virally suppressed after 3 years regardless of the care delivery model (97% intervention vs 95% control, RR 1.02, 95% CI 1.00-1.03).

Conclusion: Streamlined care was associated with better engagement in care for all groups and viral suppression for ART-experienced patients with viremia in this randomized comparison of patients ART eligible at study start who linked to care after universal HIV testing.

Table 1. Effect of streamlined care on engagement and viral suppression among patients eligible for ART by WHO 2013 guidelines linked to care by baseline care status

	ART-experienced with baseline viral suppression*			ART-experienced with baseline viremia†			ART-naive with baseline CD4 ≤350		
	Intervention (N=1,646)	Control (N=1,312)	RR (95% CI)	Intervention (N=330)	Control (N=238)	RR (95% CI)	Intervention (N=514)	Control (N=351)	RR (95% CI)
Time in care (TIC)‡	86%	81%	1.07 (1.01-1.13)	81%	73%	1.11 (1.01-1.21)	74%	67%	1.10 (1.03-1.17)
Viral suppression at year 3*§	97% (N=1,377)	95% (N=1,097)	1.02 (1.00-1.03)	67% (N=254)	47% (N=172)	1.41 (1.04-1.92)	83% (N=344)	78% (N=243)	1.06 (0.95-1.19)

* Viral load <500 copies/mL
† Viral load ≥500 copies/mL
‡ Proportion of total follow up time adherent to visit schedules: ((total follow up time - cumulative time late to appointments)/total follow up time)
§ Proportions reported for number of available viral loads (as noted)

46 COLLABORATIVE DATA-TO-CARE MODEL IMPROVES HIV CARE OUTCOMES IN PLWH IN PHILADELPHIA

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Background: Among the 19,199 people living with HIV (PLWH) in Philadelphia, 6,401 (33%) were out of care (OOC) in 2017. Engagement in care is integral to decreasing HIV transmission and achieving Ending the HIV Epidemic outcomes. This analysis aims to characterize persons OOC and assess outcomes of a collaborative health department/medical provider data-to-care randomized control trial.
Methods: OOC patients were randomized to Standard of Care (SOC) or Intervention, in which Disease Intervention Specialists assisted patients with reengagement. Criteria for inclusion were age >18, in-care at a participating clinic during a 12-month eligibility period and no care in the following 6 months. Chi-square testing was used to determine differences in demographics between study arms. Multivariable logistic regression was used to assess predictors of 3 outcomes: re-engagement (CD4/VL within 90 days), retention (2 or more CD4/VLs at least 90 days apart within 1 year) and viral suppression (VL <200 c/mL within 1 year).
Results: 449 OOC PLWH were randomized to each study arm between 8/2016-12/2017, with no significant differences in demographic characteristics between arms. The majority of patients were evenly distributed across age groups >25, 65% were Black, 76% were male, 42% were MSM, and 21% were HIV/non-AIDS at diagnosis. Across arms, 53% were re-engaged, 52% were retained at 1 year, and 60% were virally suppressed at 1 year. Patients randomized to the intervention were 2.22 (95% CI: 1.69-2.92), 1.89 (1.44-2.48) and 1.44 (1.10-1.90) times as likely as SOC patients to re-engage in care, become retained in care, and achieve viral suppression, respectively, when controlling for race, birth sex, age, transmission category and disease stage at diagnosis.
Conclusion: Results indicate that a collaborative data-to-care intervention can improve re-engagement in care, retention in care and viral suppression among PLWH who are OOC. Next steps include expansion of this model to determine feasibility of city-wide implementation.

Table 1. Randomization Assignment and Demographic Predictors of HIV Care Outcomes

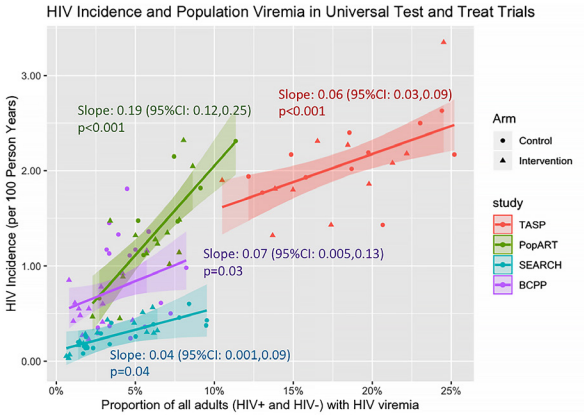
				Adjusted OR					
				90-day Re-engagement* (n=472)		Retention* (n=463)		Viral Suppression* (n=539)	
	Total	Intervention†	Standard of Care†	OR	95% CL	OR	95% CL	OR	95% CL
Assignment*	n (%)	n (%)	n (%)						
Standard of Care	449 (50)			1.00		1.00		1.00	
Intervention	449 (50)			2.22	1.69 2.92	1.89	1.44 2.48	1.44	1.10 1.90
Race									
White	169 (18.87)	85 (18.9)	84 (18.7)	1.00		1.00		1.00	
Black	588 (65.48)	292 (65.0)	296 (65.9)	0.81	0.56 1.17	0.84	0.58 1.20	0.79	0.54 1.14
Hispanic	114 (12.69)	57 (12.7)	57 (12.7)	0.62	0.38 1.03	0.75	0.46 1.24	0.86	0.52 1.42
Other/Unknown	27 (3.01)	15 (3.3)	12 (2.7)	0.53	0.23 1.25	1.00	0.42 2.34	0.78	0.33 1.84
Birth Sex									
Male	683 (76.06)	351 (78.2)	332 (73.9)	1.00		1.00		1.00	
Female	215 (23.94)	98 (21.8)	117 (26.1)	1.04	0.70 1.54	1.01	0.68 1.49	1.12	0.75 1.67
Age						*		*	
18-24	9 (1)	s	s	1.00		1.00		1.00	
25-34	223 (24.83)	117 (26.1)	106 (23.6)	3.62	0.71 18.56	13.65	1.16 161.22	3.85	0.77 19.15
35-44	220 (24.5)	110 (24.5)	110 (24.5)	3.58	0.69 18.51	14.39	1.21 171.75	4.69	0.94 23.52
45-54	212 (23.61)	100 (22.3)	112 (24.9)	5.56	1.07 28.97	22.38	1.87 268.23	6.11	1.21 30.90
55+	234 (26.06)	117 (26.1)	117 (26.1)	5.01	0.97 25.99	22.37	1.87 267.68	8.17	1.62 41.25
Transmission Category									
Heterosexual	235 (26.17)	109 (24.3)	126 (28.1)	1.00		1.00		1.00	
MSM	397 (44.21)	209 (46.6)	188 (41.9)	0.86	0.57 1.31	0.92	0.61 1.39	1.03	0.68 1.57
IDU	181 (20.16)	96 (21.4)	85 (18.9)	1.27	0.84 1.93	1.10	0.73 1.66	0.90	0.59 1.38
MSM IDU	56 (6.24)	23 (5.1)	33 (7.4)	0.82	0.43 1.55	0.70	0.37 1.33	0.80	0.42 1.53
NIR	16 (1.78)	6 (1.3)	10 (2.2)	0.93	0.33 2.63	0.73	0.26 2.07	1.04	0.36 2.98
NRR	s	s	s	>999.99	<0.001 >999.99	>999.99	<0.001 >999.99	>999.99	<0.001 >999.99
Perinatal	9 (1)	s	6 (1.3)	2.98	0.65 13.65	21.36	1.72 264.89	0.85	0.21 3.49
Pediatric	s	s	s	>999.99	<0.001 >999.99	1.68	0.14 19.69	0.29	0.03 3.34
Concurrent AIDS Diagnosis									
No	712 (79.29)	361 (80.4)	351 (78.2)	1.00		1.00		1.00	
Yes	186 (20.71)	88 (19.6)	98 (21.8)	1.06	0.75 1.50	0.97	0.69 1.37	0.97	0.69 1.37

* p<0.01
† There were no statistically significant differences in demographic makeup between randomization arms.

47 POPULATION-LEVEL VIREMIA PREDICTS HIV INCIDENCE ACROSS UNIVERSAL TEST & TREAT STUDIES

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Background: Improved understanding of the extent to which increased population-level viral suppression will reduce HIV incidence is needed. Using data from four large Universal Test and Treat Trials, we evaluated the relationship between viremia and incidence and its consistency across epidemic contexts.
Methods: We analyzed data from 105 communities in the PopART (21 communities in South Africa and Zambia, ~ 25,000 adults each), BCPP (30 communities in Botswana, ~3,600 adults each), ANRS 12249 TasP (22 communities in South Africa, ~1,300 adults each) and SEARCH (32 communities in Uganda and Kenya, ~5,000 adults each) studies. Communities ranged from rural to urban and varied in the mobility of their populations and their sex ratio (~30% to 50% male). HIV incidence was measured via repeat testing between 2012-2018. Population viremia ¬– % of all adults (HIV+ or HIV-) with HIV viremia – was estimated at midpoint of follow-up based on HIV prevalence and non-suppression among HIV+, with adjustment for differences between the measurement cohort and underlying population. Community-level regression, adjusted for study, was used to quantify the association between HIV incidence and viremia and to evaluate cross-study heterogeneity.
Results: HIV prevalence (measured in 257,929 total persons, PopART: 37,006; BCPP: 12,570; TasP: 20,978; SEARCH: 187,375), ranged from 2% to 40% by community. Non-suppression among HIV+ (measured in 39,928 persons, PopART: 6,233; BCPP: 2,318; TasP: 6,617; SEARCH: 16,209) ranged from 3% to 70%. HIV incidence (measured over 345,844 person-years, PopART: 39,702; BCPP: 8,551; TasP: 26,832; SEARCH: 270,759) ranged from 0.03 to 3.4 per 100PY. Population-level viremia was strongly associated with HIV incidence; pooling across studies, HIV incidence decreased by 0.07/100PY (95% CI: 0.05,0.10, p<0.001) for each 1% absolute decrease in viremia. Incidence was significantly associated with viremia in each study; however, both strength of the incidence-viremia relationship (slope) and projected incidence at 0% viremia (intercept) differed (Figure).
Conclusion: Lower population-level HIV viremia was associated with lower HIV incidence in all four Universal Test and Treat Studies, conducted in a wide range of epidemic contexts in sub-Saharan Africa. Differences in external infection rate (due to variation in community size, mobility, and sex ratio) may have contributed to heterogeneity between studies.



48 DECREASING COMMUNITY VIREMIA IS ASSOCIATED WITH DECREASING HIV INCIDENCE IN AUSTRALIA

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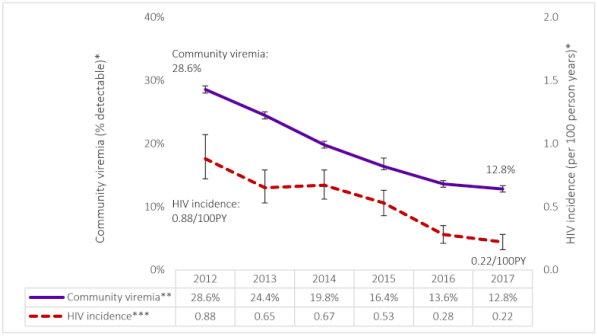
Background: Considerable public health resources have been dedicated to implementing HIV 'treatment-as-prevention' in an effort to reduce new infections. Although promising, no large-scale studies have yet evaluated the community-level impact of treatment-as-prevention on direct measures of HIV incidence among gay and bisexual men (GBM). This study assessed the temporal relationship between community viremia and HIV incidence among GBM living in New South Wales and Victoria, Australia's most populous states.
Methods: For 2012-2017, we established a longitudinal cohort of HIV-positive (n=12,200) and HIV-negative (n=45,719) GBM using data from a targeted sentinel surveillance system of 49 sexual health clinics, general practices, community HIV-testing sites and hospitals. Among GBM with diagnosed HIV,

annual prevalence of viremia was calculated for each patient's last viral load test of a calendar year (≥200 RNA copies/mm$_3$) while mathematical modelling was used to estimate the proportion of HIV-positive GBM living with undiagnosed HIV infection (assuming 100% viremia); these outcomes were combined to estimate 'community viremia'. A correlation coefficient was calculated to assess the temporal relationship between community viremia and HIV incidence, which was directly measured among HIV-negative sentinel surveillance patients using the repeat testing method. To account for the introduction of HIV pre-exposure prophylaxis (PrEP) in 2016, the analysis was repeated for the 2012-2015 period only.

Results: HIV viremia among diagnosed GBM decreased from 27.9% in 2012 to 3.7% in 2017 (p<0.001) while the proportion living with undiagnosed HIV decreased from 10.0% to 8.4% (p=0.01). As shown in Figure 1, annual community prevalence of HIV viremia decreased from 28.6% in 2012 to 12.8% in 2017 (p<0.001) while HIV incidence decreased from 0.88/100 person years in 2012 to 0.22/100 person years in 2017 (p<0.001). The correlation coefficient between annual community prevalence of viremia and HIV incidence from 2012 to 2017 was 0.94 (p<0.001) and for 2012 to 2015 was 0.90 (p<0.001).

Conclusion: Decreasing community viremia among GBM was strongly associated with decreasing HIV incidence, including before the implementation of PrEP. Our findings justify the significant investment in HIV treatment initiatives, highlighting that these should be sustained as key elements of HIV prevention.

Figure 1. HIV incidence (clinical cohort) and community viremia (clinical cohort and mathematical modelling) among gay and bisexual men in the Australian states of New South Wales and Victoria, by year



	2012	2013	2014	2015	2016	2017
Community viremia**	28.6%	24.4%	19.8%	16.4%	13.6%	12.8%
HIV incidence***	0.88	0.65	0.67	0.53	0.28	0.22

* Shown with 95% confidence intervals; **Community viremia estimated by combining the prevalence of viremia among diagnosed men with an estimated prevalence of viremia among undiagnosed men; *** HIV incidence calculated via repeat testing among HIV-negative men

49LB COMMUNITY ART INCREASES VIRAL SUPPRESSION AND ELIMINATES DISPARITIES FOR AFRICAN MEN

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Background: Community-based HIV testing, same-day ART start, and decentralized monitoring and ART refills could increase viral suppression, particularly among priority groups who engage less in clinic-based HIV care, such as men who are more likely to have detectable HIV viral load.

Methods: We conducted a multi-site, household randomized trial of community-based ART compared to clinic services in rural and peri-urban areas of Sheema District, Uganda, and KwaZulu Natal, South Africa - the Delivery Optimization for ART (DO ART) Study. Community-based HIV testing was conducted at home and in mobile vans. People living with HIV (PLWH) who were not on ART with CD4>100 cell/mL were eligible for randomization to: 1) same-day community-based ART start with quarterly monitoring and ART refills through mobile vans, 2) ART start at the clinic with monitoring and refills through mobile vans in the community (hybrid approach); or 3) clinic-based ART (standard of care). The primary outcome was HIV viral suppression at 12 months, assessed by modified intent to treat analysis using regression analysis; testing first for superiority and then non-inferiority (relative 5%) if not superior.

Results: Between May 2016 and March 2019, 1,531 PLWH not on ART were randomized: 708 (46%) were men and 36% were <30 years. Retention at 12 months was 95%. Compared to standard clinic care, community-based ART increased viral suppression (63% vs. 74%, RR=1.18, 95% CI: 1.07-1.29) and the hybrid approach was non-inferior (63% vs. 68%, RR=1.08, 95% CI: 0.98-1.19, p=0.005 for non-inferiority). Both community strategies significantly increased viral suppression among men: community-based ART (73%, RR=1.34, 95% CI: 1.16-1.55) and hybrid approach (66%, RR=1.19, 95% CI: 1.02-1.40), compared to standard of care (54%). Viral suppression was similar for men (73%) and women (75%) in the community ART arm - compared to 54% for men and 73% for women in the clinic arm.

Conclusion: Among PLWH who were not on ART, community-based HIV testing, same-day ART initiation, mobile van monitoring and ART resupply, significantly increased viral suppression compared to clinic-based ART. The UNAIDS 90-90-90 goal of 73% suppression was met for men and women in the community-based ART arm, eliminating disparities in viral suppression by gender. Combining decentralized ART initiation and refill is an effective strategy to increase viral suppression which should be implemented and evaluated in different contexts and populations who are not virally suppressed.

50 IN VIVO MODELS FOR THE EVALUATION OF NOVEL HIV CURE INTERVENTIONS

J. Victor Garcia-Martinez, *University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Animal models have contributed extensively to biomedical investigation and specifically to virtually all areas of HIV research. Animal models provide a complex substrate for the evaluation of novel therapeutic interventions at very early stages that would not be suitable for testing in humans. They allow for exquisite control of variables that are normally impossible to control in human clinical studies such as the strain of virus, inoculum dose, and the timing and route of exposure. In addition to the evaluation of the success of any given intervention, they permit a very complete analysis of its mechanism of action, it's possible risks such as toxicity and it's benefits regarding efficacy all in a highly reproducible and reliable manner. Because animal models infected with HIV and treated with antiretroviral therapy can establish HIV persistence in vivo, they provide a unique tool for the evaluation of novel approaches to reverse latency. Furthermore, they allow for the evaluation of novel approaches for the killing of latently infected cells that have been reactivated. Currently, two animal models have been used for the majority of the published research in HIV CURE: non-human primates and humanized mice. There are significant differences between these two models that make them highly complementary to each other. This lecture will review the implementation of both models for HIV cure and provide recent examples of how both models synergize to provide helpful insight into the reproducibility and efficacy of novel interventions aimed at finding an HIV CURE.

51 LRA 2.0: IMMUNE-BASED LATENCY REVERSAL

Ann Chahroudi, *Emory University, Atlanta, GA, USA*

Long-lasting, latently-infected resting CD4+ T cells are the greatest obstacle to curing HIV infection, as these cells can persist despite decades of treatment with antiretroviral therapy. One approach towards a cure is to reactivate HIV from its latent state, thus promoting virus mediated killing and/or facilitating immune recognition and clearance of infected cells. Interventions that successfully reverse latency, when combined with strategies to enhance the antiviral immune response, may result in a reduction in the size of the persistent HIV reservoir. This presentation will review promising latency reversal approaches that take into consideration the immunologic aspects of virus persistence. Emerging results from in vivo studies in humanized mice and nonhuman primates will be discussed. The immunologic and virologic effects of the selected latency reversal agents will be highlighted.

52 T-CELL AND HEMATOPOIETIC STEM CELL GENE THERAPIES FOR HIV CURE

Christopher Peterson, *Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

Since the first reported cure of an HIV-1-infected individual over a decade ago, anti-HIV cell and gene therapies have remained a primary focus of numerous HIV cure efforts. To date, hematopoietic stem and progenitor cell (HSPC) transplantation remains the only known path to cure. Although this approach is not feasible for the vast majority of patients, lessons from Berlin, London, and elsewhere have contributed a wealth of knowledge regarding less toxic and more generalizable strategies. This presentation will discuss the current and most promising aspects of cell and gene therapy-based HIV cure approaches, offer a comparison of the pro's and con's of targeting HSPCs,

T-cells, and other subsets, and review lead candidates for scalable delivery of these therapies, namely in resource-limited settings. First and foremost, any curative intervention must be at least as safe and feasible as lifelong ART. A careful examination of the fundamental aspects of cure in HIV-infected stem cell transplantation patients lays out a compelling road map towards a gene therapy-based strategy, focused on enhancing virus-specific immunity. One such strategy involves adoptively transferred T-cells, for example cells modified to express chimeric antigen receptors (CARs). CAR T-cells have enabled long-term remission in cancer and have recently shown similar promise for HIV-1. However, since the maximum time frame during which latently infected cells may reappear following ART interruption is unknown, curative interventions must assume the need for lifelong protection. Although T-cell immunotherapies currently display a superior safety profile, HSPC-derived therapies may offer persistent antiviral functions capable of recognizing recrudescent virus that appears months or years after removal of suppressive therapy. Finally, scalability is an essential facet for any cell and gene therapy approach and must be developed in parallel with "proof of principle" strategies that are frequently only applicable in developed nations. By investing heavily in viral vectors, nanoparticles, and other so-called in vivo delivery platforms that are portable, affordable, and can be administered without the need for costly biomedical infrastructure, we may yet achieve the high bar of permanent HIV remission in the absence of suppressive therapy.

53 TOWARD DURABLE CONTROL OF HIV-1 WITH eCD4-Ig

Michael Farzan, *The Scripps Research Institute, La Jolla, CA, USA*

eCD4-Ig is an exceptionally broad HIV-1 entry inhibitor that uniquely neutralizes all of the 270 HIV-1, HIV-2 and SIV isolates it has been tested against, in every case with IC80 values < 10 µg/ml. eCD4-Ig's breadth and potency derives from the fact that it closely and simultaneously mimics the HIV-1 receptor CD4 and the HIV-1 coreceptor. Consistent with this breadth, eCD4-Ig is much harder to escape than broadly neutralizing antibodies (bNAbs). To date full escape has not been observed either in cell culture or rhesus macaques and viruses which partially escape eCD4-Ig in both cases pay clear fitness costs. Adeno-associated virus (AAV)-expressed eCD4-Ig functions as an effective vaccine alternative, and protects rhesus macaques from repeated high-dose viral challenges with both SHIV-AD8 and SIVmac239. Unlike bNAbs and other multispecific antibody-like inhibitors, eCD4-Ig markedly improves the endogenous ADCC activity of patient sera. It does so by altering the conformation of HIV-1 Env, allowing otherwise dormant V3 and CD4i antibodies to bind Env. To determine whether eCD4-Ig could suppress an established infection, six SHIV-AD8-infected rhesus macaques were placed on combined anti-retroviral therapy (ART) 12 weeks after infection and inoculated with AAV-eCD4-Ig 42 to 50 weeks post-infection. ART was subsequently lifted and viral loads and eCD4-Ig concentrations where monitored for now two years. We observed that relatively low concentrations of AAV-expressed eCD4-Ig (3-19 µg/ml) prevent viral rebound of an established SHIV-AD8 infection after ART cessation all six macaques, albeit with sporadic viral 'blips observed in most animals. Macaques "functionally cured" in this manner could provide an ideal platform to monitor the impact of latency-reversing agents on the reservoir of latently infected cells, and to determine if an entry inhibitor with potent ADCC activity can itself change the rate of reservoir decay. Stable HIV-1 remissions may also be appealing and useful to humans, for example limiting transmission from individuals who cannot or will not use conventional ART, enabling long-term drug holidays, and providing a backstop for an imperfect sterilizing cure. Efforts to increase the robustness and consistency of these functional cures will be described.

54 SYPHILIS CAUSES STILLBIRTH: PENICILLIN IS PREVENTION

Melanie Taylor, *WHO, Geneva, Switzerland*

WHO estimates 660,000 cases of mother-to-child transmission of syphilis (congenital syphilis) occurred in 2016, resulting in 350,000 adverse birth outcomes inclusive of over 200,000 stillbirths and neonatal deaths. By comparison, UNAIDS estimates approximately 180,000 new cases of HIV occurred in 2016 among children ages 0-14 years. Although over 90% of countries include screening of pregnant women for syphilis in national antenatal care guidance, efforts to ensure high screening coverage have seen limited improvement, resulting in static estimates of congenital syphilis in the setting of stable or increasing syphilis prevalence among general and high-risk populations of adults. In 2016, WHO estimated 66% coverage of syphilis screening among pregnant women with an estimated global syphilis prevalence in this group of 0.69% (0.70% in 2012).

In 2014, WHO launched the initiative "Elimination of Mother-to-Child Transmission of HIV and syphilis" (EMTCT). While 14 countries have been validated by WHO for this achievement, high burden countries in several regions are challenged to achieve the WHO EMTCT criteria of 95% coverage of antenatal care, syphilis testing and treatment of infected pregnant women with benzathine penicillin. Limited national prioritization and stakeholder engagement have resulted in lower coverage of syphilis screening as compared to HIV screening in pregnant women. Recent global shortages of benzathine penicillin have challenged treatment coverage as this medication is currently the only WHO-recommended treatment for pregnant women with syphilis. Newer technologies including rapid syphilis tests and rapid dual HIV/syphilis tests have offered the opportunity for same-visit testing and treatment of syphilis. The rapid dual HIV/syphilis test offers numerous advantages to separate tests and can be purchased at a similar price to that of a single HIV test. Implementation of the rapid dual HIV/syphilis tests can result in the immediate equalization of syphilis screening coverage to that of HIV among pregnant women. Studies to evaluate alternative treatment regimens for syphilis that could be appropriate for use in pregnant women are underway.

55 CHLAMYDIA AND GONORRHOEA IN PREGNANCY: SILENCE OF THE GERMS

Nicola Low, *University of Bern, Bern, Switzerland*

Sex causes pregnancy, HIV infection and bacterial sexually transmitted infections (STI). Every year, women aged 15-49 years will experience about 63.8 million new infections caused by Chlamydia trachomatis (chlamydia) and 37.1 million caused by Neisseria gonorrhoeae (gonorrhoea). These estimated incidence rates are highest in southern sub-Saharan Africa and Oceania regions and in women under 25 years. About 2.2 million women aged 15-24 years are living with HIV infection and they are at higher risk of chlamydia and gonorrhoea than HIV-uninfected women. Most of these infections are clinically silent and undiagnosed. The high prevalence of STI in pregnant women in some countries could pose risks to the fetus and newborn. Among pregnant women in South Africa, Botswana, Brazil, and Papua New Guinea, chlamydia prevalence of 10-20% has been observed, with gonorrhoea prevalence of 5-10% in South Africa and Papua New Guinea and 1-2% in Botswana and Brazil. Chlamydia and gonorrhoea, when transmitted during labour, can cause neonatal conjunctivitis and chlamydia can cause neonatal pneumonia. During pregnancy, chlamydia and gonorrhoea have also been associated with other adverse outcomes, including preterm birth, premature rupture of membranes, low birth weight and perinatal death. These associations are not consistent, however; they are subject to confounding and biases in selection and measurement. Chlamydia and gonorrhoea in pregnancy do not seem to increase the risk of HIV mother-to-child transmission. Further research is needed to understand the causal role of chlamydia and gonorrhoea at different stages of pregnancy, and to understand biological mechanisms and the role of other co-infections and interactions with the vaginal microbiota. To prevent adverse pregnancy outcomes, robust evaluation of interventions is needed. In a cluster-randomised trial in Rakai, Uganda, presumptive antimicrobial treatment versus syndromic management reduced infection prevalence and several adverse outcomes, but resulted in overtreatment. There are no completed randomised trials of antenatal screening for C. trachomatis and/or N. gonorrhoeae globally. Near-patient molecular diagnostics will make screening in low- and middle-income settings more feasible. A cluster crossover trial in Papua New Guinea comparing near-patient screening with syndromic management will end in December 2020 and planned trials in China, Ethiopia, and South Africa will add to the evidence base.

56 MOTHER-TO-CHILD TRANSMISSION OF HEPATITIS B: CAN IT BE ELIMINATED?

Yusuke Shimakawa, *Institut Pasteur, Paris, France*

Viral hepatitis, the 7th leading cause of death worldwide, is now integrated into the United Nations Sustainable Development Goals. Consequently, the WHO developed a global strategy to eliminate viral hepatitis as a public health threat by 2030, aiming to reduce the incidence of chronic infection with hepatitis B virus (HBV) by 90% and its mortality by 65%. To achieve these elimination goals, it is essential to prevent perinatal mother-to-child transmission (MTCT) of HBV. Compared to horizontal transmission, MTCT is associated with an increased risk of developing chronic HBV infection, and also with an elevated risk of liver disease progression in those who became a chronic carrier. Moreover, a

successful implementation of infant vaccination program over the last decades using a combined vaccine (pentavalent: DTP-hepB-Hib) at 6-10-14 weeks of life effectively prevented horizontal transmission of HBV but not MTCT; this may lead to a change in HBV epidemiology with an increase in the relative contribution of MTCT among new infections. In order to prevent MTCT, the WHO recommends that, in addition to at least two doses of infant vaccine, all neonates should receive the first dose of monovalent hepatitis B vaccine as soon as possible after birth, preferably within 24 hours (birth dose vaccine: HepB-BD). However, this strategy is not well implemented, particularly in sub-Saharan Africa, because many African countries have not yet integrated HepB-BD in the national immunization program. Moreover, even the countries that started HepB-BD face logistical challenges for its timely administration due to high frequency of child birth outside health facilities. Recently, there is accumulating evidence, particularly from Asia, suggesting the efficacy and safety of peripartum antiviral prophylaxis using nucleos(t)ide analogues in pregnant women with high HBV DNA levels, in addition to neonatal immunoprophylaxis with HepB-BD and hepatitis B immune globulin (HBIG). This additional strategy, combined with high HepB-BD coverage, may certainly accelerate the elimination of HBV MTCT, if these evidence-based interventions are carefully tailored to women living in low- and middle-income countries where the access to HBV DNA test or HBIG is still severely limited.

57 BEYOND THE STIGMA: A SORELY NEEDED PERSPECTIVE ON HSV

Anna Wald, *University of Washington, Seattle, WA, USA*

HSV-1 and 2 infections are common across the globe with recent prevalence estimates of 3709 million cases of HSV-1 (including 140 million cases of genital HSV-1 infection) and 417 million cases of HSV-2 infection. Women are at higher risk and acquire HSV-2 at a younger age than men. Prevalent HSV-2 increases risk of HIV acquisition 2-3 fold. An estimated 14,000 infants contract neonatal HSV infection each year, a frequently fatal disease. The risk of transmission to the newborn is highest if a woman acquires genital herpes toward the end of pregnancy. Current standard of care is to treat women with recurrent genital herpes with suppressive antivirals toward the end of pregnancy; although this approach may reduce cesarean sections, it has had no effect on the incidence of neonatal herpes. The risk of neonatal herpes in infants born to women with established infection is very low. Implementation of control strategies is hampered by lack of evidence-based interventions. Patient management is limited by lack of commercial accurate serologic assays; only partial effectiveness of antiviral for HSV in reducing the risk for sexual transmission, and persistent stigma associated with this infection. While resistance to currently available therapies occurs almost exclusively among immunocompromised patients, alternative therapies for such patients are inadequate and no new drugs have been developed for several decades. A number of vaccines are in development, mostly aimed at therapeutic use. Lack of knowledge about immune correlates of protection complicates the evaluation of candidate vaccine products. However, elimination of HSV infections is likely to be achieved only through prophylactic immunization.

58 REFLECTIONS ON THE UK EPIDEMIC

Valerie Delpech, *Public Health England, London, UK*

For the third year running, reports of new HIV diagnoses among men and women fell dramatically in the England largely driven by a decline in new diagnoses among gay, bisexual and other men who have sex with men (GBM) residing in London. A CD4 back-calculation model indicates that transmission among GBM has fallen since 2012 – from 2,800 new infections (95% credible interval (CrI) 2,600 to 3,000) that year, to 800 (CrI 500 to 1,400) in 2018 (a 71% drop). Over this period the estimated number of GBM with undiagnosed infection more than halved to 3,600 – with an overall prevalence of 88 per 1,000. In contrast the prevalence of HIV among men and women who acquired HIV heterosexually is overall low (1.1 per 1,000) and greater among black Africans (36 per 1,000). Furthermore, in 2018 about two-thirds of heterosexuals diagnosed were born abroad and half probably acquired HIV abroad. Overall an estimated 3,200 heterosexuals were unaware of their infection in 2018, the majority were women.

The fall in transmission is a success story of combination prevention in the making. Universal and free access to testing and treatment to all citizens is at the core of this success, together with a dedicated HIV sector. Targeted prevention and testing began early in the response. Substantial increases in testing across all groups occurred in the past decade. HIV tests by GBM at STI clinics increased from 61,000 to 165,000 and a doubling of repeat testers to over 40,000.

Treatment guidelines have recommended the early initiation of treatment since 2015. By 2018, >80% of people newly diagnosed begin treatment within 3 months (regardless of gender or sexuality) compared to 53% in 2014. The proportion reaches 90% in certain high throughput clinics in London. Test and Treat strategies have led to the exceedance of the UNAIDS 90:90:90 target across all populations (these were 93:97:97 in 2018).

Scaling up of PrEP is relatively recent with informal use since 2015. By 2018 over 15,000 GBM were receiving PrEP through an STI clinic across England - with demand outstripping supply (uptake among other higher-risk persons remains very low). The expected introduction of a large-scale national PrEP programme is likely to accelerate the decline in HIV incidence provided test and treat strategies are sustained at high levels for all communities.

59 30-PLUS YEARS OF HIV IN RAKAI: THE EPIDEMIC RECEDES

Joseph Kagaayi, *Rakai Health Sciences Program, Kalisizo, Uganda*

HIV was first documented in Rakai, Uganda in the early 1980s. For over 30 years, the Rakai Health Sciences Program (RHSP) tracked the epidemic, and in 1994, established the Rakai Community Cohort Study (RCCS) among 10,000-20,000 residents ages 15-49 residing in agrarian/trading communities. In 2011, hyper-endemic fishing communities were added. A trial of sexually transmitted infection control for HIV prevention (1994-1999), nested in the RCCS, did not reduce HIV incidence. However, secondary data analyses showed that higher viral load (VL), early and late stages of HIV infection, and uncircumcised men were key drivers of the epidemic. The protective effect of safe male circumcision (SMC) was later confirmed in three trials, one of which was nested in the RCCS. Reduction of VL with ART became the basis for treatment-as-prevention. Since 2004, with PEPFAR/CDC-Uganda support, RHSP has scaled-up combination HIV interventions (CHI). RHSP now leads implementation in 12 districts, overseeing 161 clinics with over 110,000 persons on ART and over 250,000 circumcisions to-date. Recently, we evaluated trends in SMC and ART coverage, VL suppression, sexual behaviors, and HIV incidence and prevalence in 30 agrarian/trading and four fishing communities. In agrarian/trading communities, HIV prevalence was 15.9% in 1994 and incidence was 1.5/100 person-years. Between 2004-2016, ART coverage rose from 0% to 69%; VL suppression rose to 75%; SMC coverage increased from 15% to 59%. Except for delayed sexual debut among adolescents (15-19), we did not observe other changes in sexual behaviors. Between 2004 and 2016, HIV incidence declined by 42% (1.17 to 0.66/ 100 person-years) while prevalence remained relatively stable. In fishing communities, ART coverage increased from 16% to 82%; VL suppression rose from 34% to 80% and SMC increased from 35% to 65% between 2011 and 2016. HIV incidence declined by 48% (3.43 to 1.59/100 person-years). Despite these reductions, HIV incidence remains above epidemic control rates. Ongoing epidemiological/phylogenetic studies in the RCCS suggest that in-migration and hard-to-reach persons contribute to ongoing transmissions. In conclusion, CHI reduced HIV incidence, but challenges remain. The RCCS has proved invaluable for discovery, intervention testing, and evaluation of real-world impact on HIV incidence. By combining research with intervention delivery, each informing the other, RHSP been able to translate science into population-level impact.

60 BATTLING HIV IN THE US RURAL SOUTH

Leandro A. Mena, *University of Mississippi Medical Center, Jackson, MS, USA*

The South's disproportionate burden of HIV and health care disparities is driven in part by many socioeconomic, cultural and structural factors. This talk will describe challenges to HIV prevention and care especially in the rural South as well as promising strategies aiming to promote equitable access to HIV services throughout the region.

61 HOW DO WE STOP THE BAND FROM PLAYING ON IN THE US?

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

Concerted efforts and significant investments in HIV prevention and care resulted in a 69% decline in mortality and a 48% reduction in new diagnoses in the US since the mid-1990s. However, despite over $20B of Federal funding in domestic HIV efforts, new diagnoses have stabilized at about 38,000 for nearly a decade, down only 7.0% from 2012. The US epidemic is not a national epidemic but rather a collection of microepidemics disproportionately affecting racial/ethnic and sexual minorities with 43% of new diagnoses among Blacks, 69% attributed to male-to-male sexual contact and 52% occurring in the Southern

States. If current rates persist, 41% of black MSM and 22% of Hispanic MSM in the US will be diagnosed with HIV during their lifetimes. On February 5, 2019, at the State of the Union Address, the President announced the intention to End the HIV epidemic in the US by reducing new infections by 75% within 5 years and by 90% within 10 years. To reach these goals, the Department of Health and Human Services is proposing to target 48 counties plus Washington, DC and San Juan, Puerto Rico plus 7 Southern States that together comprise 50% of new HIV diagnoses. What will it take for this plan to be successful? We have the tools but fundamental differences in access to health care, local legislation, as well as racism, structural stigma, homelessness, and HIV laws/policies that will make implementation challenging.

62 PREVENTING HIV AMONG PEOPLE WHO INJECT DRUGS: PLUS ÇA CHANGE, PLUS ÇA MÊME CHOSE

Steffanie A. Strathdee, *University of California San Diego, San Diego, CA, USA*

In 1997, I presented at CROI on a new HIV outbreak that I helped identify among people who inject drugs (PWID) in Vancouver, Canada, where HIV incidence peaked at 18.6 per 100 person years. The response was to expand needle exchange programs (NEPs), medication for opioid use disorder (MOUD) and mobile HIV testing. Later, Vancouver opened North America's first supervised injection facility (SIF) and adopted a policy of HIV treatment as prevention (TasP). HIV incidence among PWID plummeted and no social harms associated with its NEP or SIF were documented. In contrast, except for a 2-year period, US Congressional law prevented the use of federal funds to support NEPs until 2015. The US is now in the midst of its most serious opioid epidemic with several injection drug use-associated HIV outbreaks, over 40,000 new HCV infections each year and co-occurring epidemics of overdose, endocarditis and syphilis. What has been done to prevent HIV outbreaks among PWID? This presentation will identify missed opportunities and in some cases, progress made to prevent HIV outbreaks in rural settings. For example, a modeling study estimated that if Scott County, IN had launched an earlier response, 200 HIV infections could have been prevented. In W.Virginia, ongoing HIV outbreaks in Huntington and Charleston are exacerbated by restrictions and/or closure of NEPs and an effort to make them illegal, alongside a moratorium on new methadone programs. In these and other U.S. states, structural barriers to accessing MOUD are the rule rather than the exception, although innovations like hospital-based MOUD programs show promise. Across the U.S, only one (underground) SIF exists. As we approach the 4th decade of the HIV pandemic, we know how HIV is transmitted among PWID and their networks. A plethora of scientific evidence shows that harm reduction programs can avert HIV epidemics. Yet at the federal level, most funding from the U.S. Office of National Drug Control Policy is spent on law enforcement/interdiction and little on prevention of drug use, which could have important downstream effects. Preventing HIV and co-occurring syndemics among PWID necessitates addressing the structural drivers of addiction including homelessness, unemployment, lack of health insurance and cycles of incarceration. The US needs to abandon its war on people who use drugs and treat addiction as a medical condition rather than a moral failing

63 SEX DIFFERENCES IN HIV

Eileen P. Scully, *Johns Hopkins University School of Medicine, Baltimore, MD, USA*

Biological sex confers specific immunologic advantages and challenges to both men and women. These differences lead to distinct patterns of immune responses and differing susceptibility to infections and to autoimmune and inflammatory pathology. There are data demonstrating sex-specific features of HIV acquisition, pathogenesis and the dynamics of the HIV reservoir, but many open questions remain. Despite the high burden of HIV infection among women, estimated at more than 50% of adults in 2018, enrollment of both cis and transgender women in clinical trials and basic research cohorts has been variable. In some domains, a notable lack of representation undermines the confidence that the data can be applied to all people living with HIV infection. However, sex differences represent a rich source for discovery. A comparative biology approach can leverage differences in immune responses and viral control to highlight pathways critical for vaccine development, cure interventions, or prevention of inflammatory comorbidity for both men and women. This same lens can be used to better understand the health risks and specific clinical needs for transgender men and women. Further, insuring that interventions are efficacious in women as well as men is essential to achieve the global goals for prevention, treatment and reduction in morbidity. To address these questions, both women and men must be enrolled in studies and the impact of both sex and gender assessed. This mandate to study both sexes is compelling from a scientific rigor and discovery perspective, and also meets our ethical responsibility to insure our innovations will work for all people living with HIV.

64 TARGETING THE KSHV TYROSINE KINASE AND VIRAL LYTIC REACTIVATION WITH INHIBITORS

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Background: Kaposi's Sarcoma-associated herpesvirus (KSHV) is the cause of three human malignancies, Kaposi's Sarcoma, Primary Effusion Lymphoma and the plasma cell variant of Multicentric Castleman's Disease. Previous research has shown that several cellular tyrosine kinases play crucial roles during several steps in the virus replication cycle. Two KSHV proteins also have protein kinase function: open reading frame (ORF) 36 encodes a serin-threonine kinase, while ORF21 encodes a thymidine kinase (TK), which has recently been found to be an efficient tyrosine kinase.

Methods: In vitro kinase assays, virus replication assays, construction of recombinant KSHV mutants with a kinase-deficient orf21 gene, virus inhibition assays, in vivo endothelial tumor formation assays

Results: In this study, we explore the role of the ORF21 tyrosine kinase function in KSHV lytic replication. By generating a recombinant KSHV mutant with an enzymatically inactive ORF21 protein we show that the tyrosine kinase function of ORF21/TK is not required for the progression of the lytic replication in tissue culture, but that it is essential for the phosphorylation and activation to toxic moieties of the antiviral drugs zidovudine and brivudine. In addition, we identify several tyrosine kinase inhibitors, approved for clinical use against human malignancies, which potently inhibit not only ORF21 TK kinase function, but also viral lytic reactivation and the development of KSHV-infected endothelial tumors in mice. The most potent inhibitors of KSHV TK autophosphorylation, KSHV reactivation and KSHV-dependent tumor formation in a xenograt model were dasatinib, ibrutinib and ponatinib.

Conclusion: Since the identified kinase inhibitors target both cellular tyrosine kinases supporting productive viral replication and the KSHV tyrosine kinase, these drugs (dasatinib, ibrutinib, ponatinib), which are already approved for clinical use, may be suitable for repurposing for the treatment of KSHV-related tumors in AIDS patients or transplant recipients.

65LB A ROLE FOR IRON METABOLISM AND FERROPTOSIS IN KAPOSI SARCOMA HERPESVIRUS PATHOGENESIS

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Background: Iron is an essential element for normal cellular function, and many tumor cells satisfy their high iron requirement via altered expression of proteins that regulate iron metabolism. While iron fuels tumor growth, it presents a paradox: how to maintain redox homeostasis and resist ferroptosis, a ROS-reliant and iron-dependent form of regulated cell death. Many tumor types resist the ferroptotic cascade via increased expression/activity of antioxidant ferroptosis suppressor pathways (FSPs). To date, two complementary but non-redundant pathways have been identified: a canonical glutathione (GSH)-dependent pathway and, more recently, a novel FSP that relies on ubiquinol (the reduced form of CoQ) to prevent lethal lipid peroxidation. Our goal is to determine how the oncogenic Kaposi sarcoma herpesvirus (KSHV) manipulates host iron metabolism and antioxidant defense to promote Kaposi sarcoma (KS) tumorigenesis while resisting ferroptosis.

Methods: Lymphatic endothelial cells (LEC) de novo-infected with KSHV-BAC16 were used for this study. Expression of host genes involved in iron metabolism and ferroptosis resistance was evaluated by RNA-seq, qPCR, immunoblot, FACS and IFA. Cellular iron content was measured by ICP-MS. Markers of pro/antioxidant status (e.g., ROS, GSH) were measured via quantitative colorimetric assay. Susceptibility to ferroptosis was evaluated using selective inducers and inhibitors, and measured via cell viability and lipid peroxidation assays.

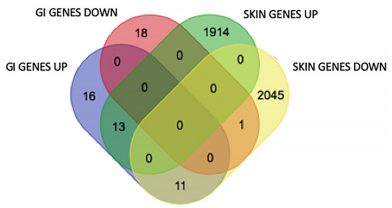
Results: Our data indicate that KSHV manipulates the host iron regulon to promote iron acquisition and an iron-responsive growth phenotype. However, despite these changes, infected cells do not succumb to ferroptosis. Notably, KSHV significantly upregulates the expression of xCT, the small subunit of system xc- that functions as the upstream node of the GSH-dependent FSP.

Chemical inhibition of xCT induces ferroptotic death only in KSHV-infected LEC, suggesting that enhanced xCT function is central to the ability of infected cells to resist ferroptosis. KSHV also upregulates the oxidoreductase FSP1 (formerly AIFM2), the key component of the novel CoQ-dependent FSP, identifying a second ferroptosis escape mechanism in infected cells.
Conclusion: We have identified unique vulnerabilities in KSHV-infected cells that reflect the delicate pro/antioxidant balance required to facilitate growth and survival. Our work suggests that selective induction of ferroptosis in KSHV-infected cells represents a promising anti-KS strategy.

66 GENE EXPRESSION PATTERNS IN SKIN VS GASTROINTESTINAL KAPOSI SARCOMA LESIONS

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Background: Kaposi sarcoma (KS), caused by Kaposi sarcoma herpesvirus (KSHV), is a multicentric tumor characterized by abnormal vasculature and proliferation of KSHV-infected spindle cells. KS involves the skin (sk) but can also affect the gastrointestinal tract (gi) in severe cases. Little is known about host and viral gene expression differences in patients with KS lesions. Here, we performed RNA sequencing of sk and gi KS lesions from HIV+ patients with KS to understand the similarities and differences in the gene expression pattern.
Methods: We obtained fresh sk and gi KS lesions with matched normal sk and gi samples. Total RNA was extracted from samples and RNA expression was analyzed using paired-end RNA-Seq. Differential gene expression was measured by comparing KS lesions to normal matched samples. We used programs STAR and DESeq2 to identify differentially expressed genes with a False Discovery Rate cut-off of 0.05.
Results: Six samples were obtained (sk (4) and gi (2)) from 5 HIV+ patients with KS. All tumors were stage T1. Only 2 pts had received prior KS therapy. In sk KS, cellular gene networks associated with cell adhesion (extracellular matrix), immune response, angiogenesis, and proteolysis were dysregulated when compared with normal skin. There were 13 cellular genes increased in both sk and gi KS lesions (Figure 1). Of these genes those that were clinically significant included FLT4 , which encodes for a receptor of VEGF-C and VEGF-D, and RIOX1, a histone demethylase and potential independent prognostic factor for venous invasion and lymphatic duct invasion in colon cancer. The most expressed viral genes were a mixture of latent and lytic genes in sk KS samples. There were more lytic viral genes detected in gi KS as compared to sk KS, which may be due to more advanced KS or a difference in lytic activation in gi tissues. One patient had both sk and gi KS (with matched normal samples), which demonstrated 19 genes that were strongly increased in both tissues and included cellular genes ADAMTS4, RIOX1, ACAN.
Conclusion: This is one of the first studies comparing sk and gi KS that highlights differences in viral gene and clinically relevant host gene expression between these tissues. By analyzing these gene expression patterns, this ongoing study will improve our understanding of KS pathogenesis.



67LB IMPACT OF VALGANCICLOVIR THERAPY ON SEVERE IRIS–KAPOSI SARCOMA–ATTRIBUTABLE MORTALITY

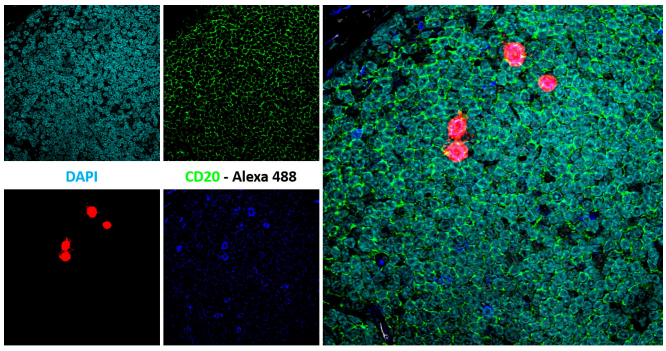
Patricia Volkow[1], Beda Daniela Islas Muñoz[1], Leslie Chávez-Galán[2], Lucero Ramón-Luing[2], Dora Patricia Cornejo Juárez[1], Judith Cruz-Velázquez[1], for the Kaposi Sarcoma
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Background: High HHV-8 viral load (VL) has been associated with severe Kaposi sarcoma (S-KS). KS Immune reconstitution inflammatory syndrome (IRIS) can occur in patients after starting cART with associated high mortality. Ganciclovir has anti-HHV8 activity. Our objective was to investigate if valganciclovir started before cART could diminish HHV-8-VL and reduce the incidence of S-KS-IRIS and its atributable mortality.
Methods: ORCT (Clincal Trials NIH ID NCT03296553) of patients with disseminated KS (DKS), approved by IRB, participants signed informed consent. Inclusion criteria: AIDS cART naïve patients with at least two of the following: pulmonary disease, 30 skin lesions, lymphedema, lymph node involvement, GIT involvement. Exclusion criteria: other malignant disease, steroid treatment, active Hepatitis B or C, CMV end-organ disease; and APACHE >15. S-IRIS-KS definition: abrupt clinical exacerbation of KS after starting cART and at least 3 of the following parameters: thrombocytopenia, anemia, hyponatremia, hypoalbuminemia or fever. Experimental group (EG) started valganciclovir 900 mg BID 4 weeks before cART and continued until week 48; control group (CG) started cART at week 0. Treating physician determined Vincristine/Bleomycin administration. Scheduled visits: weeks 0,1,2,4,8,12,16,24, and 48. In each visit HIV-VL, HHV-8 VL (ELITe M GB KIT) CD4 and CD8 count by flow cytometry.
Results: 38 patients were randomized, 19 in each group; one patient stopped valganciclovir and was excluded. Three patients died due to S-IRIS-KS in the CG, two died in the EG (opiod overdose and H1NI pneumonia). Four patients developed 12 episodes of S-IRIS-KS in the CG (IR of 0.21 per/100 patient-days), two patients, one episode each in the EG (IR 0.038 per/100 patient-days) p=0.007. In multivariate poisson or negative binomial models, higher-baseline CD4 decreased and higher HHV8-VL increased consistently the risk of S-IRIS-KS; Valganciclovir treatment reduced S-SIRI-KS events (IRR= 0.06, 95%CI 0.004-0.7 p=0.024) and the number of patients with at least one S-IRIS-KS episode (, IRR 0.24, 95%CI 0.03, 2.27, p= 0.21).
Conclusion: Valganciclovir reduced episodes of S-IRIS-KS and its attributable mortality. Measurement of HHV-8 VL may be important in the clinical care of DKS.

68 SURVEILLANCE OF RHESUS MACAQUE TISSUES IDENTIFYING GAMMAHERPESVIRUS INFECTION SITES

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Background: Gammaherpesviruses are a clinically significant cause of cancer and are primarily transmitted via saliva. However, the specific sites of viral replication in oral tissues resulting in salivary shedding are poorly understood. Rhesus macaques (RM) are naturally infected with three gammaherpesviruses: retroperitoneal fibromatosis herpesvirus (RFHV), an ortholog of KSHV, rhesus lymphocryptovirus (RLCV), closely related to EBV, and rhesus rhadinovirus (RRV). Rhesus macaques have been used as models of gammaherpesvirus-associated malignancies in the context of SHIV/SIV infection and offer an opportunity to study oral biology of gammaherpesviruses in greater detail.
Methods: Oral fluid and oral tissues from 30 RM experimentally infected with SIV or not were collected during necropsy. These included buccal and gingival tissue, parotid, submandibular and sublingual salivary glands, submandibular lymph nodes, adenoid, palatine and inguinal tonsil, soft palate and tongue. DNA was extracted and tested by qPCR for RRV, RLCV, and RFHV viral load. In situ hybridization targeting viral DNA was performed, for all 3 viruses, in all tissue types and highly positive tissues were used to phenotype the cells harboring viral DNA.
Results: Rhesus gammaherpesviruses were detected in the oral fluid and oral tissues of all 30 animals examined; many were positive for more than one virus. By qPCR, the highest levels of RFHV were identified in gingiva, tongue, and submandibular lymph nodes while the highest levels of RLCV and RRV were detected in adenoid and palatine tonsil. Using ISH, most infection events for all three viruses were visualized in lymphoid tissues including lymph node and palatine tonsil. Multiplexing ISH with antibody-based phenotyping revealed a broad range of infected cell types including B- and T-lymphocytes, fibroblasts, epithelial cells, and NK-cells. Certain infected cell types, especially for RFHV, remain unidentified and phenotyping experiments are ongoing.
Conclusion: This is the first study examining RRV, RLCV, and RFHV viral load in rhesus oral tissues and oral fluid and may provide insights into human gammaherpesvirus biology within the oral compartment.



Mandibular Lymph node of an SIVmac239 Acute-Infected *Rhesus macaque* showing next generation *in situ hybridization*, RNAscope, targeting EBV homolog RLCV viral DNA(Cyanine 3.5, red) and immunofluorescent multiplexing with CD20 (Alexa 488, green) and FSP1 (Alexa 647, far-red or blue), and nuclear counterstain DAPI (light blue). Composite image indicates RLCV infection of FSP1+ fibroblasts.

69 CONJUNCTIVAL CANCER IN PEOPLE LIVING WITH HIV: THE SAM STUDY

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Background: Conjunctival cancer has been associated with HIV in sub-Saharan Africa but, the evidence on its epidemiology is scarce. According to the 2014 National Cancer Registry (NCR) report, the incidence of eye cancer was 1.13 and 1.25 per 100 000 of the population in males and females respectively. We aimed to determine the incidence of conjunctival cancer amongst people living with HIV (PLWHIV) and the associated risk factors.

Methods: The South African HIV Cancer Match (SAM) study used privacy preserving record linkage to create a large cohort of cancer in PLWHIV from national laboratory and NCR data 2004-2014. We used the ICD-0-3 coding to identify conjunctival cancers. We calculated crude incidence rates of conjunctival cancer and used Cox regression to obtain hazard ratios (HR) of CD4 cell count, age, sex and calendar period, stratified by province.

Results: Over 12 547 950 person-years of follow-up, 1 359 incident conjunctival cancer cases were diagnosed in the SA cohort of 4 766 614 PLWHIV. Approximately 94% (n=1 274) of conjunctival cancers were squamous cell carcinomas. The median age at entry into the cohort was 33 years (Interquartile Range [IQR]: 26-41 years) and 38 years (IQR: 33-44 years) at cancer diagnosis. The median CD4 cell count at baseline was 294 cells/µl (IQR: 159-467 cells/µl). There was an upward trend in CD4 cell counts across the years from a median of 240 cells/µl in 2004 to 340 cells/µl in 2014. The crude conjunctival cancer IR was 11.0 per 100 000 person-years (95% Confidence Interval [CI]: 10.2-11.4). Being male, lower CD4 cell count, earlier calendar period and older age were all associated with higher rates of conjunctival cancer (Table 1).

Conclusion: To our knowledge, this is the largest epidemiological study of conjunctival cancer in PLWHIV ever done. Our results indicate that immunodeficiency as indexed by lower CD4 counts, immune senescence and prolonged UV light exposure (both indexed by age) are strongly associated with conjunctival cancer risk. The decrease in incidence in more recent calendar periods might reflect increased ART coverage across time and initiation of ART at higher CD4 cell counts. Our analysis suggests that effective HIV control is essential for the prevention of conjunctival cancers. We recommend symptom screening and communication of conjunctiva cancer risk to PLWHIV as well as their clinicians

Table 1: Crude incidence rates of conjunctival cancer per 100,000 person-years and hazard ratios from multivariable Cox regression model

	No. of Conjunctival cancer cases	Incidence rate (95% CI)	Hazard ratio (95% CI)
First CD4 count [cells/µL]			
<=200	784	19.8 (18.5-21.2)	1
201-350	327	9.48 (8.50-10.6)	0.54 (0.48-0.62)
350-500	133	5.60 (4.72-6.63)	0.35 (0.29-0.42)
>=501	112	4.18 (3.47-5.03)	0.31 (0.25-0.38)
Calendar period			
2004-2006	455	17.0 (15.5-18.6)	1
2007-2010	636	9.58 (8.87-10.4)	0.65 (0.57-0.75)
2011-2014	265	8.26 (7.33-9.32)	0.73 (0.61-0.87)
Age category [years]			
0-9	1	0.16 (0.02-1.15)	0.02 (0.00-0.13)
10-19	6	1.25 (0.56-2.77)	0.12 (0.06-0.28)
20-29	263	7.24 (6.42-8.16)	0.60 (0.52-0.69)
30-39	641	14.4 (13.3-15.5)	1
40-49	338	14.7 (13.2-16.3)	0.98 (0.86-1.12)
50-59	86	10.4 (8.44-12.9)	0.71 (0.57-0.89)
60+	19	10.3 (6.56-16.1)	0.74 (0.47-1.16)
Sex			
Female	461	9.98 (9.34-10.6)	1
Male	895	13.0 (11.9-14.3)	1.13 (1.01-1.27)

* adjusted for CD4 cell count, calendar period, age and sex. Stratified by province of first HIV test
*Incidence rates per 100 000 person-years

70 CLEARANCE OF HPV ANAL HIGH-GRADE INTRAEPITHELIAL LESIONS WITH LOW-DOSE POMALIDOMIDE

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Background: People with HIV (PLWH) have an increased risk of anal cancer. This is preceded by high-grade squamous intraepithelial lesions (HSIL). Spontaneous clearance of HSIL is associated with systemic T-cell response to human papillomavirus (HPV) oncogene E6. Pomalidomide may enhance immune responses to HPV and be therapeutic in HSIL.

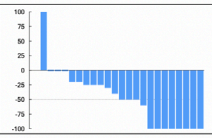
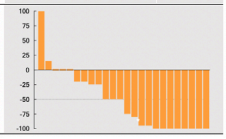
Methods: This phase II single centre study (NCT3113942) recruited participants with persistent (>12 months) biopsy-proven anal HSIL. Therapy was oral pomalidomide 2mg 21/28 days for 6 months. PLWH were eligible if on ART with viral load (VL)<200 copies/mL and CD4 count >200 cells/µL. Primary outcome was response at end therapy (CR defined as histological clearance; PR as ≥50% reduction in area); secondary included response after a further 6 months without therapy. Immune activation was assessed by flow cytometry. Antigen-specific CD4+ T-cell responses to HPV16 E6 and E7 were assessed by OX40 assay.

Results: 26 participants enrolled, 24 evaluable for response. All male; median age 54 (range 41-74). 10 (38%) PLWH: median CD4 700 cells/uL (320-1070), all HIV VL <20 copies/mL. All AIN3 HSIL, median duration HSIL 37 months (15-86), median octants 2 (0.5-5); HPV16 in 55%; multiple high risk HPV types in 50%. Overall response (CR+PR) was 52% (CI: 31-73) at end therapy, increasing to 63% (95% CI 40-81) after 6 months observation. Responses were comparable in PLWH.

Adverse events (AEs) were mild and self-limited, including cytopenias, constipation, rash, with no idiosyncratic AEs in PLWH. HIV suppression was maintained. Over 137 cycles (c), attributable grade (g) 3/4 events were g3 neutropenia (4c) and g3 angina (1c).

Systemic CD4+ T-cell responses to HPV E6 but not E7 increased during therapy, peaking day 14: baseline 0.06%, IQR 0.01 – 0.12%), median increase day 14 0.13% (IQR: 0.02 – 0.26%), p=0.001. CD4+ and CD8+ cell activation (CD38, HLA DR, CD38+HLA-DR) increased during therapy.

Conclusion: Low dose pomalidomide was well tolerated and induced durable continuing clearance of anal HSIL of multiple genotypes in even in chronic extensive disease irrespective of HIV status. Induction of HPV-specific CD4+ responses and immune activation support an immunological mechanism of action.

		Immediately Following Therapy (Primary Endpoint)			Six Months Following Completion of Therapy		
	Enrolled (Assessable)	Overall Response	Complete Response	Partial Response	Overall Response	Complete Response	Partial Response
Combined	26 (24)	12 (52%, 95%CI 31-73)	8 (35%)	4 (17%)	15 (63%, 95%CI 40-81)	8 (33%)	7 (29%)
HIV negative	16 (15)	7 (50%, 95%CI 23-77)	4 (29%)	3 (21%)	9 (60%, 95%CI 32-84)	5 (33%)	4 (44%)
HIV positive	10 (9)	5 (56%, 95%CI 21-86)	4 (44%)	1 (11%)	6 (67%, 95%CI 30-92)	3 (33%)	3 (33%)
Percent Change In Involved Area From Baseline	26 (24)						

71 INCREASED CANCER RISK WITH LOWER CD4/CD8 RATIO AMONG ADULTS WITH HIV IN NA-ACCORD

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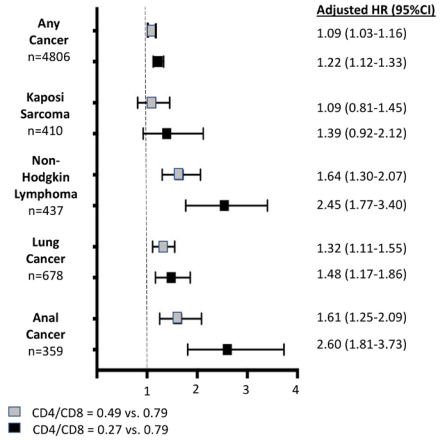
Background: Persons living with HIV (PLWH) are at increased risk for a number of cancers. Altered immunity is one proposed mechanism driving this excess risk of cancer. Low CD4/CD8 ratio in treated PLWH is associated with immune senescence, activation, and inflammation which may contribute to carcinogenesis. However, there is no clinical consensus of which ratio values that best predict cancer risk. This study examined whether low CD4/CD8 ratio predicted cancer risk (excluding non-melanoma skin cancer (NMSC)) in the North America AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

Methods: Adults without a history of any cancer (excluding NMSC) prior to cohort entry and with ≥1 CD4/CD8 value in 12 NA-ACCORD cohorts between 1998-2016 were included. Cancer outcomes were validated in each cohort. Risk of cancer and 6-month-lagged CD4/CD8 ratio were evaluated in multivariable, time-updated Cox proportional hazard models adjusting for age, sex, race, hepatitis C virus coinfection, lagged CD4 count (cells/mL) and lagged, log-transformed HIV RNA (copies/mL). Models for any and for specific cancers were censored at earliest occurrence of death, other cancer diagnoses, loss to follow-up (gap in care ≥ 1.5 years), end of cohort observation period or December 31, 2016. Observation time was censored during periods of missing laboratory data. Continuous variables, including CD4/CD8, were modeled using restricted cubic splines with 4 knots.

Results: Among 75,161 PLWH, there were 5046 incident cancer diagnoses. Most frequent cancers were lung cancer (n=714), non-Hodgkin lymphoma (NHL, n=459), Kaposi sarcoma (KS, n=440), and anal cancer (n=375). Median age at cohort entry was 43 years, 90% were male, and 44% were white. The median CD4/CD8 ratio during the observation period was 0.49 (interquartile range: 0.27-0.79). Adjusted hazard ratios for CD4/CD8 ratio and any cancer and specific cancers are shown in the Figure. For any cancer and specific cancers, non-linear CD4/CD8 ratio was inversely associated with cancer risk in adjusted models ($p<0.001$).

Conclusion: Low CD4/CD8 ratio was consistently associated with increased cancer risk, independent of CD4 count and HIV RNA. Further research into the causes of CD8 cell inflation and persistent immunologic disturbance in PLWH is needed. CD4/CD8 ratio may serve as useful clinical biomarker for cancer risk in PLWH.

Figure: Hazard ratios for 50th and 25th compared to 75th percentile of the 6-month lagged CD4/CD8 ratio for all cancers and for specific cancers, adjusting for sex, race, age, hepatitis C virus coinfection, lagged CD4 cell count, and lagged HIV RNA, stratified for cohort.



72 WHOLE-BODY PET IMAGING OF THE HIV RESERVOIR USING RADIOLABELED VRC01

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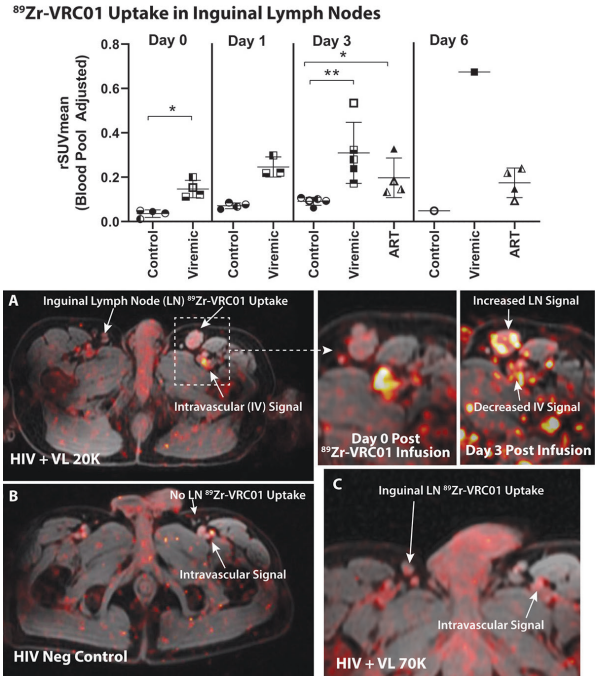
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Background: HIV largely resides in anatomical regions that are inaccessible to routine sampling, and non-invasive methods to understand the tissue-wide burden of HIV are urgently needed. We report on the first-in-human PET-magnetic resonance (MR) imaging studies of HIV infection using a radiolabeled HIV Env-specific mAb, 89Zr-VRC01.

Methods: PET-MR imaging using 89Zr-VRC01 ($t_{1/2}$=73h) was performed on 5 viremic participants (plasma HIV-1 RNA ranging from 3,459 to 789,705 c/mL), 4 ART-suppressed participants (duration of ART ranging from 3.5 to 280 months), and 5 uninfected controls. PET-MR imaging was performed 2h, 6h, 24h, 72h (day 3), and, in a subgroup of 6 participants, 132h (day 6) following a single 1 mCi injection of 89Zr-VRC01. Radiotracer maximum and mean standard uptake values (SUVmax, SUVmean) adjusted for blood pool background signal were quantified for various lymphoid and other anatomical regions of interest.

Results: Adjusted 89Zr-VRC01 SUVs were significantly higher in inguinal and axillary lymph nodes, nasal-associated lymphoid tissue (NALT), and bone marrow in viremic participants compared with uninfected controls (all $P<0.05$). SUVmax/mean (NALT, bone marrow) and SUVmean (inguinal lymph node) were significantly higher in ART-suppressed individuals compared with uninfected controls, and generally lower than in viremic participants. The greatest differences between SUVs in HIV-infected and control participants were observed 72h after tracer injection, although differences in tracer uptake in inguinal lymph node tissue were observed up to 6 days following tracer injection (Figure). 89Zr-VRC01 inguinal lymph node SUVmax in viremic and ART-suppressed participants positively correlated with the frequency of p24 expressing cells measured by flow cytometry in fine needle aspirates ($p=0.017$). 89Zr-VRC01 tracer uptake in lymphoid tissues was lower in participants who were on suppressive ART for longer periods of time.

Conclusion: HIV envelope-specific PET imaging was able to detect differences between HIV-infected individuals, including those on suppressive ART, and uninfected participants. Importantly, PET tracer uptake correlated with measures of HIV protein expression in tissue. These data suggest that PET imaging of HIV-infected cells has the potential to localize and quantify multiple anatomical HIV reservoirs in a wide range of HIV persistence and curative studies.



73 ANTIGEN-DRIVEN CLONAL SELECTION SHAPES THE FATE OF HIV-INFECTED CD4+ T CELLS IN VIVO

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Background: Although proliferation of infected CD4+ T-cells is a major mechanism of HIV persistence, the causes of this phenomenon remain unclear. We hypothesized that recurrent antigenic exposure contributes, via clonal selection, to the expansion and maintenance of HIV-infected cells.
Methods: We enrolled 10 HIV+/CMV+ donors on ART. PBMC were briefly stimulated with CMV lysates, GAG peptides or αCD3/28 antibodies. We sorted responding (CD40L+CD69+) and non-responding memory (CD40L-CD69-CD45ROhi) CD4+ T-cells. Single genome sequencing was used to identify identical proviruses. To study HIV-infected clones, we sorted cells in small pools at limiting dilutions and subjected to whole genome amplification. Proviruses in Ag-specific clones were analyzed by IPDA, integration site and full-length sequencing. We used TCR sequencing to study VDJ rearrangements in sorted cells and infected clones. A viral outgrowth assay (VOA) was used in one donor to identify clones carrying infectious proviruses.
Results: PBMC stimulation yielded the expected frequencies of CMV- and GAG-specific CD4+ T-cells (mean 2.8% and 1.1%, respectively). Cells responding to non-specific CD3/28 stimulation (mean 33%) were used as a control. Proviruses in CMV-specific cells showed a higher proportion of identical sequences (0.73 vs 0.28, p<0.0001) and higher clonality (mean Gini 0.6 vs 0.2, p=0.0002) than the non-specific control. GAG-specific cells had detectable but less abundant identical sequences. Clonal proviruses were confirmed by integration site analysis. Some clones had integrants in genes previously identified in other individuals on ART, such as BACH2, STAT5B and MKL1. TCR sequencing confirmed a higher clonality of CMV-specific cells compared to GAG-specific and non-responding memory cells (mean clonality 0.2 vs 0.05 vs 0.03, respectively). Most clones carried defective proviruses (hypermutation, deletions, inversions). In one individual, the VOA from CMV-specific cells identified the same isolate in 4 wells that matched identical DNA sequences from CMV-specific cells collected 8 months previously, suggesting the persistence of a CD4 clone selected over time in response to CMV and that harbored an infectious provirus.
Conclusion: We provide in vivo evidence that clonal expansion of HIV-infected cells is common for CMV- and GAG-specific CD4+ T-cells, demonstrating that responses to antigens represent selective forces affecting the persistence of both defective and infectious proviruses.

74 DISTINCT CHROMOSOMAL INTEGRATION SITE CONFIGURATION IN HIV-1 ELITE CONTROLLERS

Chenyang Jiang[1], Ce Gao[1], Xiaoming Sun[1], Xiaodong Lian[1], Stephane Hua[1], Joshua Chevalier[2], Kevin Einkauf[2], Eric Serrao[3], Alan N. Engelman[3], Mary Carrington[4], Bruce D. Walker[1], Mathias Lichterfeld[2], Xu G. Yu[1]
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Background: HIV-1 elite controllers (EC) represent a rare group (< 0.5%) of infected individuals who maintain undetectable viral loads in the absence of antiretroviral therapy (ART). However, the distinguishing features of proviral reservoir cells in these individuals are unclear.
Methods: Matched integration site and proviral sequencing (MIP-Seq) was applied to PBMC from 11 EC to investigate chromosomal integration sites (IS) of intact HIV-1 proviruses. Chromatin accessibility and gene expression in autologous CD4 T cells were measured by ATAC-Seq and RNA-Seq. CD4 T cells from 12 EC and 11 HIV-1 negative individuals (HIVN) were infected with a HIV-1 construct, followed by chromosomal IS analysis.
Results: In total, 92 IS of intact proviruses were identified in EC, of which 33 were at unique chromosomal locations. Remarkably, we noted that a significantly larger proportion of intact proviruses from EC were located in non-genic, centromeric satellite DNA, compared to 73 unique (100 in total) intact proviral sequences from long-term ART-treated individuals (unique IS: 21% vs. 0%, p=0.0002; all IS: 17% vs. 0%, p<0.0001). Moreover, in comparison to ART-treated patients, IS of intact proviruses from EC were atypically enriched in genes encoding for members of the Zinc Finger Protein family, particularly for KRAB-ZNF on chromosome 19, which contain constitutive heterochromatin (unique IS: 22% vs. 2%, p=0.0091; all IS: 40% vs. 1%, p<0.0001). In addition, we identified significantly increased chromosomal distances from IS of intact proviruses to the most proximal host gene transcriptional start sites (median: 29.3 kb vs. 9.4 kb, p=0.0002) and to accessible chromatin (median: 73.1 kb vs. 8.8 kb, p=0.0004) in CD4 T cells from EC, relative to ART-treated patients. Furthermore, >120,000 HIV-1 IS from in vitro infected CD4 T cells from EC and HIVN demonstrated that satellite DNA (0.04%-0.12%) and KRAB-ZNF genes (0.49%-0.85%) were infrequently targeted, irrespective of the study cohort.
Conclusion: Integration sites of intact proviruses in EC show features of deep latency, likely as the result of selection mechanisms that preferentially eliminated proviruses integrated in chromosomal regions more permissive to viral transcription. This highly distinct chromosomal integration site configuration in EC represents a structural correlate of natural viral control that eradication strategies may have to induce in order to promote a long-term drug-free remission of HIV-1 infection.

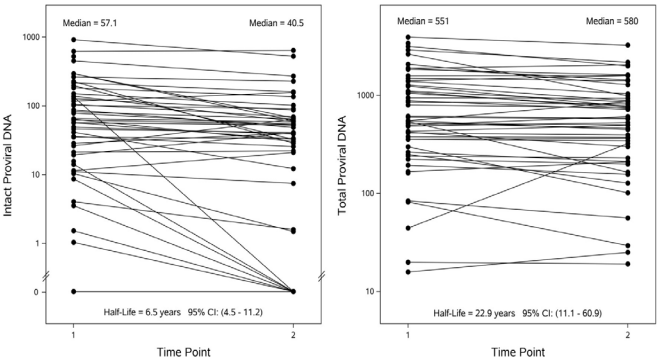
75 INTACT PROVIRAL DNA LEVELS DECLINE IN PEOPLE WITH HIV ON ANTIRETROVIRAL THERAPY

Rajesh T. Gandhi[1], Joshua C. Cyktor[2], Ronald Bosch[3], Hanna Mar[3], Gregory Laird[4], Albine Martin[4], Ann Collier[5], Sharon Riddler[2], Bernard J. Macatangay[2], Charles Rinaldo[2], Joseph J. Eron[6], Robert Siliciano[7], Deborah McMahon[2], John W. Mellors[2], for the ACTG A5321 team
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Background: The intact proviral DNA assay (IPDA) is a new, more-specific ddPCR-based measure of the replication-competent HIV reservoir. Little is known, however, about whether intact proviral DNA levels decline over time on ART and whether the levels correlate with other measures of HIV persistence or with immune activation.
Methods: Participants in ACTG A5321 with chronic HIV and well documented virologic suppression on ART had the following measurements performed on blood samples: intact proviral DNA, total proviral DNA (sum of defective, hypermutated and intact proviruses), total HIV DNA by qPCR targeting 3' integrase, cell-associated HIV RNA (CA-RNA), plasma HIV RNA single copy assay (SCA), T cell activation, and inflammation (IL-6, IP-10, sCD14, sCD163, neopterin,

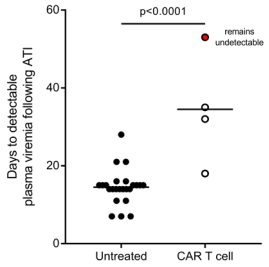
TNF-alpha, hsCRP). Testing was performed at median of 7.1 yr after ART initiation (time point 1) and again a median of 3.7 yr later (time point 2).
Results: Fifty participants (26% female) were evaluated. Intact proviral DNA levels declined significantly between time point 1 (n=50) and time point 2 (n=48): median of 57 and 41 copies/million CD4 cells, respectively; p<0.001 (Figure). By contrast, total proviral DNA was stable: median of 551 and 580 copies/million CD4 cells, respectively. The estimated (median) half-life of decline for intact proviral DNA (n=44 participants) was 6.5 yrs (95% CI 4.5, 11.2), whereas that for total proviral DNA was 22.9 years (95% CI, 11.1 to 60.9). Six participants had decline in intact proviral DNA to undetectable levels. Higher on-ART intact proviral DNA levels correlated with higher on-ART total HIV DNA (r=0.48), higher CA-RNA (r=0.46) and higher SCA (r=0.39) (time point 1; all p-values ≤0.005). No associations were seen between on-ART intact proviral DNA levels and on-ART T cell activation or inflammation.
Conclusion: In people on long-term ART, intact proviral DNA levels decline significantly (half-life 6.5 yr), whereas total proviral DNA remains stable over the same time period (half-life 22.9 yr). A subset of individuals had a decline in intact proviral DNA to undetectable levels. The overall decline in intact proviruses implies that cells containing replication-competent proviruses are being lost. Defining the mechanisms involved should inform strategies to accelerate HIV reservoir depletion. The more dynamic nature of the intact proviral landscape, compared with total proviral HIV DNA, supports the use of the IPDA to assess the impact of interventions targeting the HIV reservoir.

Fig: Intact proviral DNA & total proviral DNA/million CD4 cells at time point 1 (median 7.1 yr on ART) and time point 2 (median 3.7 yr later)



76 CHIMERIC ANTIGEN RECEPTOR T CELLS CONTROL SHIV REPLICATION IN POST-ATI MACAQUES

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Background: An effective strategy to achieve antiretroviral therapy (ART)-free remission in HIV+ individuals will likely require active and passive approaches. We optimized CD4-based Chimeric Antigen Receptor (CD4CAR) molecules to actively target infected cells, and combined with CCR5 editing to passively protect CD4CAR T cells against infection. This approach was modeled in nonhuman primates (NHPs) infected with simian/human immunodeficiency virus (SHIV) and suppressed long-term on ART. Our goal was to quantify the impact of NHP deltaCCR5 CD4CAR T cells on viral rebound following analytical treatment interruption (ATI).
Methods: Rhesus macaques (n = 4) were infected with SHIV, and suppressed by ART for at least 1 year prior to intervention. Autologous T cells were edited with NHP CCR5 CRISPR ribonucleoproteins, then modified with lentiviral vectors expressing HIV/SHIV-specific CD4CAR. CAR T cell products were infused without a conditioning regimen. Transplanted animals received a single dose of cell-associated viral envelope antigen to boost the persistence of these cells in vivo. Flow- and PCR-based assays were used to characterize the T cell infusion product and the persistence of these cells in blood and tissues. Plasma viral load was monitored weekly before and after T cell infusion and ATI.
Results: Adjustments to the manufacturing protocol augmented the ratio of CD4 to CD8 CAR T cells, increasing the persistence of CAR+ CD4 lineages in vivo. Infusion of cell-based antigen was well tolerated and led to significant increases in the percentage of CAR+ T cells in peripheral blood. Following ART withdrawal, viral rebound was delayed in all animals; one remains undetectable at 53 days post-ATI.
Conclusion: Previous studies in patients and NHPs demonstrated low-level persistence of virus-specific CAR T cells in vivo, relative to CAR T cells for cancer. To our knowledge, ours is the first study to boost virus-specific CAR T cells in infected, suppressed hosts, and to delay/control post-ATI viral rebound via CAR T cell therapy. Due to the lack of a cytotoxic conditioning regimen, the safety profile of our approach is highly favorable. Our data reinforces the promise of deltaCCR5 CD4CAR T cell therapies for viral reservoir reduction in HIV+ individuals, including a Phase I clinical trial underway at the University of Pennsylvania (NCT03617198).



77 DELAY IN VIRAL REBOUND WITH TLR7 AGONIST, N6-LS, AND PGT121 IN SHIV-INFECTED MACAQUES

Denise C. Hsu[1], Decha Silsorn[2], Rawiwan Imerbsin[2], Amarendra Pegu[3], Dutsadee Inthawong[2], Jumpol Sopanaporn[2], Alexandra Schuetz[1], James Demarest[4], Merlin L. Robb[5], John R. Mascola[3], Romas Geleziunas[6], Richard A. Koup[3], Dan Barouch[7], Nelson L. Michael[5], Sandhya Vasan[5]
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Background: Toll-like receptor (TLR)-7 agonist and PGT121 administration have previously delayed viral rebound and induced SHIV remission after antiretroviral therapy (ART) interruption in macaques that started ART 7 days post SHIV-SF162P3 infection. We evaluated the impact of TLR-7 agonist and dual broadly neutralizing antibodies (bnAb) on viral rebound in SHIV-infected macaques.
Methods: Male rhesus macaques (n=16), pre-screened to exclude protective MHC alleles, were inoculated at wk0 with SHIV-1157ipd3N4 intrarectally. ART (tenofovir, emtricitabine and dolutegravir) was initiated on Day14. Active arm (n=8) animals received oral GS-986, every 2 weeks from wk14-32 and intravenous N6-LS and PGT121 every 2 weeks from wk24-32 unless anti-drug antibodies (ADA) developed. ART was ceased when plasma levels of N6-LS and PGT121 were <0.25mg/mL. Control animals (n=8) received intravenous saline. Plasma SHIV RNA was assessed by qPCR (limit of detection 10 copies/mL) and soluble markers of immune activation by multiplex assay using Luminex.
Results: All animals were SHIV-infected with median SHIV RNA of 5.7 (range 4.1-6.8) $\log_{10}$ copies/mL on day14. After ART initiation on day14, SHIV RNA became undetectable in all animals by wk8 and remained undetectable until ART interruption. Due to varying ADA, animals received 7-10 doses of GS-986, 2-5 doses of PGT121 and 2-5 doses of N6-LS. At 24hrs post GS-986 dosing, plasma levels of IFNα, IL-1RA, IL-2, IL-6, IL-10, IL-15, MCP-1, MIP-1b, TNF, GM-CSF, IL-13 and MIP-1a increased significantly and viral blips were not detected. In the active arm, %Ki-67+ NK cells also increased at wk24 when compared to wk14 (p=0.031). Total HIV DNA levels in PBMC prior to ART interruption were not significantly different between arms. Median time to viral rebound was 6 weeks in active arm and 3 weeks in control arm (p=0.024, Figure 1). There was no significant difference in post rebound peak or set-point viremia between groups.
Conclusion: Administration of GS-986 and dual bNAbs was associated with a modest delay in viral rebound. The effect of timing of ART initiation on seeding of the viral reservoir likely influenced the ability to achieve remission. Evaluating this strategy in humans is warranted.

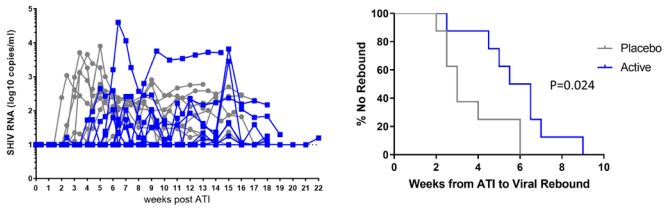


Figure 1: Viral rebound dynamics post analytical treatment interruption (ATI).

78LB COMBINED ACTIVE AND PASSIVE IMMUNIZATION IN SHIV-INFECTED RHESUS MONKEYS

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Background: Our group and others have previously reported that therapeutic immunization can result in post-rebound virologic control in SHIV-infected rhesus monkeys following ART discontinuation, and that administration of broadly neutralizing antibodies (bNAbs) can delay or prevent viral rebound. The potential of combined active and passive immunization as an HIV-1 cure strategy has not previously been evaluated.

Methods: 49 rhesus monkeys were infected with SHIV-SF162P3 and initiated ART (TDF/FTC/DTG) on day 9 of infection. Following 24 weeks of continuous daily suppressive ART, animals received 4 immunizations with Ad26/MVA vaccines at weeks 24/36/48/60 (N=12), 5 infusions of 10 mg/kg PGT121 every 2 weeks from weeks 64-72 (N=12), both Ad26/MVA vaccines and PGT121 (N=10), or sham controls (N=15). All groups except the sham controls received 10 doses of 0.15 mg/kg of the TLR7 agonist vesatolimod (VES) by oral gavage (every 2 weeks from weeks 50-72). At week 86, ART was discontinued and viral rebound was monitored for 140 days.

Results: Ad26/MVA vaccination resulted in increased magnitude and breadth of SHIV-specific cellular and humoral immune responses. PGT121 infusion resulted in 14 weeks of therapeutic antibody levels followed by a decline to undetectable levels prior to ART discontinuation. VES administration led to activation of multiple cellular immune subsets including CD4+ T lymphocytes. Following ART discontinuation, 100% (15 of 15) of sham controls exhibited rapid viral rebound, and all animals in this group remained viremic by day 140 following ART discontinuation. 100% (12 of 12) of the Ad26/MVA + VES vaccinated animals also rebounded, but 3 animals demonstrated post-rebound virologic control to undetectable levels. In contrast, only 66% (8 of 12) of PGT121 + VES treated animals and 60% (6 of 10) of Ad26/MVA + PGT121 + VES treated animals rebounded (P=0.016, Fisher's exact test compared with sham controls). Moreover, only 40% (4 of 10) of Ad26/MVA + PGT121 + VES treated animals were viremic by day 140 following ART discontinuation (P=0.001, Fisher's exact test compared with sham controls).

Conclusion: Combined active and passive immunization with TLR7 stimulation resulted in both delayed viral rebound and post-rebound virologic control following ART discontinuation in SHIV-infected rhesus monkeys that initiated ART during acute infection. This multi-pronged approach represents a novel HIV-1 cure strategy.

79LB COMBINATION IL-15 THERAPY IN A SHIV NHP MODEL

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Background: Latent reservoirs of replication-competent HIV-1 persist in patients on antiretroviral therapy (ART) and represent the major obstacle to HIV eradication efforts. Considerable effort has been directed to develop and evaluate novel remission strategies to enhance virus-specific immune responses in ART-suppressed patients.

Methods: We conducted 2 studies in SHIV-infected ART-suppressed rhesus macaques (RM) to evaluate the IL-15 superagonist, N-803 to enhance virus-specific effector cells, in conjunction with broadly neutralizing antibodies (bNAbs, 10-1074 and 3BNC117). Thirty-six RMs were rectally infected with SHIV-AD8. RMs received ART at ~50 days post infection (Study 1, n=20 and Study 2, n=16) and virologic suppression was maintained for 65 or 60 weeks PI for each study, respectively. In Study 1, ART-suppressed monkeys received 6 doses of N-803 alone (n=5), 2 doses of 10-1074 alone (n=5), a combination of N-803 and 10-1074 (n=5), or vehicle control (n=5). In Study 2, ART-suppressed RMs received 6 doses of N-803 and 3 doses of both 10-1074 and 3BNC117 (n=8) or the vehicle control (n=8). Plasma SHIV RNA levels were measured and viral DNA were quantified in PBMC, colon and lymph node (LN) biopsies taken pre- and post- treatment. Modulation of immune populations, including T, B and NK cells, were monitored longitudinally. After monitored washout of bNAbs in plasma, ART was discontinued.

Results: In both studies, blood NK cells showed peak activation at 48hrs post N-803 administration throughout the dosing period. Memory T cells were preferentially activated by N-803, and CD8+ T cells demonstrated more robust expansion during the dosing period. No immune activation of PBMC was associated with bNAb treatment. We observed no change in integrated SHIV DNA between pre- and post- treatment timepoints in either PBMC or LN tissues (Study 1). In Study 1, plasma viral rebound kinetics in RMs treated with either N-803 or 10-1074 alone, or in combination, were comparable to the control group after ART discontinuation. However, 3 of 5 combination treated RMs showed durable control of viremia after initial low-level rebound. In Study 2, 6 of 8 combination-treated (N-803/bNAbs) RMs exhibited durable control of viremia beyond week 25 following initial low-level rebound.

Conclusion: Repeated co-dosing of N-803 and bNAbs is safe and may facilitate long-term viral control and remission in the absence of ART.

80 A MENDELIAN RANDOMIZATION ANALYSIS OF PROTEIN BIOMARKERS AND CVD IN PERSONS WITH HIV

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Background: Treated HIV+ persons have excess risk for CVD yet the mechanisms explaining this remain poorly understood. Here we used a Mendelian randomization (MR) approach to assess causality of circulating proteins on CVD risk among participants in INSIGHT trials.

Methods: We identified participants in 4 clinical trials conducted by INSIGHT (FIRST, ESPRIT, SMART and START) who experienced a clinical event (composite outcome of AIDS, serious non-AIDS including CVD, and death) and individually matched them (1:2) with study-specific controls who did not. Baseline plasma samples were used to measure protein levels using 5 panels made by OLINK (panels: CVD2, CVD3, immune response, cardiometabolic and inflammation). Genome-wide genotypic data was available for all. Proteins that passed quality control were screened for an association with the CVD outcome (MI, coronary revascularization, stroke, CVD death) while controlling for matching, demographics, hypertension, diabetes and study specific treatment group effects using a 5% significance level. Proteins associated with CVD outcomes were then tested for an association with genetic variants within 5Kb of the corresponding protein-coding gene while controlling for matching, demographics and study. Significant SNPs (family-wise p<5% for each protein) were used to construct haplotypes. The number of copies of the most common haplotype was used as an instrumental variable in a linear MR analysis (with a 5% level test). If only a single significant SNP was detected, that SNP was used as an instrument. It can be demonstrated that this protein screening approach controls the family-wise error rate at 5% across all MR tests.

Results: This analysis included 1493 participants (500 cases; 131 with CVD) with mean follow-up of 6 years. Of the 459 distinct proteins represented at least once on the panels, 389 passed quality control measures. Of these proteins, 89 were associated with CVD. Of these 89, 38 were associated with at least 1 SNP in the corresponding gene. MR analysis detected IL6RA, AXL, CHI3L1, SCGB3A2, GAS6 and IL1RL2 as potential causal factors that impact CVD outcomes (replicating a previous finding for IL6RA among HIV- people). Table 1 summarizes these associations of proteins/SNPs with CVD risk.

Conclusion: Application of MR methods demonstrated potential causal effects of 6 proteins on CVD outcomes among a global population. These proteins warrant further study as interventional targets.

Protein symbol	Risk difference (95% CI)	p-value	Number of significant SNPs	Risk difference from instrument (95% CI)	p-value for instrument
AXL	$0.0136\ (9.45\times10^{-4},\ 0.0262)$	0.035	1	0.186 (0.0283, 0.343)	0.021
CHI3L1	$0.0118\ (6.94\times10^{-4},\ 0.0230)$	0.037	4	$-0.0381\ (-0.0754,\ -8.56\times10^{-4})$	0.045
GAS6	$0.0137\ (1.36\times10^{-3},\ 0.0260)$	0.029	2	$-0.0874\ (-0.158,\ -0.0168)$	0.015
IL1RL2	$-9.02\times10^{-3}\ (-0.0167,\ -1.33\times10^{-3})$	0.022	4	0.555 (0.138, 0.972)	0.009
IL6RA	$0.0133\ (5.45\times10^{-5},\ 0.0265)$	0.049	68	$0.0199\ (7.47\times10^{-5},\ 0.0398)$	0.049
SCGB3A2	$0.0176\ (5.80\times10^{-3},\ 0.0294)$	0.003	24	$0.107\ (6.16\times10^{-3},\ 0.208)$	0.038

Table 1: Summary of associations between protein levels and CVD outcomes. The risk differences are for the absolute risk difference associated with a 1 decile increase from the median of the protein level. The p-values reported in the final column are adjusted for the number of Mendelian randomization tests based on a sequential testing strategy.

81 RISKS OF METABOLIC SYNDROME, DIABETES, AND CARDIOVASCULAR DISEASE IN ADVANCE TRIAL

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Background: In the ADVANCE trial, more patients taking first-line TAF/FTC+DTG developed clinical obesity compared to TDF/FTC+DTG and TDF/FTC/EFV. Common associations with obesity include type 2 diabetes, cardiovascular disease (CVD), and metabolic syndrome. This analysis aimed to quantify these risks using standard risk algorithms.

Methods: In ADVANCE, 1,053 treatment-naïve patients in South Africa (99% black, 59% female) were randomized to 96 weeks of TAF/FTC+DTG, TDF/FTC+DTG, or TDF/FTC/EFV. Weight, lipids, fasting glucose, and blood pressure (BP) were measured at baseline and week 48, and used to calculate 10-year risks of CVD and type 2 diabetes using the Framingham, QRISK, and QDIABETES equations. Participants were included in the analysis if they were between the age of 25-84 years and had complete laboratory data for all parameters in risk equations. Treatment emergent metabolic syndrome was calculated at week 48 using the International Diabetes Federation definition and differences between groups were tested using a two-sample test of proportions.

Results: 296 (TAF/FTC+DTG), 286 (TDF/FTC+DTG), and 306 (TDF/FTC/EFV) participants were included in this analysis at baseline. Vital signs and laboratory parameters were similar at baseline across all treatment arms, 82(9%) participants were being treated for hypertension, 12(1%) had diabetes, and 45(5%) had metabolic syndrome. Changes from baseline to week 48 are displayed in Table 1. The risk of developing diabetes was higher in TAF/FTC+DTG compared to TDF/FTC+DTG (p=0.0051). Statistically significant differences were shown in the risk of CVD (Framingham and QRISK) between TAF/FTC+DTG and TDF/FTC/EFV. Treatment-emergent metabolic syndrome was 8%(TDF/FTC+DTG), 6%(TDF/FTC+DTG) and 3%(TDF/FTC/EFV), with statistically significant differences between TAF/FTC+DTG and TDF/FTC/EFV (p=0.021).

Conclusion: Treatment with TAF/FTC+DTG led to greater rises in weight, lipids and glucose than TDF/FTC+DTG, with small predicted 10-year risks of CVD and diabetes. There are concerns that these tools may either over- or underestimate risks in HIV and African populations. Longer term studies, with clinical or reliable surrogate endpoints in local HIV-positive populations are needed to validate these risk assessment tools.

Table 1.0: Summary of median changes from baseline across lab parameters and risk scores

Changes to week 48, median (IQR)	Group 1 TAF/FTC+DTG (n=251)	Group 2 TDF/FTC+DTG (n=256)	Group 3 TDF/FTC+EFV (n=248)	Group 1 vs. 2	Group 1 vs. 3	Group 2 vs. 3
Weight (kg)	+5.80 (+1.7, +9.8)	+2.40 (0.0, +5.5)	+0.50 (-2.5, +4.4)	**p<0.001**	**p<0.001**	**p<0.001**
Systolic BP (mmHg)	+2.00 (-6.0, +10.0)	+0.00 (-9.0, +10.0)	-1.00 (-8.5, +8.0)	p=0.251	p=0.028	p=0.450
Total cholesterol (mmol/L)	+0.09 (-0.3, +0.5)	-0.11 (-0.5, +0.2)	+0.32 (-0.1, +0.8)	**p<0.001**	**p<0.001**	**p<0.001**
LDL (mmol/L)	+0.10 (-0.2, +0.5)	-0.05 (-0.4, +0.2)	+0.15 (-0.2, +0.5)	**p=0.001**	p=0.161	**p<0.001**
HDL (mmol/L)	+0.11 (-0.1, +0.3)	+0.11 (-0.1, +0.3)	+0.31 (+0.1, +0.6)	p=0.363	**p<0.001**	**p<0.001**
Fasting glucose (mmol/L)	+0.50 (+0.1, +0.9)	+0.30 (0.0, +0.8)	+0.60 (+0.3, +1.0)	**p=0.047**	**p=0.020**	**p<0.001**
Risk Scores						
Framingham	+0.07 (-0.2, +0.4)	-0.02 (-0.4, +0.3)	-0.03 (-0.3, 0.2)	p=0.0366	**p=0.0053**	p=0.638
QRISK	+0.10 (+0.0, +0.2)	+0.10 (+0.0, +0.2)	+0.0 (0.0, +0.1)	p=0.804	**p<0.001**	**p=0.0018**
Qdiabetes	+0.40 (+0.1, +1.6)	+0.20 (0.0, +1.0)	+0.40 (+0.2, +1.2)	**p=0.0051**	p=0.858	**p=0.0014**

QRISK and QDiabetes are adjusted for race. Risk scores show risk of heart attack/stroke/diabetes over the next 10 years, per 100 people (QDiabetes +0.40= 4 additional cases of diabetes per 1,000 people treated with TAF/FTC+DTG over the next 10 years)
Differences between groups were tested using non-parametric methods given the positive skew in distributions in risk (all p-values derived from Mann-Whitney U tests). The Bonferroni test was used to adjust for multiple comparisons when looking at risk scores (significance level of p=0.0056).

82 CYP2B6 GENOTYPE AND WEIGHT-GAIN DIFFERENCES BETWEEN DOLUTEGRAVIR AND EFAVIRENZ

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Background: Two African trials reported more weight gain with dolutegravir (DTG) than efavirenz (EFV), especially in women. EFV is toxic to mitochondria and is associated with lipoatrophy. We hypothesised that CYP2B6 metaboliser genotype, which predicts EFV exposure, would determine amount of weight gained and fat distribution in patients starting EFV-based ART.

Methods: Participants enrolled in the EFV/TDF/FTC arm of the ADVANCE trial who consented to genetic testing were included. CYP2B6 metaboliser genotype was classified as extensive, intermediate, and slow. Outcomes included change in weight gain and trunk and limb fat on DXA from baseline to week 48 by CYP2B6 genotype. Weight gain was compared between CYP2B6 extensive metabolisers in the EFV/TDF/FTC arm and the DTG/TDF/FTC arm.

Results: 171 participants had genetic testing done. CYP2B6 metaboliser genotypes were 51 extensive, 74 intermediate, and 46 slow; median age 32 years (IQR 28–37); 57% women; median BMI 23.7 kg/m$_2$ (IQR 20.2–27.5); and median CD4 count 292 cells/uL (IQR 172–406). The percentage change in weight from baseline over 48 weeks differed by CYP2B6 metaboliser genotype (p=0.004; Kruskal-Wallis), but differences were more marked in women over time (see figure). In men CYP2B6 metaboliser genotype was associated with percentage change in weight initially (week 12 p=0.007; week 24 p=0.053), but the effect attenuated over time. The percentage change in limb fat on DXA (n=148) from baseline to 48 weeks differed significantly by CYP2B6 metaboliser genotype in women (p=0.008), with highest percentage increase in extensive metabolisers, but not in men (p=0.680). Percentage change in trunk fat on DXA from baseline to 48 weeks was not significantly different by CYP2B6 metaboliser genotype in women (p=0.082) or men (p=0.732). The percentage change in weight from baseline to 48 weeks was similar between CYP2B6 extensive metabolisers in the EFV/TDF/FTC arm and the DTG/TDF/FTC arm (p=0.939).

Conclusion: In Africans starting EFV-based ART CYP2B6 metaboliser genotype was associated with weight gain and, in women, with changes in limb fat. The similar weight gain observed between CYP2B6 extensive metabolisers in the EFV/TDF/FTC arm and the DTG/TDF/FTC arm suggests off-target effects (e.g. mitochondrial toxicity) impairing weight gain in EFV slow/intermediate metabolisers could explain the greater weight gain observed with DTG in African trials.

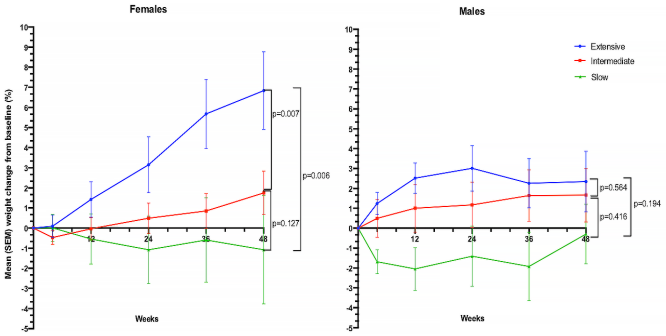


Figure. Percentage weight change from baseline by *CYP2B6* metaboliser genotype over 48 weeks stratified by sex.

83 CHANGES IN BODY MASS INDEX AND THE RISK OF CARDIOVASCULAR DISEASE: THE D:A:D STUDY

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Background: Several studies have shown an increase in weight in HIV-positive people receiving some contemporary antiretrovirals (ARV). We assess the effect of changes in body mass index (BMI), from different baseline BMI levels, on the risk of cardiovascular disease (CVD) and diabetes mellitus (DM).

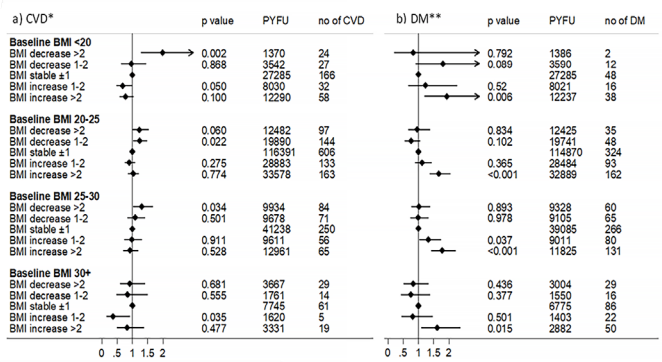
Methods: We followed D:A:D study participants on ARV therapy from their first BMI measurement (baseline) to the first endpoint or earliest of 1/2/2016 or 6 months after last follow-up. The endpoints were CVD (composite of myocardial

infarction/stroke/invasive cardiovascular procedure) and DM. Participants were stratified according to their baseline BMI as <20, 20-24.9, 25-29.9 and >30 kg/m_2. BMI was lagged by 1 year, and changes from baseline BMI were calculated for each participant, with values carried forward. Poisson regression models were used, adjusted for baseline BMI and key confounders that did not lie on the causal pathway for each outcome, with BMI change fitted as a time varying covariate.

Results: We included 43,011 participants with 2,104 CVD and 1,583 DM events over 365,287 and 354,898 person years of follow up (rate:CVD 5.8/1000 (95% confidence interval (CI) 5.5–6.0); DM 4.5/1000 (95% CI 4.2–4.7)). Participants were largely male (74%) with baseline mean age of 40 years and baseline median BMI of 23.0 (IQR: 21.0- 25.3). Risk of CVD by change in BMI from baseline, stratified by baseline BMI strata are shown in Figure 1a with little evidence of an increased risk of CVD with an increased BMI in any baseline BMI strata. Overall there was no statistically significant interaction between baseline BMI strata and BMI change (p=0.16). There was some evidence of an increased rate of CVD with a decrease in BMI of more than 2 kg/m_2, especially in those with a baseline BMI<20 kg/m_2. An increase in BMI was associated with an increased risk of DM across all baseline BMI strata (Figure 1b).

Conclusion: While increases in BMI across all levels of baseline BMI were not associated with an increased risk of CVD, such changes were consistently associated with increased risk of DM. There was also some evidence of an increased risk of CVD with a decrease in BMI. The extent to which these results apply to HIV-positive people with increased weight while receiving contemporary ARVs are uncertain.

Figure 1. Risk of CVD (a) and DM (b) by BMI change within baseline BMI strata



**CVD: Adjusted for age, race, mode of transmission, sex, recent abacavir and other NRTI use, cumulative protease inhibitor use, CD4 count, family history of CVD, smoking status; **DM: Adjusted for age, race, mode of transmission, sex, stavudine use, triglycerides, CD4 count, smoking status and HDL (high-density lipoprotein); PYFU= person years follow up*

84 LOSARTAN TO REDUCE INFLAMMATION AND FIBROSIS ENDPOINTS IN HIV DISEASE (LIFE-HIV)

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Background: Persistent inflammation and incomplete immune recovery among persons with HIV are associated with increased disease risk. Angiotensin receptor blockers (ARB) have been shown to down-regulate inflammation and fibrosis, in part, via inhibition of NFkB and TGFb pathways, respectively. We hypothesized that the ARB losartan would reduce inflammation, inhibit fibrosis, and concurrently improve immune recovery.

Methods: Treatment effects of oral losartan (100mg) versus placebo were investigated in a randomized (1:1), double-blind, placebo-controlled trial, among persons with HIV of age ≥50 years, receiving ART, with plasma HIV RNA <200 copies/mL and a CD4+ count ≤600 cells/mL. Blood was collected at baseline and months 1, 3, 6, 9, and 12. Inflammation and fibrosis biomarkers (Table) were measured using ELISA, electrochemiluminescence, and immunoturbidimetric methods, and T-cell and monocyte phenotypes were assessed with flow cytometry among a subset of participants. Baseline-to-12-month changes in (log-2 transformed) biomarkers and (untransformed) cell phenotypes were compared between the losartan and placebo arms using linear mixed models.

Results: One hundred and eight participants were randomized (n=52 to losartan; n=56 to placebo); 97% had a month 12 visit and 99% of expected visits were completed overall. Median age was 57 years, baseline and nadir CD4+ count were 408 and 120 cells/mm_3; 96% were male, 56% white, 20% current smokers, 26% taking lipid-lowering medication, and 49% taking an integrase strand transfer inhibitor. The table reports baseline levels of blood inflammation and immune measures, as well as the treatment effect of losartan versus placebo. Losartan treatment was not associated with an improvement in any of these measures, nor with CD8+ T-cell memory subsets and activation (data not shown). Losartan reduced systolic and diastolic blood pressure by 6 and 5mmHg, respectively, and raised serum creatinine by 0.05mg/dL (p<0.01 for all). Losartan was not associated with more serious adverse events.

Conclusion: Among older persons with HIV and viral suppression, losartan did not improve blood measures of inflammation, immune activation, fibrotic activity, nor T-cell immune recovery. Losartan treatment is unlikely to reduce inflammation associated co-morbidities among persons with HIV infection to a clinically meaningful degree, beyond the established benefits from lowering blood pressure

BLOOD MEASURES	Losartan (L) Baseline Median (IQR)	Placebo (P) Baseline Median (IQR)	L vs. P Difference in Change over 12 Mo. (% or absolute)[b] (95% C.I.)	L vs. P *P*-value[b]
Inflammation and coagulation				
IL-6 (pg/mL)[b], *primary outcome*	0.91 (0.67, 1.30)	1.04 (0.75, 1.41)	0.6% (-14.7, 18.7)	0.94
sTNFR-1 (pg/mL)[b]	1193 (1049, 1379)	1161 (1027, 1353)	1.6% (-1.8, 5.1)	0.37
D-dimer (μg/mL)[b]	0.26 (0.13, 0.47)	0.23 (0.15, 0.31)	-8.1% (-31.1, 22.5)	0.56
Monocyte activation				
sCD163 (ng/mL)[b]	824 (578, 989)	711 (537, 890)	-4.1% (-8.6, 0.7)	0.09
Neopterin (ng/mL)[b]	9.48 (7.03, 12.48)	8.94 (7.25, 12.20)	5.0% (-3.3, 14.2)	0.25
sCD14 (pg/mL)[b]	1383 (1247, 1616)	1330 (1163, 1612)	-2.3% (-6.3, 1.8)	0.27
CD14+CD16+ monocytes[c] (%)	2.2 (1.5, 3.8)	1.5 90.0, 2.5)	-0.2 (-1.6, 1.2)	0.77
CD14dimCD16+ monocytes[c] (%)	2.9 (2.3, 3.8)	2.3 (0.0, 6.3)	-0.0 (-1.4, 1.4)	0.96
Fibrosis				
Hyaluronic Acid (ng/mL)[b]	41.5 (27.7, 69.4)	39.8 (26.0, 75.3)	-0.7% (-11.7, 11.8)	0.91
Beta-crosslaps (ng/mL)[b]	0.37 (0.28, 0.60)	0.40 (0.27, 0.54)	3.1% (-5.9, 13.0)	0.51
T-cell immune recovery				
CD4+ T-cell count (cells/μL)	420 (286, 487)	399 (319, 511)	8.3 (-12.4, 29.0)	0.43
CD4+ T-cell, naïve[c] (%)	15.8 (10.2, 22.5)	24.4 (16.4, 38.8)	-0.1 (-5.5, 5.3)	0.97
CD4+ T-cell, CM[c] (%)	35.9 (28.0, 45.6)	44.7 (16.7, 48.2)	-0.3 (-5.2, 4.6)	0.90
CD4+ T-cell, EM[c] (%)	42.2 (26.8, 50.5)	15.3 (13.0, 39.0)	0.2 (-4.3, 4.6)	0.93

[a]p-value is for comparison of change on losartan versus change on placebo considering all of follow-up, adjusted for baseline; [b]Changes over follow-up analyzed on log-2 scale for plasma biomarkers of inflammation and coagulation fibrosis; for these biomarkers the difference in change is reported as percent difference. All other changes reported on the absolute scale. [c]T-cell phenotype memory subsets were measured and analyzed in n=33, and monocyte activation phenotypes in n=26; IL-6 (interleukin-6; primary outcome), TNFR-1 = tumor necrosis factor receptor-1; naïve defined by CD27+CD45RO-; CM = central memory defined by CD27+CD45RO+; EM = effector memory defined by CD27-CD45RO+

85 EFFECTS OF HIV INFECTION AND IMMUNE REGULATION ON LONGITUDINAL LUNG FUNCTION DECLINE

Jing Sun[1], Jacquie Astemborski[1], Sarath Raju[2], M. Brad Drummond[3], Robert H. Brown[2], Shruti H. Mehta[1], Richard D. Moore[2], Meredith C. McCormack[2], Gregory D. Kirk[1], for the Study of HIV Infection in the Etiology of Lung Disease (SHIELD) cohort

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Background: People living with HIV (PWH) have higher prevalence of lung function abnormalities compared to demographically and behaviorally similar people without HIV (HIV-). However, high quality longitudinal data describing the impact of HIV and of immune dysregulation on lung function decline over prolonged observation by age remains limited.

Methods: Data from the Study of HIV Infection in the Etiology of Lung Disease (SHIELD) cohort was used to evaluate the role of HIV and aging on lung function decline. Pre-bronchodilator FEV1 was repeatedly measured by spirometry at semiannual visits from 2009 to 2017 using ATS standards. HIV serostatus, HIV RNA, CD4 and CD8 counts were measured either in study or routine clinical visits. Time-varying CD4 nadir was defined as lowest CD4 observed up until each visit. Linear regression with generalized estimating equations, adjusted for age at entry, race, gender, current smoking status, and life-time pack-years, was used to evaluate longitudinal change in annualized FEV1 by HIV serostatus, CD4:CD8, and CD4 nadir.

Results: Of 1156 HIV+ and 1168 HIV- participants with 8341 person-years of follow-up, median age at entry was 50 years, 85% were black, 65% male, 79% current smokers, median cigarette exposure was 19 pack-years, and median % predicted FEV1 was 90%. Among PWH, 38% had CD4 <200, 59% had detectable HIV RNA, 78% had CD4:CD8≤0.8. At entry, PWH had 133 ml lower FEV1 compared to HIV- (p<0.01). FEV1 declined significantly faster among PWH before age of 50, but declined at similar rate after age of 50

(Table). Within the subset with available data (N=1518), PWH with immune dysregulation (CD4:CD8<0.8) had lower (-120ml, p<0.01) and faster decline (-6ml per year faster, pinteraction=0.02) of FEV1 compared to HIV-. PWH with CD4 nadir<200 also had lower (-159ml, p<0.01) and faster decline (-6ml/year faster, pinteraction=0.02) of FEV1 compared to HIV- adjusted for current CD4 and covariates.

Conclusion: Among these participants with heavy tobacco exposure, lung function was significantly lower among PWH compared to HIV- and declined more rapidly in PWH than HIV- in those age <50. Low CD4 nadir (independent of current CD4) and immune dysregulation had a significant impact on lung function decline, irrespective of age. This finding suggests that HIV may manifest with impaired lung function in earlier ages. It also addresses the importance of achieving immune regulation in order to preserve lung function among PWH.

Table. Marginal estimation of maximum FEV1 over time by HIV serostatus and stratified by age groups in SHIELD.

	Age<50			Age≥50		
	Coef.*	SE	P-value	Coef.*	SE	P-value
HIV	**-133**	**33**	**<0.001**	**-113**	**29**	**<0.001**
HIV*time interaction	**-14**	**4**	**0.002**	2	3	0.399
Time, year	**-32**	**3**	**<0.001**	**-44**	**2**	**<0.001**
Female	**-992**	**34**	**<0.001**	**-858**	**30**	**<0.001**
Black	**-450**	**46**	**<0.001**	**-373**	**58**	**<0.001**
Age at study entry, every 5 years	**-30**	**3**	**<0.001**	**-34**	**3**	**<0.001**
Lifetime smoking, pack year	**-5**	**1**	**<0.001**	**-2**	**1**	**0.003**
Current smoker	-17	20	0.418	-16	12	0.202

* Difference in FEV_1 in ml.

86 AZITHROMYCIN FOR TREATMENT OF HIV-RELATED CHRONIC LUNG DISEASE IN AFRICAN CHILDREN

Rashida A. Ferrand[1], Grace McHugh[2], Andrea M. Rehman[1], Hilda Mujuru[3], Mark Nicol[4], Sarah Rowland-Jones[5], Trond Flaegstad[6], Tore Gurtteberg[6], Victoria Simms[1], Elizabeth L. Corbett[1], Helen A. Weiss[1], Edith D. Majonga[2], Katharina Kranzer[1], Jon O. Odland[6], for the BREATHE Trial Group

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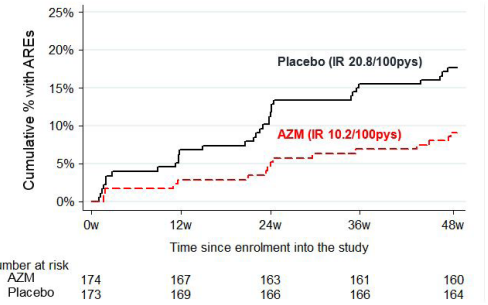
Background: HIV-related chronic lung disease (HCLD) in children and adolescents is associated with substantial morbidity, despite antiretroviral therapy (ART). HCLD may be a consequence of repeated respiratory tract infections and/or dysregulated immune activation. Macrolides have anti-inflammatory and antimicrobial properties, and we hypothesized that azithromycin (AZM) would improve lung function and morbidity through preventing respiratory tract infections and controlling systemic inflammation.

Methods: We conducted a randomized double-blinded, placebo-controlled trial among children aged 6-19 years on ART with HCLD (defined as FEV1 Z-score<-1) in Malawi and Zimbabwe. Once-weekly AZM (with weight-based dosing) or placebo was administered for 48 weeks. Primary outcome was mean difference in FEV1 Z-score. Secondary outcomes were mortality, hospitalisations and acute respiratory exacerbations (ARE). Outcomes were adjusted for age, sex, trial site and HIV viral load (VL) at baseline, using robust standards errors for multiple event data.

Results: A total of 347 children were recruited (49% female, median age 15.3 years) of whom 44% had a VL>1000copies/ml and 74% were on first-line ART; 90% were taking cotrimoxazole prophylaxis and the median CD4 count was 571cells/μl. Previous treatment for tuberculosis was reported by 28% and chronic cough by 9%, and 44% had an abnormally high respiratory rate. We randomized 174 to AZM and 173 to placebo. At the end of 48 weeks of treatment, the mean difference between arms in FEV1 Z-score was 0.06 (95% CI 0.10, 0.21; p=0.48). There was a significant difference in incidence of ARE, adjusted incidence rate ratio 0.50 (95% CI 0.25, 1.00; p=0.05) (Figure 1). The rate ratio for hospitalizations was 0.24 (0.06-1.07, p=0.061) comparing AZM to placebo. Mortality was 0/100pyrs in the AZM vs 1.95/100pyrs in the placebo arm.

Conclusion: This is the first ever trial of an intervention to address HCLD in children. While once-weekly AZM had no effect on pulmonary function, it reduced mortality, hospitalizations and incidence of AREs. AZM is an effective intervention in reducing morbidity associated with HCLD in children and adolescents.

Figure 1



87 BIC/FTC/TAF POSTEXPOSURE PROPHYLAXIS PROTECTS MACAQUES AGAINST RECTAL SHIV INFECTION

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Background: Current guidelines recommend 4 weeks of daily ARVs for post-exposure prophylaxis (PEP) after an HIV exposure, though the optimal duration of PEP is not known. An effective short-course regimen could simplify HIV prevention after an exposure, or provide an option for event-driven post-exposure prophylaxis (PrEP) as a simplified alternative to long-term daily regimen. Here, we evaluated PrEP/PEP regimens with Emtricitabine(FTC)/Tenofovir Alafenamide(TAF) combined with different doses of Bictegravir(BIC) in a non-human primate model of SHIV exposure.

Methods: A pharmacokinetic study was conducted in rhesus macaques with varying amounts of BIC + FTC/TAF (200/25 mg) to select BIC dose. Two efficacy studies were performed with 6 to 8 repeat low dose SHIV162P3 rectal challenges 2 weeks apart to minimize residual drug exposure. Two oral doses of ARVs were administered at different times relative to virus exposure. In Study 1, BIC/FTC/TAF (25/200/25mg) or FTC/TAF (200/25mg) was given at -2h/+24h (n=6), +24/+48h (n=6), or +48h/+72h (n=6 or 5). Follow-up Study 2 tested 100mg BIC in combination with FTC/TAF, (100/200/25mg) given at +6h/+30h, +12/+36h, +24h/+48h, +48h/+72h or FTC/TAF (200/25mg) at +6h/+30h or +12/+36h (n=6 each). A Kaplan-Meier survival analysis was conducted and a log-rank test was used to compare time to infection relative to placebo controls.

Results: After 8 virus challenges in Study 1, BIC/FTC/TAF (25/200/25mg) protected 6/6 animals in the -2h/+24h group, 1/6 animals in the +24/+48h group and 0/6 animals in the +48/+72h group (Table 1). FTC/TAF alone protected 5/6 animals in the -2h/+24h group, 1/6 in the +24/+48h group and 0/5 in the +48/+72h group. After 6 virus challenges in Study 2, BIC/FTC/TAF (100/200/25mg) protected 5/6 animals in the +6h/+30h group, 6/6 animals in the +12/+36h, 4/6 animals in the +24h/+48h, and 3/6 animals in the +48h/+72h group (Table 1). In contrast, FTC/TAF (200/25mg) protected 3/6 animals in the +6h/+30h group and 4/6 animals in the +12/+36h group.

Conclusion: Two doses of FTC/TAF + BIC (100mg) initiated up to 24h after rectal virus exposure were protective in a SHIV/macaque model. FTC/TAF + BIC (25mg) provided similar protection to FTC/TAF alone and were only efficacious when used as -2/+24h regimen. These results provide support to further study FTC/TAF + BIC (100mg) as a simplified event-driven PEP regimen.

Table 1. Results of NHP PrEP/PEP Studies with B/F/TAF

Study 1 (8 challenges)				Study 2 (6 challenges)			
Treatment (mg)	**Timing of Treatment**	**Protected (n/N)**	**p-value***	**Treatment (mg)**	**Timing of Treatment**	**Protected (n/N)**	**p-value***
Placebo Control	multiple	0/6		**Placebo Control**	multiple	1/6	
B/F/TAF (25/200/25)	-2/+24h	6/6	<0.001	**B/F/TAF (100/200/25)**	+6/+30h	5/6	0.020
B/F/TAF (25/200/25)	+24/+48h	1/6	0.074	**B/F/TAF (100/200/25)**	+12/+36h	6/6	0.004
B/F/TAF (25/200/25)	+48/+72h	0/6	0.187	**B/F/TAF (100/200/25)**	+24/+48h	4/6	0.028
F/TAF (200/25)	-2/+24h	5/6	<0.001	**B/F/TAF (100/200/25)**	+48/+72h	3/4	0.093
F/TAF (200/25)	+24/+48h	1/6	0.244	**F/TAF (200/25)**	+6/+30h	3/6	0.301
F/TAF (200/25)	+48/+72h	0/5	0.743	**F/TAF (200/25)**	+12/+36h	4/6	0.061

* Log-rank (Mantel-Cox) test with comparison to placebo control.

88 ON-DEMAND HIV POSTEXPOSURE PROPHYLAXIS BY TAF/EVG VAGINAL INSERTS IN MACAQUES

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Background: Topical products for HIV prevention that can be administered on-demand, either pre- or post-viral exposure, remain an advantageous regimen for end-users that have infrequent or clustered intercourse or are unable to take daily pills. CONRAD has developed a topical insert co-formulated with tenofovir alafenamide fumarate (TAF) and elvitegravir (EVG) to provide end-users a flexible on-demand dosing regimen that may align with their needs and lifestyle. Recently, we showed in a macaque model that mimics vaginal HIV transmission in women that a vaginal insert containing a fixed-dose combination of TAF and EVG was highly effective in preventing SHIV infection when administered 4 hours before virus exposure. Here, we investigated the efficacy of the same TAF/EVG insert when administered 4 hours after SHIV exposure.
Methods: Normal cycling pigtail macaques (n=11) were exposed vaginally to SHIV162P3 once-weekly for 13 weeks. Six macaques received TAF/EVG inserts (20/16 mg) and 5 received a placebo. Inserts were placed in the posterior vagina near the cervix 4 hours after each SHIV exposure. Infection was monitored weekly by serology and RT-PCR of SHIV RNA in plasma. The concentrations of TAF, TFV, and EVG in plasma and TFV-DP in PBMCs were measured at 4 hours in a second group of 6 macaques that received the same TAF/EVG inserts once-weekly for 13 consecutive weeks.
Results: Four of the 5 macaques that received placebo inserts became infected with SHIV after a median of 4 challenges (range 2-13). In contrast, all 6 macaques that received TAF/EVG inserts 4h after SHIV exposure remained protected after 13 challenges and a 20-week follow-up period (p=0.009; log-rank test). The calculated PEP efficacy of TAF/EVG inserts was 100%. Of the 78 plasma specimens collected 4h post insert dosing, EVG was only detected in 1 sample (15 ng/ml); none had detectable TFV or TAF. Conversely, TFV-DP was detected in 42/59 PBMC samples; median level in samples with detectable TFV-DP was 147.5 [range=15-993] fmol/10^6 cells.
Conclusion: Vaginal administration of a single TAF/EVG insert several hours after virus exposure fully protected macaques against SHIV infection, thus increasing flexibility and expanding our established window of protection to 4 hours before or after sex. The observed high levels of TFV-DP in PBMCs by topical delivery of TAF is unique and may have contributed to protection. Our data support the clinical development of TAF/EVG inserts for on-demand PrEP/PEP for HIV prevention.

89LB WEEKLY ORAL ISLATRAVIR PROVIDES EFFECTIVE PEP AGAINST IV CHALLENGE WITH SIVMAC251

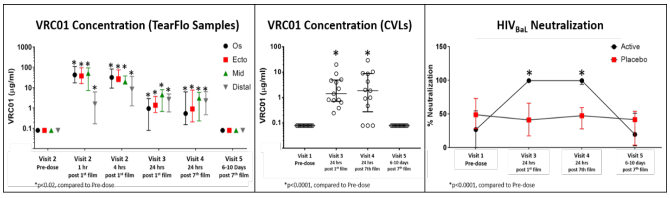
Martin Markowitz[1], Agegnehu Gettie[2], Leslie St. Bernard[1], James Blanchard[2], Brooke Grasperge[2], Kerry Fillgrove[3], Lingling Xue[3], Neal Dube[3], Daria Hazuda[3], Jay Grobler[3]
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Background: Islatravir (ISL, MK-8591, EFdA) is a novel nucleoside reverse transcriptase translocation inhibitor with robust antiviral activity and has demonstrated efficacy as weekly oral PrEP in the SHIV/Rhesus macaque (RM) rectal challenge model for doses ranging from 0.1 mg/kg to 3.9 mg/kg. We tested ISL's efficacy as post-exposure prophylaxis (PEP) in the SIV/RM IV challenge model.
Methods: 12 RM were challenged IV with 10 AID50 of SIVmac251. After 24 hr, 6 animals received 3.9 mg/kg ISL and 6 animals served as untreated controls. Treated animals in Stage I received a total of 4 weekly oral doses of ISL and were monitored for SIV infection for 7 wk after the 4th dose of ISL. In Stage II uninfected animals from Stage I were challenged as in Stage I and beginning 24h later 3 weekly oral doses of ISL at 3.9 mg/kg was initiated. Animals were monitored for 7 wk after the 3rd dose of ISL. Uninfected animals entered Stage III and were similarly challenged and treatment initiated at 24 h with 2 weekly oral doses of ISL at 3.9 mg/kg and animals monitored for 7 wk after the 2nd dose of ISL. Finally in Stage IV, uninfected animals were challenged IV and 24 hours later treated with a single oral dose of ISL at 3.9 mg/kg and followed for 7 wk. Animals were monitored for infection using RT-PCR and proviral DNA amplification. Virus-specific antibody responses were measured using a commercial assay. Plasma ISL levels as well as ISL-triphosphate (ISL-TP) levels in PBMC were measured longitudinally.
Results: All untreated control animals were viremic 7 days after IV challenge with SIVmac251. 6/6 treated animals were completely protected in Stages I-III (Fisher's exact test P=0.0022). ISL-TP levels became undetectable in PBMC 3 weeks on average after the last ISL oral dose. In Stage IV, two of 6 animals became infected with wild type SIVmac251, one with viremia at day 14 ([ISL-TP] < 0.02 pmol/10^6 PBMCs) and another at day 49 (Fisher's exact test P=0.06).
Conclusion: As few as 2 weekly oral doses of ISL at 3.9 mg/kg given 24h after IV challenge with SIVmac251 completely prevented infection. However, a single ISL dose 24h after IV challenge failed to provide statistically significant protection. As the ISL-TP $T_{1/2}$ in human PBMCs (79-214 hr) is substantially longer than RM (50 hr), it is conceivable that a single low oral dose given within 24 hours of HIV exposure may provide effective PEP. These results support the potential utility of ISL as a simplified PEP agent.

90 PHASE I PLACEBO-CONTROLED SAFETY, PK, AND PD STUDY OF MB66 ANTI-HIV AND ANTI-HSV FILM

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Background: Monoclonal antibodies(mAbs)show promise as multipurpose prevention technology.The MB66 intravaginal film contains 10 mg each of anti-HIV(VRC01) and anti-HSV(HSV8) mAbs to provide protection against two incurable viral infections.
Methods: The active film or vehicle control film was randomly assigned at a 1:1 ratio to 29 healthy sexually abstinent women who were instructed to insert 1 film daily for 7 days.Visits and clinical sampling occurred predose at 1, 4, 24 hrs after the 1st dose and 24 hrs, 6-10 days after the 7th dose. Cervicovaginal lavage samples (CVLs) were assayed by Luminex for 16 cytokines that have been associated with HIV transmission,by TZM-bl assay for HIV neutralization[strains:Q23-1 (R5 clade A), BaL (R5 clade B),and LAI (X4 clade B)],and by Plaque Reduction NeutralizationTest for HSV-2 neutralization [HSV-2 strain G].CVLs and TearFlo samples(4 vaginal sites)were assessed by ELISA for VRC01 and HSV8 mAb concentrations.
Results: There were 45 AEs;19 were deemed related to study product, but were balanced between active and placebo film (p's=1.0).There were no serious AEs(SAEs) and no significant differences in levels of proinflammatory cytokines, Nugent Scores,vaginal pH between Active and Placebo film groups(p's>0.10). Acceptability and willingness to use the product were judged to be high by post-use ACASI questionnaire.Concentrations of VRC01 and HSV8 increased significantly in vaginal secretions following insertion of Active film.Antibody levels in TearFlo samples peaked at 1 hr post-dosing (median:35 µg/mL) but remained significantly elevated at 24 hours post 1st and 7th film. (median: ~ 1.8 µg/mL). In light of an estimated dilution factor of 35 for the TearFlo samples,the extrapolated VRC01 concentrations range from 63-1,225 times IC_{50} for VRC01(~1 µg/mL).CVLs from the active film group, collected 24 hr after 1st film and 7th films,significantly neutralized all 3 HIV strains and HSV-2.
Conclusion: Repeated doses of MB66 film was safe and tolerated.Significant HIV-1 and HSV-2 neutralization (ex vivo) was observed at 24 hrs,7 films. Antibody levels in vagina had concentrations consistent with protection for up to 24 hrs.



Oral Abstracts

91 NEAR-PERFECT ACCURACY OF A REAL-TIME URINE TENOFOVIR TEST COMPARED TO LAB-BASED ELISA

Matthew A. Spinelli[1], Warren Rodrigues[2], Guohong Wang[2], Michael Vincent[2], David Glidden[1], Randy Stalter[3], Patricia A. Defechereux[1], Madeline Deutsch[1], Robert M. Grant[1], Kenneth Ngure[4], Nelly R. Mugo[3], Jared Baeten[3], Monica Gandhi[1], for the Partners PrEP and IBrEATHe

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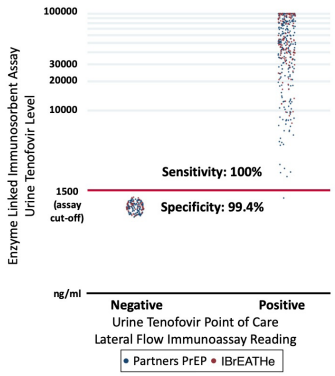
Background: Therapeutic drug monitoring measures adherence to tenofovir (TFV)-based PrEP more accurately than self-report but has not been available at the point-of-care (POC) until now. We developed an ELISA using a highly-selective antibody to TFV in urine and previously validated it against spectrometry-based methods with high accuracy. We have now developed a lateral flow immunoassay (LFA) using this antibody, which permits testing at the POC. A cut-off for the LFA of 1,500 ng/ml was previously selected from a directly observed therapy study to accurately classify recent dosing. The objective of this analysis was to compare a novel POC test for PrEP to laboratory-based ELISA in diverse patient populations.

Methods: Urine samples were analyzed using the ELISA and POC LFA test from two cohorts of PrEP users taking tenofovir disoproxil fumarate/emtricitabine: the Partners PrEP Study, which recruited heterosexual men and women, and the IBrEATHe Study, which recruited transwomen using estrogen and transmen using testosterone hormone therapy. We calculated the sensitivity and specificity of the POC test compared to laboratory-based ELISA at a cut-off of 1,500 ng/ml.

Results: Overall, 684 urine samples were tested from 324 participants in the two cohorts. In Partners PrEP, 454 samples from 278 participants (41% cisgender women) were tested; the median age was 33 years (interquartile range [QR] of 28-39). In IBrEATHe, 231 samples from 46 individuals (50% transwomen) were tested; the median age was 31 (IQR 25-40). Overall, of the 505 samples with tenofovir (TFV) levels greater than or equal to the cut-off using lab-based ELISA, 505 of the POC test results were also positive, yielding 100% sensitivity. Of the 179 samples with TFV levels below the cut-off, 178 were negative with the POC test, yielding 99.4% specificity. The accuracy of the POC LFA was 99.8% compared to ELISA.

Conclusion: In 324 women and men (both cisgender and transgender) taking PrEP, the sensitivity, specificity, and accuracy of a novel POC test for urine TFV all exceeded 99% when compared to a lab-based ELISA method. Given the association of low urine TFV levels with HIV seroconversion events, the simplicity of using the LFA, and its expected low cost, this POC test is a promising tool to support adherence to PrEP that could be widely scalable to real-world clinical settings. Adherence support using this POC test should be evaluated in a randomized controlled trial.

Figure: Comparison of a Novel Point of Care Urine Tenofovir Test to a Laboratory-Based ELISA Assay



92 LONGER-TERM SAFETY OF F/TAF AND F/TDF FOR HIV PREP: DISCOVER TRIAL WEEK-96 RESULTS

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Background: In DISCOVER, a multinational, double-blind, randomized controlled trial, F/TAF compared to F/TDF demonstrated noninferior efficacy for HIV prevention and improved bone mineral density (BMD) and renal safety biomarkers at week (W) 48. We now report W96 safety outcomes.

Methods: We evaluated renal and lipid parameters and weight changes in participants on F/TAF vs F/TDF through W96. BMD was evaluated in a substudy and also examined in younger participants (age <25 yrs) who are still accruing bone mass. We also examined glomerular function, proteinuria, and biomarkers of proximal tubular injury (PTI; β2M/Cr, RBP/Cr) in participants ≥50 yrs of age and those with moderate renal impairment (eGFR 60—<90 mL/min).

Results: Among 5387 participants evaluated, unlike those on F/TDF (n=2693), F/TAF users had significantly increased BMD, with the magnitude of between-group differences increasing between W48 to W96 (Table 1). Participants <25 yrs had greater declines in BMD on F/TDF with a greater magnitude of difference between groups than those ≥25 yrs. Overall, F/TAF users had increases in eGFR and declines in UPCR and PTI biomarkers. Older participants on F/TDF had a greater magnitude of decline in eGFR and a greater increase in UPCR and PTI markers compared to younger F/TDF users. Similarly, those with eGFR 60—<90 mL/min had greater statistically significant changes in PTI markers, if on TDF, compared with those with eGFR ≥90 mL/min. Those on F/TAF had stable lipids through W96, whereas those on F/TDF had decreases in lipids at W48 and W96. Those on F/TDF had a smaller weight increase than those on F/TAF through W96 (Table 1).

Conclusion: These DISCOVER data allow for the largest single-variable comparison of the two tenofovir prodrugs without underlying HIV infection and in the absence of third antiretroviral agents. Overall, those on F/TAF had increased BMD compared to declines in those on F/TDF, with more pronounced differences in younger participants. Older participants on F/TDF and those with impaired renal function had more adverse impact on renal biomarkers. Lipid and weight changes were consistent with the known lipid-lowering and weight suppressive effects of TDF, respectively. F/TAF is a safe, longer-term option for PrEP, with certain subgroups experiencing a greater magnitude of benefit in BMD and renal biomarkers.

Table 1.

	F/TAF (N=2694)	F/TDF (N=2693)
Renal		
Overall		
BL eGFR, mL/min / Δ W96*	**123** (105, 143) / **-0.6** (-11, 10)	**121.2** (104, 142) / **-4** (-13, 5)
BL urine RBP:Cr ratio, µg/g / % Δ W96*	**101** (73, 141) / **0.2** (-27, 36)	**104** (75, 146) / **21** (-14, 74)
BL urine β2M:Cr ratio, µg/g / % Δ W96*	**84** (61, 132) / **-15** (-45, 24)	**86** (63, 134) / **14** (-26, 100)
≥50 years of age		
BL eGFR, mL/min / Δ W96*	**103** (88, 122) / **-1** (-10, 6)	**100** (89, 117) / **-6** (-14, 2)
BL urine RBP:Cr ratio, µg/g / % Δ W96*	**111** (83, 176) / **0.5** (-28, 33)	**117** (83,117) / **34** (-6, 122)
BL urine β2M:Cr ratio, µg/g / % Δ W96*	**104** (65, 184) / **-21** (-55, 20)	**99** (69, 171) / **36** (-23, 185)
eGFR 60 to ≤90 mL/min		
BL eGFR, mL/min / Δ W96*	**83** (78, 87) / **3** (-4, 11)	**83** (77, 87) / **-1** (-7, 6)
BL urine RBP:Cr ratio, µg/g / % Δ W96*	**112** (79, 166) / **2** (-30, 46)	**114** (77, 198) / **53** (-6, 177)
BL urine β2M:Cr ratio, µg/g / % Δ W96*	**98** (66, 195) / **-14** (-55, 45)	**111** (67, 255) / **86** (-15, 451)
BMD, g/cm² (mean [SD])		
Overall		
BL hip / % Δ W96*	**1.03** (0.15) / **0.65** (2.96)	**1.02** (0.13) / **-1.01** (2.97)
BL spine / % Δ W96*	**1.13** (0.16) / **0.95** (3.40)	**1.13** (0.14) / **-1.39** (3.54)
<25 years of age		
BL hip / % Δ W96	**1.07** (0.23) / **1.21** (3.11)	**1.05** (0.14) / **-1.7** (3.34)
BL spine / % Δ W96	**1.13** (0.21) / **1.39** (2.69)	**1.12** (0.13) / **-1.2** (4.75)
Fasting lipids,¥ body weight		
Overall		
BL TC, mg/dL / Δ W96*	**172** (150, 197) / **-2** (-18, 15)	**173** (150, 197) / **-13** (-29, 5)
BL LDL cholesterol, mg/dL / Δ W96*	**99** (81, 120) / **-1** (-15, 14)	**100** (81, 121) / **-7** (-21, 5)
BL HDL cholesterol, mg/dL / Δ W96*	**49** (42, 59) / **-1** (-7, 4)	**50** (41, 60) / **-4** (-10, 1)
BL TC:HDL ratio / Δ W96	**3.4** (2.8, 4.3) / **0.1** (-0.3, 0.5)	**3.4** (2.8, 4.2) / **0.0** (-0.4, 0.4)
BL triglycerides, mg/dL / Δ W96*	**90** (67, 130) / **3** (-21, 29)	**90** (66, 130) / **-4** (-27, 21)
BL body weight, kg / Δ W96*	**80.7** (72.0, 91.0) / **1.7** (-1.0, 4.8)	**80.0** (71.3, 90.5) / **0.5** (-2.2, 3.5)

Values median (Q1, Q3) unless otherwise specified. *P <0.001. P-values: body weight from analysis of covariance (ANCOVA) model including BL F/TDF for PrEP and treatment as fixed effects BL weight as a covariate; for eGFR, urine RBP:Cr ratio, and urine β2M:Cr ratio from Van Elteren test stratified by BL F/TDF for PrEP to compare the 2 study arms; for BMD from ANOVA model with BL F/TDF for PrEP and treatment as fixed effects. ¥For fasting lipids, subject who took lipid modifying agents were excluded.
β2M, beta-2 macroglobulin; BL, baseline; eGFR, estimated glomerular filtration rate (Cockcroft Gault); RBP, retinol binding protein; TC, total cholesterol.

93 INITIATING PREP DURING ACUTE HIV INFECTION: WHAT IS THE RISK FOR ARV DRUG RESISTANCE?

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Background: Pre-exposure prophylaxis (PrEP) is very effective at preventing HIV infection. However, there is risk for antiretroviral drug (ARV) resistance if the 2-drug PrEP regimen is given to individuals with acute HIV infection.
Methods: Individuals at risk for HIV infection were screened with 4th generation HIV antibody/antigen (4thG) testing at the Thai Red Cross Anonymous Clinic (TRCAC), the largest HIV testing center in Thailand, performing over 40,000 tests annually. PrEP (TDF/FTC) was offered as part of a combined HIV prevention package, and could be started the same day. Qualitative HIV RNA (Aptima HIV-1, Hologic, USA) was done on 4thG non-reactive specimens using pools of up to 17 specimens to identify acute HIV infection (AHI), with result available in 24-48 hours, and confirmation by quantitative HIV RNA (Roche AmpliPrep/Taqman v2.0). PrEP users had repeat HIV testing and counseling at 1 month, 3 months, and then every 3 months.
Results: Through October 2018, 2,442 people started PrEP at the TRCAC; 93% were male and 83% were men who have sex with men (MSM). Median age was 32 (range 17-78) years. Seven individuals, or 1/350, had AHI at PrEP initiation. All 7 with AHI were MSM aged 22-39 years. AHI was identified by pooled qualitative HIV RNA in 5 cases; median quantitative HIV RNA was 317 (range 32-16,780) copies/mL. The remaining 2 cases were diagnosed by reactive HIV serology at the 1-month post-PrEP visit: in both the qualitative HIV RNA was negative, but quantitative HIV RNA on stored pre-PrEP specimens had detectable HIV RNA at 58-86 copies/mL. PrEP was used for a median 14 (range 2-121) days. ARV resistance data were available for 6 cases: 3 cases had single resistance mutations M184V/I, conferring high-level resistance to FTC. No cases had resistance mutations to TDF. The 3 cases that developed FTC-resistance took PrEP for 30, 34, and 121 days. The 3 cases without resistance mutations took PrEP for 2, 7, and 14 days.
Conclusion: AHI at PrEP start occurs in 1/350 PrEP users at the TRCAC. Qualitative HIV RNA on pooled samples will identify most, but not all cases of AHI. If AHI is identified early, immediately initiating 3-drug antiretroviral therapy (ART) can prevent ARV drug resistance. FTC resistance begins to emerge after 2-4 weeks of PrEP use. There appears to be lower risk for resistance to TDF. If HIV infection occurs during PrEP use, ARV resistance testing should be performed and ART started immediately.

94 PEPFAR DREAMS INTERVENTION AMONG ADOLESCENT GIRLS AND YOUNG WOMEN IN RAKAI, UGANDA

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Background: In 2016, the Presidents Emergency Plan for AIDS Relief (PEPFAR) initiated the DREAMS (Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe women) programs in10 sub-Saharan Africa countries including Uganda to reduce risk of HIV and domestic violence in adolescent girls and young women aged 15-24 (AGYW). We used population-based data to evaluate the impact of DREAMS in Rakai, south-central Uganda
Methods: We identified girls aged 15-24 years who participated in Rakai community cohort study (RCCS) survey between June 2018 - August 2019 and provided information on HIV risk behaviors and were tested for HIV. Risk behaviors were sexual debut, being sexually active, having non marital sexual partners, transactional sex, alcohol use and condom use with non-marital partners. DREAMS packages assessed were; participation in any DREAMS programs, stepping stones (ST) a participatory intervention for HIV prevention and strengthening relationship skills, combined social economic approaches (CSEA), HIV testing and counseling (HTC). Generalized linear models was used to estimate prevalence rate ratios (PRR) and 95% CI associated with risk behavior outcomes.
Results: A total of 1945 AGYW participated in the RCCS; 979 (50.3%) aged 15-19 years of whom 40.5% (397) had participated in the DREAMS programs. Among women aged 20-24, 24.1% (233) had participated in DREAMS. Among girls aged 15-19, ≥10 sessions of ST were associated with significant reduction in non-marital sexual partners (aPRR 0.54 ,95% CI=0.36 -0.93), sexual debut (aPRR 0.61 ,95% CI=0.42 -0.86) and being sexually active (aPRR 0.55,95% CI=0.37 -0.81), while receiving ≥5 ST sessions was associated with a significant reduction in alcohol use (aPRR 0.23,95% CI=0.10 -0.52). Among girls aged 20-24, receiving ST had no significant impact on any risk behaviors. CSEA and HTC were not found to affect risk behaviors in either age groups.
Conclusion: In this population-based study , a minimum of 10 ST sessions of the DREAMS ST program are required to reduce risk sexual behaviors among girls aged 15-19 years but no effects were observed with CSEA and HTC. No DREAMS interventions affected risk among women aged 20-24. DREAMS should be modified.

Table 1: Impact of the DREAM Stepping Stones sessions on HIV risk Behaviors among girls aged 15-19 years

Variable	n/N (row%)	PRR (CI)	P value	aPRR (CI)	P value
Non-marital sexual partners					
Stepping stone sessions					
None	252/674(37.4)	ref			
1-4	36/101(35.6)	0.95(0.67-1.35)	0.79	0.96(0.68-1.37)	0.84
5-9	16/65(24.6)	0.65(0.39-1.09)	0.10	0.68(0.41-1.13)	0.13
10 and more	25/139(18.0)	0.48(0.32-0.72)	<0.001	**0.54(0.36-0.83)**	0.005
Sexual debut					
Stepping stone sessions					
None	316/674(46.8)	ref			
1-4	49/101(48.5)	1.03(0.76-1.39)	0.80	1.03(0.76-1.39)	0.86
5-9	22/65(33.8)	0.72(0.47-1.11)	0.14	0.72(0.47-1.12)	0.14
10 and more	36/139(25.9)	0.55(39-0.78)	0.001	**0.61(0.43-0.86)**	**0.006**
Being sexually active					
Stepping stone sessions					
None	291/674(43.2)	ref			
1-4	39/101(38.6)	0.89(0.64-1.25)	0.51	0.89(0.64-1.25)	0.51
5-9	19/65(29.2)	0.68(0.42-1.08)	0.10	0.68(0.43-1.09)	0.11
10 and more	29/139(20.9)	0.48(0.33-0.71)	<0.001	**0.55(0.37-0.81)**	**0.002**
Alcohol use					
Stepping stone sessions					
None	126/674(18.7)				
1-4	10/101(9.9)	0.52(0.28-1.01)	0.05	0.54(0.28-1.03)	0.06
5-9	4/65(6.15)	0.33(0.12-0.89)	0.03	**0.34(0.12-0.92)**	**0.03**
10 and more	6/139(4.3)	0.23(0.10-0.52)	<0.001	0.27(0.12-0.62	0.002

DREAM= Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe women; PRR=Prevalence relative risk; aPRR= adjusted prevalence relative risk;

95 STING IN THE TAIL: HOW DNA TRIGGERS IMMUNE RESPONSES TO VIRAL INFECTIONS

Zhijian (James) Chen, *University of Texas Southwestern, Dallas, TX, USA*

The presence of DNA in the cytoplasm is a danger signal that alerts the host immune system to eliminate microbial infections, but inappropriate activation of this pathway by self DNA can also lead to autoimmune and autoinflammatory diseases. My talk will focus on our discoveries of cyclic GMP-AMP synthase (cGAS) as an innate immune sensor for cytosolic DNA and microbial pathogens, including HIV. Upon binding DNA, cGAS converts GTP and ATP into cyclic GMP-AMP (cGAMP), which functions as a second messenger that binds and activates the ER membrane protein STING. STING then activates the protein kinases IKK and TBK1, which in turn activates the transcription factors NF-kB and IRF3 to induce type-I interferons and other cytokines that together combat microbial infections. I will discuss our recent work on the biochemical mechanism by which cGAMP activates STING and the downstream signaling cascade.

96 TRIM5 RECOGNITION AND RESTRICTION OF HIV-1 AND RETROVIRUSES

Owen Pornillos, *University of Virginia, Charlottesville, VA, USA*

Restriction factors and pattern recognition receptors make up innate or intrinsic cellular defenses against viral infection. TRIM5 proteins are restriction factors and receptors that recognize the incoming cores of retroviruses by binding to the capsid that surrounds and protects the core. Upon capsid binding, TRIM5 proteins accelerate dissociation of the viral core, inhibit reverse transcription of the viral genome, and activate ubiquitin-dependent interferon signaling. TRIM5 proteins contain the tripartite motif fold (RING, B-box, and coiled-coil domains) and a C-terminal domain (SPRY or CypA) that mediates direct binding to retroviral capsids. Retroviral capsids are fullerene structures composed of about 1,500 copies of the viral CA protein, which are organized on a hexagonal lattice composed of about 250 hexamers and exactly 12 pentamers. TRIM5-mediated capsid recognition is driven by avidity, requiring higher-order assembly of multiple TRIM5 protein molecules on the capsid surface. I will discuss a series of studies, which collectively show that TRIM5 binds a retroviral capsid through a mechanism of hierarchical assembly. A limited number of local interaction

modes are successively organized as increasingly higher-order structures that culminate in a TRIM5 cage surrounding the capsid. Cage formation explains the mechanism of restriction and provides the structure/function context that links core recognition to ubiquitin-dependent processes that disable the retrovirus and signal the presence of an invader.

97 HIV-1 AVOIDS BEING ZAPPED

Janet L. Smith, *University of Michigan, Ann Arbor, MI, USA*

Human cells have a variety of schemes to distinguish self from non-self molecules. The zinc finger antiviral protein (ZAP) surveils the cytoplasm and directs the destruction of RNAs from a number of viruses. How this occurs was unknown until Bieniasz and co-workers discovered that ZAP recognizes CpG dinucleotides, which are naturally depleted in animal genomes and mRNAs [1]. The sensitivity of RNA viruses to ZAP is correlated with the CpG content of the viral genome. HIV-1 has both a low CpG content and a natural resistance to ZAP, but it became ZAP-sensitive when the CpG content was increased by synonymous mutation. Thus HIV-1 seems to have evolved to avoid ZAP inhibition. The ZAP protein has a 230-amino-acid N-terminal domain (NTD) for RNA recognition; this domain includes four 'CCCH' zinc finger structures, as exist in many RNA-binding proteins. The functions of the following WWE and poly(ADP-ribose) polymerase (PARP) domains of ZAP are unknown, but may include recruitment of enzymes for RNA destruction, for example the putative endonuclease, KHNYN, that is required for antiretroviral activity. We solved a crystal structure of the human ZAP NTD with an RNA oligomer from the CpG-enriched HIV-1 genome and discovered that only zinc finger 2 (ZnF2) recognizes the CpG dinucleotide [2]. Single amino acid substitutions in ZnF2 abolished selective binding of ZAP to CpG-enhanced regions of the HIV-1 genome and also eliminated the ability of ZAP to selectively inhibit CpG-enriched HIV-1. Analogous substitutions in ZnF1,3,4 had no impact on antiviral activity. Overall, ZAP seems to constrain the nucleotide sequence of the HIV-1 genome and may provide a defense against viruses whose genomes have higher CpG content.

[1] Takata et al. & Bieniasz. Nature 550, 124-127 (2017).
[2] Meagher, Takata et al., Bieniasz & Smith. PNAS 116, 24303-24309 (2019).

98 SERINC STRUCTURE AND RESTRICTION OF HIV-1 INFECTIVITY

Valerie Pye, *The Francis Crick Institute, London, UK*

The human integral membrane protein SERINC5 potently restricts HIV-1 infectivity by inhibiting viral entry and sensitises the virus to antibody-mediated neutralisation. To eliminate the effect of SERINC5, HIV 1 encodes the endocytic adaptor protein Nef, which redirects SERINC5 to endosomal compartments, thereby preventing its inclusion into budding viral particles. Understanding the molecular basis of retroviral restriction by SERINC5 and its down-regulation by HIV-1 Nef may aid in development of antiviral therapeutic approaches. We determined the three-dimensional structures of human SERINC5 and its ortholog from Drosophila melanogaster at subnanometer and near-atomic resolution, respectively, using cryo-electron microscopy. An extensive panel of SERINC5 mutants were tested for the ability to inhibit Nef-negative HIV-1 infectivity and localisation to the plasma membrane. The SERINC structures reveal a novel protein fold comprised of ten transmembrane helices organised into two subdomains and bisected by a long diagonal helix. Clusters of conserved residues and a lipid binding groove highlight potential functional sites. Extensive structure-based mutagenesis scan identified surface-exposed regions and the interface between the subdomains, as critical for SERINC5 restriction activity. The same regions are also important for viral sensitisation to neutralising antibodies, directly linking SERINC5 restriction activity with the remodelling of HIV-1 envelope glycoprotein. SERINC5 variants, which were not surface exposed, were unable to inhibit HIV-1 infectivity arguing that the protein must be located at the plasma membrane to exert its antiviral activity. Our structures and extensive functional data provide the first insights at the molecular level of SERINC proteins and their ability to restrict HIV-1 infection.

99 NEUROHIV IN THE GLOBAL CONTEXT: ADVANCING THE CONTINUUM OF CARE AND ACHIEVING EQUITY

Kiran T. Thakur, *Columbia University, New York, NY, USA*

Though significant advancements have been made in the field of neuroHIV, neurological and mental health conditions remain major contributors to morbidity and mortality worldwide, particularly in resource-limited settings. In this talk, we will discuss how HIV impacts brain health throughout the lifespan with a discussion on the current global epidemiology of neuroHIV (including the global epidemiology of HIV neurocognitive disorder, CNS opportunistic infections, mental health disorders, etc). We will also identify epidemiological knowledge gaps, specifically highlighting gaps in resource-limited settings. We will discuss discoveries and achievements in neuroHIV since the beginning of the HIV epidemic and will highlight the importance of brain health in the HIV care continuum model. We will then discuss important facets of neurological care across the lifespan with a discussion on pediatric neuroHIV including HIV-associated neurocognitive effects in children and the impact of in-utero exposure to maternal HIV and antiretroviral medications. We will discuss neurological conditions amongst adolescents and adults, as well as gender-related issues in neurological and mental health. We will then focus on the chronic neurological care of people living with HIV, and discuss the impact of HIV on our growing global aging population. We will discuss the growth in dementia and stroke burden worldwide, and the "double burden" of traditional risk factors for cerebrovascular disease and cognitive decline and HIV infection. We will then discuss the current neurological care areas which specifically impact people living with HIV including access and availability of high quality neurological care and mental health resources, the availability of high quality drugs such as antiepileptic medications, access to diagnostic testing including laboratory infrastructure needs, and neurorehabilitation resources. We will focus on how to address disparities in care in vulnerable populations, and the associated stigma in people living with HIV with neurological conditions. We will identify mechanisms to reduce the burden of neurological conditions in people living with HIV worldwide, with an emphasis on improving access and quality of care over the coming decade. Finally, we will emphasize the importance of focusing on brain health as major priority in HIV care in the coming years.

100 HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS AND AGING IN THE GLOBAL SETTING

John Joska, *1University of Cape Town, Cape Town, South Africa*

HIV remains highly prevalent in sub-Saharan Africa with nearly 1:5 adults aged 15-49 years infected in South Africa (SA). Although SA also has the largest antiretroviral (ART) program globally, with >2 million PLWH accessing care, a significant proportion of individuals remain ART naïve. The result is two sub-populations- one at high risk of the effects of immunocompromise, and the other living with chronic HIV and the emergent problems of aging. Despite early reports that clade C was less neuro-virulent, regional data suggest that HIV tat variants are not neuro-protective. The presence of neurocognitive impairment is likely impacted by education, early life adversity, neurologic and psychiatric co-morbidity and delays in entering care. ART neurotoxicity is not well understood at a population level, but the up-coming programmatic switch to first-line dolutegravir from efavirenz in SA may help. HAND is not routinely recognized or diagnosed in routine clinical care. Screening tools such as the IHDS and CAT-rapid have been validated in South Africa, with comparable sensitivity and specificity to the USA, but few providers are comfortable using them. Other tools, such as the Community Screening Instrument for Dementia have been used widely across multiple resource-limited settings, but in older persons. Other challenges to diagnosis include the risk of over-diagnosis, especially of mild HAND, the assessment of functional impairment, and the detection of co-morbidities. There are no effective adjuvant treatments for HAND. Effective viral control is key, with CSF escape likely very uncommon. Thoughtful psycho-education, treatment support, and possibly patient-tailored medication management and problem-solving strategies may help. HIV infection in persons >60 years is common and will become a growing problem. Neurodegenerative disorders, including Alzheimer's and Vascular dementia, are prevalent in older South Africans. The contribution of HIV infection to morbidity is not well understood, even in well-resourced settings. A life-span, patient-centered approach may afford the best outcomes: improving early education, the effects of poverty, managing mid-life risk factors, early HIV diagnosis, and effective ART will probably reduce the disease burden substantially. If one is honest, current Alzheimer treatments are only modestly effective and unaffordable in low-resource settings. We will have to look for cheaper, disease-modifying treatments.

101 HIV AND MENTAL HEALTH: THE IMPACT OF THE COMORBIDITY IN RESOURCE-CONSTRAINED SETTINGS

Bibilola D. Oladeji, *University of Ibadan, Ibadan, Nigeria*

There is a complex bi-directional relationship between HIV infection and mental health. It is well recognized worldwide that the prevalence of mental

disorders including depression, anxiety disorders, and substance use disorders is higher in people living with HIV (PLHIV) compared to the general population. Reported prevalence estimates of mental and substance use disorders in PLHIV in low- and middle-income countries (LMIC) range between 19% and 50%, with depression being the commonest. This increased risk is often mediated by a mix of factors which could be biological- related the virus and its treatment, psychological- related to stigma and coping, as well as behavioral-related to adherence to medication and retention in care. The presence of mental disorders in PLHIV is often associated with an increased risk of HIV disease progression, poor adherence to antiretroviral therapy and excess mortality. An often overlooked and less well researched aspect of this relationship is the higher risk of HIV amongst people with serious mental disorders such as bipolar affective disorders, schizophrenia and schizoaffective disorders. Patients with comorbid mental disorders and HIV are more likely to delay HIV treatment initiation and more likely to engage in HIV risk behaviors and hence are potential drivers for the continued spread of the virus especially in parts of sub-Saharan Africa with high HIV prevalence rates. Whilst mental health services have become widespread in HIV care and support services in high-income countries (HIC), low- and middle-income countries that bear a disproportionate burden of the HIV infection are still lagging behind in developing appropriate services to meet the mental health needs of PLHIV. Health systems in low- and middle-income countries are commonly overburdened and characterized by poor human and financial resources which are particularly worse for mental health care. Adoption of a stepped care, task sharing approach is likely to be the most viable option. However, research evidence for the most appropriate models that can deliver effective and cost-effective integrated care in LMIC is still sparse. Meeting the UNAIDS 90-90-90 goal will require commitment to expanding culturally appropriate mental health services for PLHIV, especially in LMICs, that include prevention of transmission of the infection in people with mental disorders, early identification of mental disorders in PLHIV and the provision of evidence-based care.

102 CEREBROVASCULAR DISEASE AND HIV IN THE GLOBAL SETTING: DATA FROM ASIA AND BEYOND

Felicia C. Chow, *University of California San Francisco, San Francisco, CA, USA*

Stroke is the second leading cause of death worldwide. An estimated 1 in 4 25-year-olds globally will have a stroke during their lifespan. The largest burden of stroke (over 75% of stroke mortality and 80% of disability-adjusted life years) is shouldered by low-and-middle income countries (LMIC) where, in sharp contrast to high-income countries (HIC) that have been experiencing a decline in stroke incidence, stroke rates are steadily rising. Furthermore, strokes in LMIC occur at a younger mean age, affecting individuals during the peak of their productivity. This global stroke crisis poses a major threat to many of the same regions of the world where HIV prevalence is high. This presentation will focus on cerebrovascular disease in persons living with HIV (PLWH) in Asia, with its exceedingly high global lifetime risk of stroke, and sub-Saharan African (SSA), which has seen a rapid acceleration in stroke rates. We will review available data on the epidemiology of HIV-associated stroke in LMIC, drawing attention to similarities and differences in stroke risk factors, pathogenesis, and outcomes between LMIC and HIC. One recurring theme is the strong association between HIV and stroke in younger age groups and, similar to in the general population in LMIC, a younger age at diagnosis of first-time stroke in PLWH, underscoring the pivotal role that HIV plays in stroke in the young. We will also discuss the implications of increased cerebrovascular risk in PLWH on cognitive impairment and potential differences in the contribution of cerebrovascular dysfunction to cognitive health between women and men living with HIV. Finally, with the overall paucity of data on cerebrovascular disease in PLWH from LMIC, we will underscore gaps in knowledge where research efforts should be focused.

103 GLOBAL ELIMINATION OF HEPATITIS B VIRUS

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Chronic hepatitis B virus (HBV) infection affects 250 million persons worldwide and is the most important cause of liver cirrhosis and cancer. In 2017, the World Health Organization outlined specific targets along the prevention and care cascade to be met if the elimination of HBV as a global health threat was to be achieved. Among the proposed core interventions, global service coverage of the HBV vaccine birth dose, as well as the uptake of testing and antiviral therapy remain largely insufficient. This presentation will highlight the key determinants of global HBV elimination and discuss the main challenges that will be faced during the implementation of prevention and care interventions. It will also insist on the importance of addressing logistic and sociocultural barriers, especially in resource-limited countries where the HBV burden is highest. As many of the challenges expected to arise on the road to HBV elimination are similar to those experienced during the fight against HIV, it will be critical to learn the lessons from the past 30 years and avoid making the same mistakes. Recent improvements in the understanding of the HBV life cycle and the development of promising treatment modalities to achieve the functional cure of HBV have helped move HBV elimination up the global political agenda. However, HBV elimination will only be achieved if these scientific achievements are accompanied by the rapid uptake of HBV vaccination, testing and treatment. To succeed, HBV elimination efforts will heavily rely on innovative public health strategies, education and political will.

104 ADAPTING THE IMMUNE RESPONSE TO CURE HEPATITIS B

Barbara Rehermann, *NIH, Bethesda, MD, USA*

Approximately 257 million people worldwide are chronically infected with the hepatitis B virus (HBV). About 900,000 people die from HBV-related liver failure and/or hepatocellular carcinoma each year, which makes HBV more deadly than HIV and malaria. Unfortunately, the incidence of HBV-related mortality is projected to increase further in the coming decades. The goal of curative treatments for chronic HBV infection is a functional cure, defined as sustained loss of hepatitis B surface antigen (HBsAg) with or without anti-HBsAg antibodies. Clearance of HBsAg is a durable endpoint and associated with improved long-term clinical outcome. Unfortunately, nucleos(t)ide analogues are not sufficient to achieve cure, because they do not eliminate the covalently closed circular HBV DNA nor the HBV DNA that has integrated into the human genome. Treatment with pegylated IFNalpha can achieve this cure, albeit only in a minority (2-10%) of chronically HBV infected patients. Its immunomodulatory effects are thought to be important in this process. Although we understand many features of acute self- limited hepatitis B and natural and vaccine-induced immunity, our understanding of immune response in chronic hepatitis B is still limited. One of the keys to curing chronic infection lies in a better understanding of innate and adaptive immune responses in early childhood and the first two decades of life. New insights are emerging that HBV induces innate immune cell maturation and T-helper type 1 cell differentiation (trained immunity) in early life and that an age-related increase in inflammation contributes to changes in disease activity during later life. This presentation will review the role of innate and adaptive immune responses in the control of acute HBV infection, their modulation during the distinct clinical phases of chronic infection and immune therapeutic strategies to induce a functional cure.

105 HEPATITIS B VIRUS: NEW AGENTS

Raymond T. Chung, *Harvard University, Cambridge, MA, USA*

The goals of hepatitis B virus (HBV) treatment are to: 1) achieve sustained suppression of HBV replication, 2) decrease liver injury and 3) prevent cirrhosis, liver failure, hepatocellular carcinoma (HCC) and death. Currently available FDA-approved therapies have been able to deliver on each of these clinical goals, using well-tolerated nucleos(t)ide analogues with high barriers to resistance. However, they are limited in their ability to yield functional cure (loss of HBsAg with or without anti-HBs seroconversion). Hence, there remains a large unmet clinical need.

The ultimate clinical goal is to achieve functional cure of HBV with a finite course of treatment. However, there are many challenges to HBV functional cure. Most importantly, like HIV, HBV has a latent form, covalent closed circular DNA (cccDNA), a highly stable episomal form of the HBV genome that serves as the template for new HBV transcription in the nucleus. Moreover, a fraction of HBV DNA is also integrated into the host genome, and there is evidence that a portion of integrated HBV DNA, particularly HBsAg, can be translated. These stable forms are largely untouched by current therapies. There is also evidence that in chronic hepatitis B (CHB), the adaptive virus-specific immune response becomes exhausted, further contributing to chronicity.

The latest therapies in the pipeline seek to achieve HBsAg loss using approaches that target other, discrete steps in the HBV lifecycle as well as modulate the immune environment essential for clearance. Novel antiviral therapies in clinical development include entry inhibitors, capsid assembly modifiers to block assembly and possibly replenishment of cccDNA, RNA interference (siRNA) to block viral protein production, and nucleic acid polymers to block HBsAg release. Immunomodulatory therapies include strategies both to stimulate

innate and adaptive responses and to block inhibitory pathways. The targeting of the adaptive immune response may be particularly critical, since functional cure observed during spontaneous resolution of acute hepatitis B (sAg loss, sAb seroconversion) is heavily dependent on a brisk T cell response. In this regard, success using an anti-PD-1 approach has been observed in early studies of these agents in chronic hepatitis B. It is likely that some combination of these novel treatment approaches and existing approved agents will be necessary to achieve functional cure.

106 THE MATHEMATICS OF HEPATITIS B CURE

Alan S. Perelson, *Los Alamos National Laboratory, Los Alamos, NM, USA*

Current therapies for HBV infection generate a sterilizing or functional cure in a very small fraction of treated individuals. Thus, many new therapeutic approaches are under preclinical and clinical development. Here I will show how insights into these new therapies and HBV biology can be gained by mathematically modeling some of the accumulating experimental data. For example, by blocking new infections with the entry inhibitor Myrculdex B (Myr-B), one can gain insight into the lifespan of HBV-infected hepatocytes. Analysis of viral load decay after initiation of Myr-B therapy suggests that there may be heterogeneity in the lifespan of HBV infected cells in vivo, with some infected cells living much longer than others and producing less virus. As another example, I will show how new mathematical models are able to provide quantitative insights into the effects of monotherapy using a capsid inhibitor (CI) and combination therapies of a CI with a nucleic acid analog. Lastly, I will discuss how modeling is providing new estimates of the plasma half-life of HbsAg (as well as that of other species such as HBV DNA and ALT) which may inform therapeutic progress and duration of therapy need to achieve a functional cure.

107 DRUG-DRUG INTERACTIONS: THE UPS AND DOWNS OF ANTIRETROVIRALS PLUS CONTRACEPTIVES

Kimberly K. Scarsi, *University of Nebraska, Omaha, NE, USA*

Over half of individuals living with or at risk for HIV are of childbearing potential and in need of effective contraception to prevent unintended pregnancies. One barrier to effective hormonal contraception is drug-drug interactions (DDIs) between antiretrovirals (ARVs) and hormones. Interpreting the clinical impact of ARV-hormone DDI data is complicated by an inadequate understanding of hormone pharmacology, including the therapeutic range of different contraceptive products. For example, efavirenz decreases progestin exposure by 10-85%, depending on the progestin studied and the route of administration, yet the clinical impact of this reduction was not realized until subdermal contraceptive implants were scaled-up in combination with efavirenz-based antiretroviral therapy (ART). Specifically, data from a large cohort in Kenya described a 3-fold increase in the risk of pregnancy when progestin-releasing subdermal implants were combined with efavirenz-based ART, yet this excess risk was not observed with depot medroxyprogesterone or oral contraceptives. In addition, some data describe modestly lower ARV exposure when combined with hormones, suggesting the potential for bidirectional ARV-hormone DDIs. To investigate DDIs during ARV development, first, one study is conducted between the ARV and a combination of oral contraceptives in healthy volunteers. DDI information from that study is then extrapolated across contraceptives. This approach presumes that all types of exogenous progestins and estrogens have a similar pharmacokinetic disposition and that the route of administration does not influence the DDI potential of the combination. Recently, studies of non-oral hormones have observed differences in the extent of ARV-hormone DDIs compared to oral studies. Further, individual characteristics, including pharmacogenetics, are emerging as important determinants of the magnitude of DDIs. Taken together, applying a single oral DDI study across diverse populations, different hormones, and variable routes of administration greatly simplify the complex nature of these DDIs. As the field enters an era of HIV treatment and prevention with non-oral ARVs and ARV-hormone multi-purpose technologies to simultaneously prevent both HIV and pregnancy, there lies a critical gap in our understanding of how existing DDI data will extend to these new products across diverse patient populations.

108 CONTRACEPTIVE IMPLANT ROLLOUT IN SOUTH AFRICA

Gregory Petro, *University of Cape Town, Cape Town, South Africa*

109 CONTRACEPTION AND HIV RISK: A CONUNDRUM NO MORE

Renee Heffron, *University of Washington, Seattle, WA, USA*

This talk will provide state-of-the-art evidence on why we have come to understand that injectable depot medroxyprogesterone acetate does not impact women's susceptibility to HIV infection. It will also examine reasons why data from recent studies have had conflicting results, discuss biologic changes elicited by contraceptive initiation that are relevant for women's health beyond HIV susceptibility, and point out consequential questions in this domain that are remaining to be addressed.

110 THE STATE OF SRHR & HIV SERVICES FOR CISGENDER WOMEN: A COMMUNITY PERSPECTIVE

Wame Jallow, *International Treatment Preparedness Coalition, Gaborone, Botswana*

Globally, 19.1 million of the 36.9 million people living with HIV are cisgender women and girls. Countries are failing to meet commitments to the 2016 United Nations Political Declaration on Ending AIDS among adolescent girls and young women (ages 15 to 24), including reducing new HIV infections to below 100,000 per year by 2020, eliminating gender inequalities and all forms of gender-based abuse and violence, encouraging and supporting leadership of young people, scaling up comprehensive sexual and reproductive health education, and protecting their human rights.

In 2018, a potential safety signal associating peri-conception dolutegravir (DTG) use with neural tube defects (NTDs) was reported. It cast a harsh spotlight on chronic problems: access to and quality of essential sexual and reproductive health rights and services for women and girls at risk for or living with HIV - particularly among those ages 14-49. The policy and access fallouts from the DTG signal – including national sex-based treatment restrictions for women and adolescent girls - has underscored that they must be essential stakeholders in design, development, implementation, delivery and oversight of HIV research, guidelines, policies and services.

In sub-Saharan Africa, which is home to the world's highest HIV rate and the lowest prevalence of contraception, access to and quality of essential sexual and reproductive health rights and services are complicated by a range of gender, social, economic, geographic, provider-level, structural and other barriers, limited choices, and lack of information – especially for younger, unmarried and rural women. A survey to assess the current status of sexual and reproductive rights, and HIV services was conducted in January 2020 among women and girls living with HIV in sub-Saharan Africa. Survey participants shared barriers to, and quality of these services - including access to optimal HIV treatment, what should be included in a 'package of care' - and their research and policy recommendations for implementing and monitoring solutions.

111 RECENT ADVANCES IN THE DIAGNOSIS, TREATMENT AND PREVENTION OF TUBERCULOSIS

Gavin Churchyard, *The Aurum Institute, Johannesburg, South Africa*

Recent advances in the diagnosis, treatment, and prevention of tuberculosis (TB) will be summarized and the importance of these advances for people with HIV discussed. Gaps in current knowledge that need to be addressed to accelerate progress towards ending the TB epidemic will be identified. A roadmap for TB related presentations at CROI will be presented.

112 ENGINEERING VACCINE IMMUNITY

Shane Crotty, *La Jolla Institute for Allergy and Immunology, La Jolla, CA, USA*

Understanding the immunology of helper T cells, germinal centers, and the human naive B cell repertoire to enable better vaccine design

Most vaccines provide protection from infection through the generation of neutralizing antibodies (nAbs). The repertoire of naive B cells is the starting material from which nAbs eventually arise. Immunization strategies are increasingly targeting precise B cell specificities to mimic nAbs generated during natural infection, in an effort to maximize the potency of the vaccine-elicited Ab response. An understanding of the human B cell specificities capable of immunogen recognition can aid in immunogen design and inform decision-making for clinical trial advancement. We have developed strategies to probe for antigen-specific B cells in the human naive B cell repertoire (Science 2016, Science Translational Medicine 2018, COI 2018, and Science 2019)

Germinal centers (GCs) are the engines of affinity maturation and are the critical source of memory B cells and long-lived plasma cells. GCs are entirely dependent on T follicular helper (Tfh) CD4 T cells (Immunity 2019). Helping B

cells and antibody responses is a major function of CD4+ T cells. It has been 10 years since the publication of Bcl6 as the lineage defining transcription factor for T follicular helper (Tfh) differentiation and the requirement of Tfh cells as the specialized subset of CD4+ T cells needed for germinal centers and related B cell responses. A great deal has been learned about Tfh cells in the past 10 years. Using longitudinal tracking of GCs in draining lymph nodes, using fine needle aspirates (FNAs), we found that two independent methods of slow delivery immunization of rhesus monkeys (RM) resulted in larger GCs, more robust and sustained GC-Tfh cell responses, and GC B cells with improved Env-binding. These GC-associated cell differences correlated with the development of ~20- to 30-fold higher titers of tier 2 HIV nAbs in animals immunized via slow delivery modalities. By analyzing IgV gene usage, we were able to determine that slow delivery immunization enhances HIV neutralizing antibody and GC responses via modulation of immunodominance (Cell, 2019). Slow delivery immunization therefore engages the immune system in unique ways, and novel strategies to accomplish slow delivery immunization in human vaccines will be discussed.

113 IL-6 BLOCKADE DECREASES INFLAMMATION AND INCREASES CD127 EXPRESSION IN HIV INFECTION

Benigno Rodriguez[1], Zhengyi Chen[1], Curtis Tatsuoka[1], Scott F Sieg[1], Alan Landay[2], Grace A. McComsey[1], Brian Clagett[1], Chris T. Longenecker[1], Carey Shive[1], Keith W. Crawford[3], Daniela Moisi[1], Michael L. Freeman[1], Nicholas Funderburg[4], Leonard Calabrese[5], Michael M. Lederman[1]

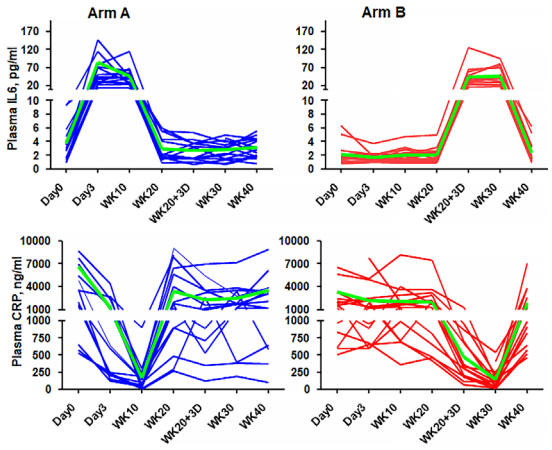
[1]Case Western Reserve University, Cleveland, OH, USA, [2]Rush University, Chicago, IL, USA, [3]NIAID, Rockville, MD, USA, [4]The Ohio State University, Columbus, OH, USA, [5]Cleveland Clinic, Cleveland, OH, USA

Background: Interleukin-6 (IL6) is a key inflammatory mediator in treated HIV infection. In vitro, we have shown that IL6 drives cell cycling and blocks responsiveness to interleukin-7 (IL-7). In vivo, plasma levels of IL6 are linked to cardiovascular risk and other end-organ complications. We hypothesized that blocking IL6 signaling in vivo could attenuate these effects.

Methods: HIV-infected persons with suppressed viremia and CD4 T cell counts >350 were enrolled in a 2x2 crossover trial of 3 monthly IV doses of the anti-IL6 receptor monoclonal antibody tocilizumab (TCZ) and matching placebo. T cell subpopulations, expression of markers of activation, senescence, cycling, and survival were quantified by flow cytometry. Soluble vascular, metabolic, and inflammation indices were measured by ELISA. Significance of treatment-induced changes was assessed by Wilcoxon signed-rank test. Mixed effects models were fitted to generate effect estimates and for covariate adjustment.

Results: Thirty-four participants were enrolled; 29 continued treatment through the crossover visit at week 20. Two discontinued due to adverse events: grade 3 rash and neutropenia. Both resolved without treatment. IL-6 receptor blockade by TCZ led to a profound decrease in plasma C-reactive protein (CRP) (-2037 ng/mL, $p<0.001$) and a dramatic increase in plasma IL-6 (42 pg/mL, $p<0.001$). PD-1 expression on naïve (-2%, $p<0.001$) and central memory (-3%, p,0.01) CD4 T cells decreased significantly; this was accompanied by a significant decrease in naïve CD4 T cell cycling (Ki-67 expression, -0.2 %, $p=0.01$) and by a significant increase in IL-7 receptor (CD127) expression on naïve (0.7%, $p=0.02$) and terminally differentiated (3%, $p=0.03$) CD8 T cells, as well as a significant decrease in plasma IL7 levels (-1 pg/mL, $p<0.001$). TCZ also led to significant decreases in soluble TNF receptor-1, soluble CD14, soluble CD40, and p-selectin. E-selectin, adiponectin. Most lipid species in plasma including oxidized LDL increased with TCZ. Lp-PLA-2 also increased modestly.

Conclusion: Blockade of IL-6 activity markedly decreases soluble markers of inflammation and indices of CD4 T activation/regulation that have been linked to morbidities in treated HIV infection. TCZ enhances expression of the IL7 receptor CD127 on some CD8 subpopulations, which may explain decreased plasma IL7 levels. The combination of these effects may result in reduced turnover and dysfunction of T cells in treated HIV infection.



114 NEUTRALIZING ANTIBODIES AND TRMS PROVIDE ENHANCED AND DURABLE RESISTANCE AGAINST HIV

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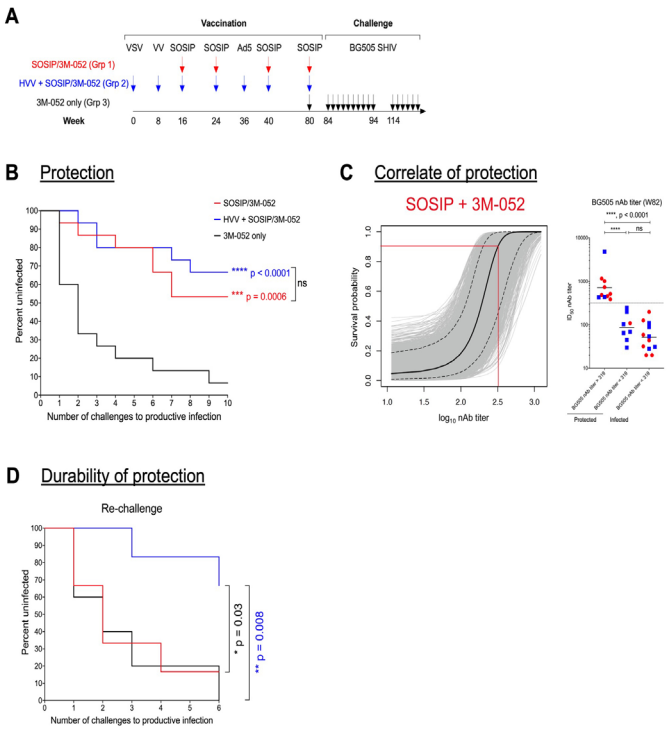
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Background: A broadly cross-reactive neutralizing antibody response is necessary to prevent infection from diverse strains of HIV. Induction of such broadly neutralizing antibodies by vaccination has been challenging but current approaches can induce autologous neutralizing antibodies (nAbs) in various animal models. Here we tested if vaccine-induced nAbs alone or in combination with cellular immune responses can protect rhesus macaques (RMs) against intravaginal challenges with the autologous strain of virus representative of circulating HIV-1 strains.

Methods: We immunized three groups of RMs as follows: group 1 with a trimeric HIV envelope protein (BG505 SOSIP.664) adjuvanted with the TLR7/8 ligand 3M-052, alone to induce nAbs; group 2 with a heterologous viral vector regimen expressing SIVmac239 Gag to induce tissue-resident memory CD8 T cells (TRMs, which traffic to and reside in mucosal tissues), as well as with BG505 SOSIP.664/3M-052 as in group 1; and group 3 as controls with 3M-052 alone. One month after the final protein vaccination, we challenged the animals weekly, in total 10 times, with SHIV-BG505 via the intravaginal route to measure vaccine-induced protection. We then identified immune correlates of protection. Finally, vaginal tissues were isolated from four protected animals from group 2 following necropsy, and were stimulated ex vivo with cognate Gag peptides to reactivate TRMs. The impact of TRM activation was analyzed by CITE-seq single-cell RNA sequencing to identify a possible mechanism(s) by which the TRMs enhanced protection.

Results: The protein and HVV immunizations were immunogenic as measured by high autologous nAb titers and Gag-specific T cell responses, respectively. Following 10 weekly vaginal challenges with SHIV-BG505, protection was observed in both immunization groups: 53.3% and 66.7% in groups 1 and 2, respectively. A nAb titer above ~300 represented the primary correlate of protection in group 1 animals. Surprisingly, in group 2, nAb response was not the primary correlate. A majority of the protected animals had nAb titers <300 suggesting that the TRMs reduced the nAb threshold associated with protection. Furthermore, protection observed in group 2 was durable as these animals resisted six additional challenges five months later with the same virus. Ex vivo restimulation of TRMs in vaginal tissues revealed rapid induction of local antiviral immunity.

Conclusion: TRMs can reduce nAb threshold and provide durable protection against HIV.



115LB HUMAN NK CELLS DEVELOP ANTIGEN-SPECIFIC IMMUNOLOGICAL MEMORY OF HIV

Stephanie Jost[1], Olivier Lucar[1], Haley Dugan[2], Marcus Altfeld[3], Paul Goepfert[4], R. Keith Reeves[1]

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Background: Beyond their ability to eliminate infected cells without the need for prior sensitization, murine, non-human primate and human natural killer (NK) cells have been shown to mediate virus-specific recall responses. However, whether NK cells can mediate HIV antigen-specific immunological memory in humans remains to be demonstrated.

Methods: Using calcein acetoxymethyl ester- or flow cytometry-based cytotoxicity assays, we tested the ability of bulk and clonally expanded individual NK cells to lyse MHC-devoid K562 cell lines or autologous B-LCLs left unpulsed or pulsed with pools of self-antigen-, CMV-, CMV/EBV/influenza (CEF)-, HIV Gag- or HIV Env-derived overlapping peptides. Study participants included HIV-negative healthy donors (HD; n=6) and people living with HIV (PLWH) virally suppressed on cART (ART; n=14), untreated viremic (UT; n=14) or elite controllers (EC; n=4). Phenotypic analysis was performed using up to 28-color flow cytometry on a BD FACSymphony instrument.

Results: Significant anti-HIV Gag activity (range: 8%-50% killing) by bulk NK cells was exclusively detected in half of all PLWH, while killing of BCLs pulsed with the CEF peptide pool, or killing of MHC-devoid K562 cell lines, was comparable between PLWH and HD. NK cells from half of EC had detectable HIV Gag-specific cytotoxic activity and displayed the most robust responses. Strikingly, 35% of all tested NKCL (n=165) generated from 22 PLWH (59% NKCL from 8 ART, 18% NKCL from 14 UT) showed positive responses to HIV (at least twice above killing of unstimulated and above killing of self-peptide-pulsed B-LCLs). Reactive NKCL displayed anti-HIV Gag cytotoxic activity up to 43% specific lysis and anti-HIV Env cytotoxic activity up to 87% specific lysis, within the range of robust cytotoxicity normally found against tumor cells. Phenotypic analysis indicated antigen-specific memory was associated with increased NKG2C and CD57 expression. Accordingly, NKG2C receptor blockade and pulsing with single HIV-derived peptides that bind HLA-E indicated memory NK cell responses likely depend on an HLA-E-dependent recognition mechanism.

Conclusion: Collectively, our work presents the first mechanistic evidence for HIV-specific memory NK cells induced by HIV infection in humans. These data suggest that HIV-specific responses mediated by NK cells may have the potential to be harnessed for curative or other therapeutic interventions.

116 EFFICACIOUS RHCMV/SIV VECTORS ELICIT BROADLY CROSS-REACTIVE SIV-SPECIFIC CD8+ T CELLS

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Background: RhCMV68-1/SIV vaccines demonstrate a profound ability to protect against SIV challenge, with half of all vaccinated rhesus macaques clearing viremia shortly after infection. A hallmark of RhCMV68-1 vaccines is the induction of CD8 T cells that are non-classically restricted, either by MHC-II or MHC-E molecules. MHC-E restricted cells are necessary for RhCMV68-1 mediated protection, and characterizing these unconventional cells is essential to understand this unique immune response and to improve vaccine efficacy.

Methods: We developed novel single-cell methods to isolate and characterize MHC-E restricted CD8 T cells. CD8+ T cells from RhCMV68-1/SIV vaccinated rhesus macaques were stimulated with antigen in vitro (epitopic peptides or autologous SIV-infected CD4+ T cells) and responding cells were isolated on the basis of surface trapped TNF-a and CD69 expression. Next, we performed single cell RNA-seq (scRNA-seq) using the 10x Genomics platform, which enables simultaneous capture of transcriptome data and TCR clonotype from individual cells. As validation, full length TCR alpha/beta pairs were synthesized and used to transduce CD8 T-cells from SIV-naïve macaque, which were used in similar recognition assays.

Results: We characterized MHC-E restricted TCR clonotypic hierarchies from four RhCMV68-1/SIV vaccinated rhesus macaques over more than 2 years. In each animal, a small number of broadly cross-reactive TCRs represents the entire MHC-E restricted response to SIV-infected cells, with a single clone recognizing up to 7 distinct epitopes. TCR alpha/beta transductants replicated the in vivo pattern of antigen recognition. While these TCRs are specific, we further demonstrate the peptide/MHC avidity of these MHC-E restricted clones is significantly lower than conventional MHC-Ia clones.

Conclusion: These data indicate that the broad, MHC-E-restricted epitope recognition is accomplished by a small number of T cell clones using highly cross-reactive TCRs with low functional avidity relative to classical responses. These results provide insight into the mechanisms underlying RhCMV/SIV vector efficacy and demonstrate a novel set of methods that could be used to study any T cell population.

117 PD-1 BLOCKADE AT TIME OF ART WITHDRAWAL FACILITATES EARLY POST-PEAK VIRAL CONTROL

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Background: Previous studies evaluating the ability of PD-1 blockade to reduce viral reservoirs in SIV+ monkeys on ART have failed to demonstrate significant therapeutic benefit. Here, we evaluated whether PD-1 blockade, around the time of ART discontinuation, could facilitate induction of long-term post-ART control of SIV replication through the functional enhancement of SIV-specific T cells around the time of viral rebound. To address this, we initiated PD-1 blockade in SIV-infected rhesus macaques (RM) receiving ART, starting prior to ART release, with low antigen exposure, or at time of ART release with high antigen exposure.

Methods: 30 RM were IV inoculated with 200 ffu of SIVmac239 and after 12 days began receiving ART (tenofovir/emtricitabine/dolutegravir). After sustained virus suppression (<15 RNA copies/ml), RM were randomized into 3 groups (n=10 each) that received; A) 9 biweekly doses of a rhesusized anti-PD1 mAb at 3mg/Kg starting 45 days prior to ART release (low antigen exposure); B) 6 biweekly doses of anti-PD1 starting 3 days prior to ART release (high antigen exposure); or C) an isotype control mAb at the same dosing frequency as Group A. Plasma viral loads (pvl; RNA copies/ml) were quantified by qRT-PCR and T cell dynamics assessed by flow cytometry.

Results: Anti-PD1 induced increases in CD4+ and CD8+ memory T cell proliferation but had no effect on the frequency of viral blips in the low antigen exposure group vs. controls prior to ART release, suggesting PD-1 blockade did not induce SIV production. Following ART release, all RM rebounded within

17 days except for 1 RM in Group B that rebounded at day 31, indicating PD-1 blockade did not affect time to virus rebound. Moreover, rebound pvl peaked by day 21 post-ART at 4.5 logs in Group A, 4.8 logs in Group B and 4.8 logs in Group C controls. However, by 42 post-ART, we observed a ~2 log reduction of pvl in both anti-PD1 treatment groups A and B relative to Group C controls (2.5 logs and 2.6 logs vs. 4.5 logs, respectively). RM are continuing to be followed to determine long-term pvl set points.
Conclusion: PD-1 blockade had no effect on reactivation and early spread of virus following ART release, but maintaining PD-1 blockade following ART release appears to facilitate early control of virus replication, likely by enhancing the functional activity of SIV-specific T cells expanding in response to SIV replication.

118 TRACKING AND PREDICTING REBOUND IN SHIV-INFECTED INFANT MACAQUES AFTER LONG-TERM ART

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Background: Breastfeeding transmission accounts for the majority of new pediatric infections and commits infants to lifelong ART, as interruption is typically followed by return of replication and repopulation of reservoirs. A better understanding of the anatomic origin and kinetics of viral rebound during analytical treatment interruption (ATI) could inform the development of alternatives to ART-based strategies to achieve long-term viral remission in the pediatric population.
Methods: At 4 wks old, 10 rhesus macaques were orally-administered SHIV.CH505.375H.dCT and placed on daily ART at 8 wpi. ART was interrupted after 1 yr in a subset of animals (n=6) to assess viral rebound. Blood and tissue were collected throughout the study for flow cytometry and viral measurements. For whole-body ImmunoPET, macaques were infused with 68Ga-labeled PGT145 F(ab) and imaged by PET/CT. Scans were done once on long-term ART and twice weekly following ATI.
Results: Median viral loads at peak infection and just prior to ART were 5x105 and 1x105 copies/mL, respectively. During ATI, rebound viremia was detected within 10-24 d, with variable peak viral loads that reached levels seen at ART initiation. Post-treatment control within 4 wks of rebound was seen in 1/2 Mamu A01+ macaques. Various parameters were evaluated for their ability to predict time to viral rebound. In our model, we did not see an association between PD-1 expression on CD4+ T cells and time to rebound, as previously reported for HIV-1 infection. SHIV-DNA and -RNA persistence in blood, lymph node, and colorectal CD4+ T cells was also evaluated. Just prior to ATI, the highest levels of SHIV-RNA were found in the colorectal compartment, suggesting this region could be an early site of viral reactivation following ART interruption. Indeed, longitudinal imaging of SHIV Env expressing cells in tissues by ImmunoPET before and immediately following ATI showed an expansion of infected cells in the GI tract prior to SHIV RNA reaching detectable levels in the plasma. A similar trend was observed in the lungs, where tissue-resident macrophages have been found to be the principal target cells of infection.
Conclusion: This work provides novel insight into the kinetics, anatomic origin, and predictors of viral rebound in a pre-clinical NHP model of pediatric HIV infection. Our preliminary data implicates the GI tract as a key site to be studied for the development of remission strategies and one to be monitored in HIV-infected children being considered for ATI.

119 PERIPHERAL BLOOD SIV/HIV ORIGINATES FROM INFECTED CELLS IN TISSUES

Leticia Kuri Cervantes[1], Maria B. Pampena[1], Marcus Buggert[2], Meagan Watkins[3], David S. Khoury[4], Kevin McCormick[1], Felicity Mampe[1], Emily Lindemuth[1], Ian Frank[1], Max G. Itkin[1], Miles Davenport[4], Brandon F. Keele[5], Katharine J. Bar[1], Ronald Veazey[3], Michael R. Betts[1]
[1]University of Pennsylvania, Philadelphia, PA, USA, 2Karolinska Institute, Stockholm, Sweden, [3]Tulane University, Metairie, LA, USA, [4]Kirby Institute, Sydney, NSW, Australia, [5]NIH, Frederick, MD, USA
Background: HIV and SIV infected CD4 T cells localize primarily to lymphoid and mucosal tissues, where they constitute >90% of infected cells in chronic infection. While largely assumed, it remains to be established if peripheral blood (PB) viremia originates from these tissues, or from infected cells directly within the vasculature. Here we assessed in rhesus macaques (RM) and humans the potential contribution of tissue-based virus production to plasma viremia (VL).
Methods: Four RM were infected i.v. with barcoded SIVmac239, and treated with the lymphocyte migration inhibitor FTY720 daily from day 7 or 28 until day 90. PB and lymphoid tissue (LT) samples were collected for cell and virus quantification. In parallel, we collected PB and thoracic duct lymph (TDL) from 11 HIV+ donors (3 viremic, 8 ART) and assessed VL in each compartment. Viral phylogeny was characterized by SGS gp160 env sequencing of plasma and TDL.
Results: In the FTY720-treated RM we observed near complete redistribution of circulating CD4 T cells into tissues within 7 days of FTY720 treatment (pre-FTY720: 513±283 CD4 T cells/µl, post-FTY720: 5±2 CD4 T cells/µl). Despite the absence of PB CD4 T cells, all animals, regardless FTY720 administration, had peak and set point plasma VL similar to historical controls. Barcode sequencing of cell-associated virus from LT and plasma virus during FTY720 treatment revealed substantial overlap in the dominant virus populations replicating in the LT and circulating in plasma. Together, these results suggest that the circulating plasma virus originated from tissues. We next assessed paired TDL and plasma from HIV+ donors. HIV RNA copies were higher in TDL vs. PB (p=0.0137; up to 10-fold higher in viremic), and the virus populations were phylogenetically indistinguishable between the compartments. Based upon the differential VLs, and incorporating viral clearance rate, plasma volume, and lymph output we calculated that ~50% of plasma virus originates from thoracic duct output, in some individuals reaching a 100% contribution.
Conclusion: Our results indicate that HIV infected cells within LT and non-LT, rather than the vasculature, are the major source of PB viremia. A large proportion of this viremia is maintained through thoracic duct lymphatic efflux, indicating that virus released from infected cells in tissues travels through lymphatics into PB.

120LB CD4+ T-CELL DEPLETION IN AFRICAN GREEN MONKEYS DOES NOT ALTER DISEASE PROGRESSION

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Background: Massive and persistent CD4+ T cell depletion is a hallmark of HIV infection, being associated with impairment of cellular immunity and opportunistic infections. The contribution of CD4+ T cell depletion to SIV/HIV-associated gut dysfunction is unknown. African Green Monkeys (AGMs), a species that do not progress to AIDS, partially recover mucosal CD4+ T cells during chronic infection and maintain gut integrity. We assessed the impact of prolonged experimental CD4+ T cell depletion on the gut integrity and natural history of SIV infection in AGMs.
Methods: Six AGMs were infected intravenously with 300TCID50 SIVsab. All animals received an anti α-CD4 antibody intravenously every three weeks, starting from 21 days post infection (dpi). Plasma viral loads (PVLs), absolute counts, proliferation and activation status of T cells, systemic and local immune activation and inflammation, gut integrity, and cardiovascular disease onset were monitored throughout the follow-up.
Results: Complete ablation of CD4+ T cells in blood and greater than 90% depletion in intestine and lymph nodes was achieved. PVLs peaked at 107 viral RNA copies/mL at 10 dpi, followed by a 4-log decrease by 28 dpi. PVLs were lower compared to SIV-infected historical AGM controls and were even undetectable in some CD4-depleted AGMs. No significant changes in T cell immune activation and proliferation levels occurred in the CD4-depleted AGMs. A transient increase of the inflammatory cytokines and chemokines (IL-1RA, Rantes, Eotoxin, MCP-1, I-TAC, MIF and IP-10) occurred only during acute infection but was resolved prior to chronic infection. Absence of gut damage was observed in situ and through the testing of iFABP, Zonulin, and sCD14 which remained stable during the follow up. sCD163 transiently increased during acute infection.
Conclusion: Despite a major and persistent (over 1 year) depletion of CD4+ T cells in blood and tissues, AGMs remained healthy and did not progress to AIDS. Gut integrity was maintained in spite of profound CD4+ T cell loss. As such, our results suggest that CD4+ T cell depletion, in the absence of increased

inflammation and immune activation is not a determinant factor for SIV-related gut dysfunction. Our results also indicate that AGMs' AIDS-resistance is independent of the CD4+ T cells.

121 INFERIORITY OF SHORT DURATION SOFOSBUVIR-VELPATASVIR FOR RECENT HCV (REACT STUDY)

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Background: Shortened duration therapy for acute and recently acquired HCV infection has been shown to be highly effective in several small non-randomised studies with direct-acting antiviral agents (DAAs), however guidelines remain conservative in their recommendations with no currently approved regimens for this indication.

Methods: The REACT study was an NIH-funded multicentre international, open-label, randomised, phase 4 non-inferiority trial examining the efficacy of short course (6 weeks, Arm A) versus standard course (12 weeks, Arm B) therapy with sofosbuvir/velpatasvir for recently acquired HCV infection (estimated duration of infection <= 12 months). Randomisation was at week 6 and stratified by site and HIV status. The primary endpoint was sustained virologic response at 12 weeks post-treatment (SVR12) reported in the intention-to treat (ITT) population. A total of 250 participants were planned for enrolment and DSMB analysis was scheduled after the first 50 participants in each arm reached SVR12. Following the initial DSMB review, a second review was scheduled following 60 participants through SVR12 in each arm.

Results: At second DSMB review, 185 participants were enrolled, 165 had been randomised and 127 were through SVR12; n=65 in Arm A and n=60 in Arm B. Of those randomised, 98% were male, and 72% HIV positive. The predominant genotype was 1 (65%) and median baseline viral load 5.6 $\log_{10}$IU/ml. 38% were reinfections. At second review (May 2019), the DSMB recommended study cessation for evidence of inferiority in the short arm (A). By ITT SVR12 was 78% (53/65) in Arm A (95%CI 70-90) versus 95% (57/60) in Arm B (95%CI 86-99) (p=0.021). Relapse occurred in 6/65 participants in Arm A (9%, 95%CI 3-19) versus 0 in Arm B (95% CI 0-6). Median baseline viral load in people with viral relapse was 6.4$\log_{10}$IU/ml (range 5.9-7.1 $\log_{10}$IU/ml). Two further participants in Arm A had virological failure at end of treatment, one had reinfection, two died, and four lost to follow-up. Three participants in Arm B were lost to follow-up.

Conclusion: In this randomised study of treatment for recently acquired HCV infection, 6 weeks sofosbuvir/velpatasvir was inferior to 12 weeks. Final analysis of the full randomised dataset will be completed October 2019.

122 INDIVIDUAL AND POPULATION-LEVEL IMPACT OF HCV TREATMENT AMONG PEOPLE WHO INJECT DRUGS

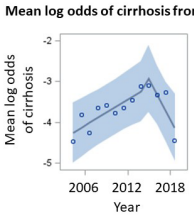
Javier Cepeda[1], David L. Thomas[2], Rachel E. Gicquelais[3], Jacquie Astemborski[3], Gregory D. Kirk[3], Shruti H. Mehta[3]
[1]University of California San Diego, San Diego, CA, USA, [2]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: The availability of highly curative direct acting antivirals (DAA) has led to calls for elimination of HCV as a public health priority. Specifically, a key target is a 65% reduction in HCV-associated mortality by 2030. Mathematical models have predicted that dramatic scale-up of DAAs can achieve this ambitious target, however this has not been assessed empirically. We evaluate temporal trends in individual and population-level liver disease burden (as a proxy for HCV-related mortality) in a community-based cohort of people who inject drugs (PWID) in Baltimore in the context of expanding DAA use.

Methods: From 2005-2018, we collected 11,471 liver stiffness measurements (LSM) using transient elastography from 1,668 PWID who were HCV antibody positive. At the individual-level, we estimated the impact of DAAs on LSM using generalized linear mixed modeling after adjusting for age, sex, race, time, alcohol use and HIV status. To assess population-level impact, we used segmented regression to determine changes in the proportion of the population with cirrhosis (LSM ≥ 12.3 kPa) within and between two periods (before and after 2015) based on presumed scale-up of DAAs in the community.

Results: Overall, 69% were male, mean age was 48, 33% were HIV co-infected, and 14% had cirrhosis at baseline. Only 2% reported ever receiving HCV treatment in 2014 which increased to 41% by 2018. After adjusting for confounders, PWID who reported receipt of DAA had significantly lower LSM (-0.88 kPa 95%CI: -0.91 kPa, -0.86 kPa, p<0.0001) compared to PWID who had not received DAAs. HIV/HCV co-infected PWID had significantly higher LSM, especially among those who not HIV virally suppressed (1.14 kPa, 95%CI: 1.08 kPa, 1.20 kPa, p<0.0001) compared to PWID who were HIV negative. At the population-level, we observed a significant rise in the proportion with cirrhosis within the cohort from 2005-2014 (mean log odds of cirrhosis increased each year by a factor of 0.13, p=0.006); however from 2015-2018, the proportion with cirrhosis declined (mean log odds decreased each year by a factor of 0.53, p=0.003, see figure).

Conclusion: Expansion of DAAs in the PWID community appears to have led to declines in liver disease progression at the individual and population level. Increasing access to all HCV infected persons, particularly those at greatest risk of liver disease progression will be critical to achieving HCV elimination targets.



123LB LARGE HIV OUTBREAK AMONG PEOPLE WHO INJECT DRUGS, WEST VIRGINIA, 2018–2019

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Background: In January 2019, the West Virginia Bureau for Public Health (BPH) detected an increase in HIV diagnoses among people who inject drugs (PWID) in Cabell County, which has experienced high rates of substance use disorder in recent years. Responding to HIV clusters and outbreaks is one of four pillars of the federal Ending the HIV Epidemic initiative and can be used to guide activities supporting the other pillars (diagnose, treat, prevent). BPH, Cabell-Huntington Health Department, and CDC collaborated to conduct a robust investigation and response.

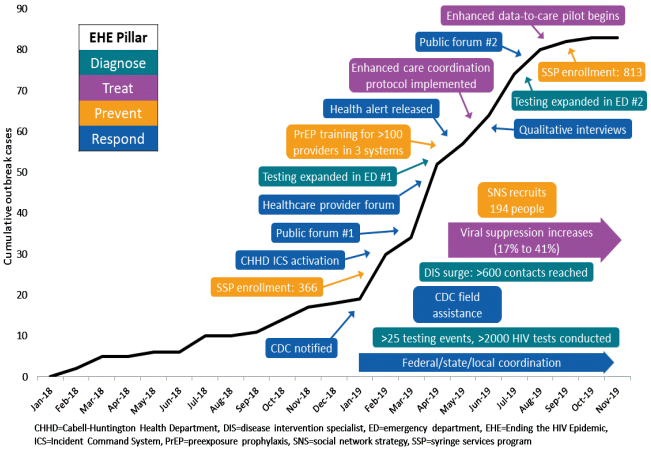
Methods: We analyzed surveillance data, including HIV-1 polymerase data, reported to BPH through November 2019; links were identified at ≤0.005 nucleotide substitutions/site. Outbreak cases were defined as HIV diagnoses during January 1, 2018–October 9, 2019 among 1) PWID linked to Cabell County, 2) their sex or injecting partners, or 3) people with linked sequences. We estimated transmission rate and timing of infections via molecular clock phylogenetic analysis and identified suspected recent infections based on initial viral load and CD4+ cell count, report of last negative HIV test, or presence in a molecular cluster. State, federal, and local partners implemented a comprehensive response.

Results: We identified 81 cases, a 2,285% increase above the 2015–2017 annual average of 2 cases. Most people were male (58%), aged 20-39 years (74%), and white (91%). Almost all (99%) were PWID; many (73%) reported unstable housing. In all, 69 (85%) had ≥1 measure of recent HIV infection. Among 45 people with an available HIV-1 sequence, 41 (91%) were in a large molecular cluster with 35/41 (85%) inferred transmissions occurring after January 1, 2018. Estimated transmission rate in the molecular cluster was 78 per 100 person-years. A comprehensive response featured activities from all four pillars (figure).

Conclusion: Evidence of rapid transmission in this outbreak—the largest relative increase over baseline in the United States since the large 2015 outbreak in rural Scott County, Indiana—galvanized robust collaboration among

federal, state, and local partners. Response interventions supported diagnosis, treatment, and prevention (including expansion of preexposure prophylaxis and syringe services); many activities are now being expanded in other counties statewide. Cluster and outbreak response requires increased coordination and creativity to improve service delivery to vulnerable communities.

Figure: Cumulative number of outbreak cases and timeline of events, West Virginia, 2018–2019



CHHD=Cabell-Huntington Health Department, DIS=disease intervention specialist, ED=emergency department, EHE=Ending the HIV Epidemic, ICS=Incident Command System, PrEP=preexposure prophylaxis, SNS=social network strategy, SSP=syringe services program

124 HCV TRANSMISSION AMONG MSM: EXTERNAL INTRODUCTIONS COULD COMPLICATE MICRO-ELIMINATION

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Background: Elimination of HCV has become a target with the introduction of highly effective direct antiviral agents (DAAs). In the Netherlands, new HCV infections including frequent reinfections almost exclusively occur in MSM. It is unclear whether unrestricted access and high uptake of DAAs is sufficient to eliminate HCV in high-risk populations such as MSM. This study presents historic trends and current dynamics of HCV among MSM in Amsterdam based on sequence data collected between 1994 and 2019.

Methods: HVR1 sequences of 232 primary HCV infections and 56 reinfections were obtained from 244 MSM in care in Amsterdam. Maximum-likelihood phylogenies were constructed for each HCV genotype separately, and time-scaled phylogenies were constructed using a Bayesian coalescent approach. Transmission clusters were determined by Phydelity, which utilizes a statistically-principled and phylogeny-informed framework. The proportion of unclustered sequences over time was calculated using year-specific transmission trees inferred from sequences up to that year.

Results: For subtype 1a (n=191) we found 19 transmission pairs and 12 transmission clusters ranging from 3 to 8 sequences. Transmission clusters of subtypes 2b (n=18) and 3a (n=17) were introduced more recently than clusters of subtypes 1a and 4d (n=62). For subtype 1a and 4d, clusters were introduced between 1998 and 2011, whereas for subtype 2b and 3a this was between 2009-2012. The estimated transmission rate (based on genetic diversity) increased around the year 2000 and plateaued 10-15 years later for subtypes 1a and 4d. The proportion of unclustered sequences of subtype 1a, the most prevalent subtype in this population, increased from approximately 40% before 2014 to about 75% in more recent years.

Conclusion: The proportion of unclustered sequences has increased among HCV infections in recent years. The most likely explanation for this is that transmission of local strains has declined as a result of intense treatment efforts whereas external (possibly international) introductions of HCV into the MSM population in Amsterdam has increased. Frequent international transmission events will complicate national micro-elimination efforts and therefore international collaboration combined with international scale-up of treatment of all diagnosed HCV infections (including reinfections) is important.

125 NEWBORN TESTING REVEALS HIGH HCV SEROPREVALENCE IN PREGNANT WOMEN FROM NEW YORK STATE

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Background: Hepatitis C virus (HCV) infections in New York State (NYS) have been rising among young adults due to increased injection drug use. In 2018 in NYS (excluding NYC), 61% of new female cases were in women of child bearing age (15-44 yrs old). Increased HCV infections in this age group are concerning as 6% of HCV RNA-positive pregnant women will transmit HCV to their baby. To plan effective public health actions, accurate HCV prevalence rates among pregnant women are needed; however, many HCV infections go undiagnosed and unreported. Babies passively acquire maternal IgG antibodies. Therefore, testing newborn blood for HCV antibodies can reveal mom's serostatus. Our goal was to perform a large-scale HCV serosurvey of pregnant women in NYS by testing newborn dried blood spots (DBS) using a high-throughput, low-cost Luminex HCV immunoassay.

Methods: All DBS submitted to NYS's newborn screening program over 6 wks were sampled by punching a 3mm circle into microplates. Aggregate data on birth weight, gestational age and mother's county of residence were recorded, and samples were blinded. A generic patient code was included to identify duplicate samples. HCV antigen-coupled beads were used to test eluted blood for HCV antibodies using a low-cost (<$0.80/well) Luminex-based immunoassay in 384-well plates. Repeated median fluorescence intensity (MFI) >1000 was considered HCV antibody reactive.

Results: Of the 29,323 DBS sampled, 25,571 (87%) were from unique babies born to mothers residing in NYS. Of these, 18,581 (73%) were tested. 148 DBS were HCV antibody reactive, for an overall NYS seroprevalence of 0.8%. Multiple DBS collected on different days were tested from 1409 individuals, 31 with repeat HCV reactive results, 1376 with repeat non-reactive results and 2 with discordant results close to the MFI cutoff. Premature birth (26%) and low birth weight (26%) were twice as common in babies born to HCV seropositive mothers than seronegative mothers (p<0.001). HCV seroprevalence in Central (2.1%) and Western/Finger Lakes (1.5%) regions, where multiple counties are designated rural, was 3-4 times higher than the rest of NYS and similar to high rates observed in other U.S. rural regions. For the year, we estimate that ~1800 babies will be born to HCV antibody positive women in NYS.

Conclusion: Newborn DBS testing using a Luminex-based immunoassay is an effective way to assess HCV burden among pregnant women.

NYS Region	# DBS collected from unique individuals in 6 weeks	# tested (% of collected)	# HCV Ab reactive	Seroprevalence % (95% CI)*	Estimated # HCV Ab reactive among all DBS collected	Estimated yearly # HCV Ab reactive
Central	2,132	1,419 (67)	30	2.1 (1.5-3.0)	45	391
Western/ Finger Lakes	3,481	2,380 (68)	36	1.5 (1.1-2.1)	53	456
Hudson/ Northeast	4,398	3,459 (79)	23	0.7 (0.4-1.0)	29	253
Long Island	3,277	2,676 (82)	17	0.6 (0.4-1.0)	21	180
New York City	12,283	8,647 (70)	42	0.5 (0.4-0.7)	60	517
Total NYS	**25,571**	**18,581 (73)**	**148**	**0.8 (0.7-0.9)**	**208**	**1,797**

DBS = dried blood spot, NYS = New York State, Ab = antibody; * Overall $\chi^2 = 57.43$, p value < .0001

126 HEPATOCELLULAR CARCINOMA RISK AMONG PERSONS WITH HIV IN NORTH AMERICA, 1996-2015

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[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]University of Washington, Seattle, WA, USA, [3]Northwestern University, Chicago, IL, USA, [4]McGill University, Montreal, QC, Canada, [5]Yale University, New Haven, CT, USA, [6]University of Pennsylvania, Philadelphia, PA, USA, [7]Harvard University, Cambridge, MA, USA, [8]Universidad Central del Caribe, Bayamon, Puerto Rico, [9]Kaiser Permanente, Oakland, CA, USA

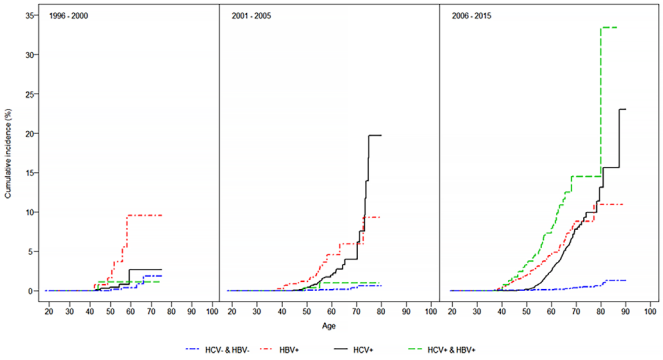
Background: People living with HIV (PWH) are often co-infected with HBV and HCV, leading to increased risk of hepatocellular carcinoma (HCC). HCC risk may have changed in the current era of potent combination antiretroviral therapy (ART). We assessed temporal trends in HCC among PWH, comparing HCC rates by viral hepatitis infection status, risk populations, and HIV disease severity in the North America AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

Methods: We examined 3 calendar periods: early- (1996-2000), mid- (2001-2005), and modern- ART (2006-2015). HCC diagnoses were identified and validated through cancer registries or medical records. HBV and HCV infection were confirmed by serologic and/or virologic test and categorized as ever, never infected, or missing. CD4 counts were measured at entry of each calendar period or the beginning of cohort-specific cancer diagnosis ascertainment. HIV RNA viral load (vl) was measured two years before HCC diagnosis or before the end of cancer diagnosis ascertainment. Poisson regression models estimated HCC incidence rates (IR) and rate ratios (aIRR), adjusted for age, sex, race, and viral hepatitis infection. Age-related cumulative incidence of HCC by calendar periods were calculated.

Results: Of 109,283 HIV patients with 723,441 person-years (pys) of follow-up, 20% were HCV co-infected, 6% HBV co-infected, 2% triple-infected, 451 developed HCC. PWH who had HBV and/or HCV co-infection were more likely than HIV-monoinfected PWH to develop HCC and did so at earlier ages. From 1996 to 2015, HCC IR increased from 0.28 to 0.75/1000 pys. As compared to HIV-monoinfected persons, PWH co-infected with HBV and/or HCV had substantially greater age-related cumulative incidence of HCC in all 3 periods (Figure). Higher HIV vl (≥500 copies/ml) and lower CD4 counts (≤500 cells/mL) were associated with higher HCC risk (aIRR: 1.8, 95% confidence interval (CI): 1.4-2.4 and aIRR: 1.3, 95% CI: 1.0-1.6, respectively). People who injected drugs had higher HCC risk compared with men who had sex with men (aIRR: 2.0, 95% CI: 1.3-2.9), even after controlling for viral hepatitis co-infection.

Conclusion: HCC rates among PWH increased significantly over time. Patients with viral hepatitis co-infection, lower CD4, higher HIV vl, or HIV transmission through injection drug use had higher HCC risk. These findings suggest the importance of HIV viral suppression and treatment of viral hepatitis among PWH in the ART era in order to reduce HCC risk.

Figure. Cumulative incidence of HCC by age and viral hepatitis co-infection groups stratified by calendar era.



127 HIV/HCV VS HCV: PLASMA AND LIVER VIRAL DYNAMICS AND IP-10 LEVELS

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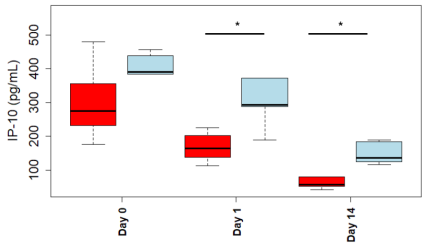
Background: HIV/HCV co-infected people have worse liver disease progression than HCV mono-infected people. Interferon-free therapies have yielded high rates of sustained virologic response after 12 weeks, but shorter therapy has not been uniformly successful in HIV/HCV co-infection. We compared how quickly the liver is cleared of infection with interferon-free therapy in HIV/HCV co-infection and HCV mono-infection.

Methods: We enrolled 10 people with chronic genotype 1a HCV infection without cirrhosis in a clinical trial of Sofosbuvir and Velpatasvir for 12 weeks; 5 people had virologically suppressed HIV on antiretrovirals. Participants underwent liver biopsies at baseline and on day 4 or 7 after treatment initiation; single-cell laser capture microdissection was performed to quantify the proportion of infected hepatocytes. Plasma viral kinetics and IP-10 levels were measured over the first two weeks.

Results: The median (range) age of participants was 55.5 (28, 66), 5/10 were female, and 8/10 were Black. The median (range) liver stiffness was 6.5 kPa (4.1, 8.6). The median (range) baseline plasma HCV RNA levels was 6.36 $\log_{10}$ IU/mL (5.68, 7.93). The median (range) proportion of HCV-infected cells was 8% (1%, 87%) at baseline and 1% (<0.3%, 7%) at second biopsy: baseline proportions and the change in proportion of infected cells correlated closely with baseline plasma HCV RNA levels (r=0.89, 0.88). The median (range) percent change in proportion of infected hepatocytes within the first week was -89.4% (-70.0, -97.7). There were no differences in plasma or liver HCV kinetics between HIV+ and HIV- at baseline or later. Median (range) IP-10 levels at baseline were 369 pg/mL (175, 479) and did not differ significantly by HIV status; however, day 1 and day 14 IP-10 levels were significant higher among HIV+ participants ($p<0.05$ for both).

Conclusion: HIV/HCV co-infected persons have rapid clearance of intrahepatic HCV, similar to HCV mono-infected persons, despite having abundant infection. However, residual immune activation appears to persist despite virologic suppression of both viruses. While this may not have different implications for virologic cures, there may be persistent effects on liver disease progression in HIV/HCV co-infection.

Figure. IP-10 levels remain higher in HIV/HCV co-infected persons taking Sofosbuvir-Velpatasvir compared to HCV mono-infected persons. *p<0.05.



128 CLINICAL PREDICTORS OF LIVER FIBROSIS PRESENCE & PROGRESSION IN HIV-ASSOCIATED NAFLD

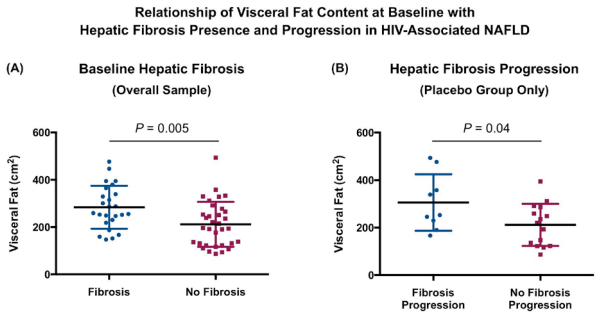
Lindsay T. Fourman[1], Takara L. Stanley[1], Meghan Feldpausch[1], Julia Purdy[2], Isabel Zheng[1], Chelsea S. Pan[1], Julia Aepfelbacher[2], Colleen Buckless[1], Andrew Tsao[1], Kathleen E. Corey[1], Raymond T. Chung[1], Martin Torriani[1], David E. Kleiner[2], Colleen Hadigan[2], Steven K. Grinspoon[1]
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Background: Nonalcoholic fatty liver disease (NAFLD) – ranging from steatosis to steatohepatitis to fibrosis – is a major cause of liver disease in HIV. While simple steatosis is regarded as relatively benign, hepatic fibrosis has been linked to all-cause and liver-specific mortality. The natural history of NAFLD in HIV, including which patients are likely to develop clinically overt disease, is not well known. In the current study, we leverage liver biopsy samples from a clinical trial of HIV-associated NAFLD to identify predictors of fibrosis presence and progression.

Methods: We recently completed a randomized trial of the growth hormone-releasing hormone analogue tesamorelin to treat NAFLD in HIV. In this study, we found that tesamorelin reduced liver fat and prevented fibrosis progression. Sixty-one participants with HIV and NAFLD were randomized to tesamorelin or placebo for 12 months. NAFLD was defined as hepatic fat fraction (HFF) ≥ 5% by magnetic resonance spectroscopy in the absence of active hepatitis B or C or excess alcohol consumption. Individuals with cirrhosis were excluded. Participants underwent liver biopsy at baseline and 12 months; histologic evaluation was performed by a single expert pathologist blinded to treatment and biopsy order.

Results: Among 58 participants with baseline biopsies, 43% had hepatic fibrosis (stage 1, 36%; stage 2, 40%; stage 3, 24%). Fibrosis was associated with greater visceral fat content at baseline (284 ± 91 cm_2 vs. 212 ± 95 cm_2, $P = 0.005$), but not subcutaneous fat or BMI. While HFF did not differ between groups, individuals with fibrosis had higher NAFLD Activity Score (3.6 ± 2.0 vs. 2.0 ± 0.8, $P < 0.0001$), ALT (41 ± 30 U/L vs. 23 ± 8 U/L, $P = 0.002$), and AST (44 ± 27 U/L vs. 24 ± 10 U/L, $P = 0.0003$). Among 24 participants randomized to placebo with paired liver biopsies, 38% had progression of fibrosis over 12 months. Higher visceral fat content at baseline (306 ± 119 cm_2 vs. 212 ± 89 cm_2, $P = 0.04$) was the only clinical predictor of fibrosis progression, which remained significant upon adjusting for BMI, HFF, and NAS Score. Age, sex, race, duration of HIV, and CD4 count did not relate to fibrosis presence or progression.

Conclusion: High rates of liver fibrosis presence and progression were observed in a cohort with HIV and NAFLD. Individuals with greater visceral fat content at baseline were more likely to have baseline fibrosis and progression of fibrosis, suggesting that these patients should be closely monitored and targeted for intervention.



Among participants with HIV and NAFLD, individuals with **(A)** hepatic fibrosis at baseline and **(B)** progression of fibrosis over 1 year had higher visceral fat content at baseline. Error bars denote mean ± standard deviation. *P*-values were determined by Student's t-test.

129 DOLUTEGRAVIR-CONTAINING ART DOES NOT REDUCE ETONOGESTREL IMPLANT CONCENTRATIONS

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Background: Concomitant use of efavirenz-containing antiretroviral therapy (ART) is known to reduce etonogestrel (ENG) concentrations, leading to reduced contraceptive effectiveness of subdermal implants. Dolutegravir (DTG)-containing ART is now the preferred first-line regimen for women of reproductive potential. However, DTG's drug-drug interactions with hormonal contraceptives have been narrowly evaluated thus far, and understanding any potential for interactions between subdermal implants and DTG is important as countries pursue national rollout of DTG-containing ART.

Methods: We conducted a prospective, open-label pharmacokinetic study among women of reproductive potential in Kisumu, Kenya. Women were either HIV-positive, virologically suppressed, and receiving DTG-containing ART for at least 30 days prior to enrollment, or HIV-negative and not receiving any antiretrovirals (control group). An ENG 68mg subdermal implant was placed as part of routine clinical care and women were enrolled in this study within 2 weeks of implant placement. Blood samples were drawn at 2, 4, 8, 12, 16, 20, and 24 weeks after study entry. We analyzed plasma ENG concentrations using a validated LC-MS/MS assay (range 25-30,000 pg/mL). We describe per visit ENG concentrations using median (range) and compare the concentrations per visit between DTG-containing ART and the control groups using geometric mean ratio (GMR; 90% confidence interval) and the Wilcoxon rank sum test.

Results: All women were black African. The median age was 35 and 25 years, and weight was 62.5 and 59.0 kg in the DTG-containing ART and control groups, respectively. Women in the DTG-containing ART group were on this ART for a median of 6.7 (range 4.3-8.3) months prior to study enrollment. ENG plasma concentrations for the DTG and control groups were 692 (470-989) and 588 (277-1050) pg/mL at week 2, respectively, and decreased to 456 (250-720) and 268 (136-496) pg/mL by week 24, respectively (Table). ENG exposure in the DTG-containing ART group was 19-54% higher compared to controls (all p<=0.05).

Conclusion: In the first of its kind study, we observed modestly higher ENG concentrations among women using DTG-containing ART vs. HIV-negative women. Our findings suggest that no detrimental drug-drug interactions exist with concomitant use of ENG implants and DTG. DTG-containing ART represents a preferable alternative to efavirenz-containing ART for women already using or desiring an ENG implant.

Table. Etonogestrel plasma concentrations (pg/mL) among DTG-containing ART and HIV-negative groups at each study visit

Study visit week	DTG-containing ART (n=23), median (range)	HIV-negative (n=25), median (range)	DTG: HIV-negative GMR (90% CI)	*p*-value^
2	691 (470-989)	589 (31-1350)	1.20 (1.02-1.40)	0.05
4	529 (391-1070)	588 (277-1050)	1.29 (1.10-1.52)	0.01
8	437 (308-906)	466 (234-732)	1.19 (1.01-1.39)	0.05
12	387 (275-976)	394 (249-611)	1.24 (1.05-1.46)	0.05
16	357 (264-776)*	337 (229-570)	1.22 (1.05-1.42)	0.03
20	356 (255-689)*	316 (239-518)	1.21 (1.04-1.40)	0.04
24	456 (250-720)*	309 (201-491)	1.54 (1.25-1.90)	<0.001

ART=antiretroviral therapy; DTG=dolutegravir; GMR=geometric mean ratio
* Only n=21, 20, and 12 participants' samples were available for study visit weeks 16, 20, and 24, respectively, at the time of this analysis
^ Calculated with exact Wilcoxon Rank sum test per study visit

130LB SAFETY AND EFFICACY OF DTG VS EFV AND TDF VS TAF IN PREGNANCY: IMPAACT 2010 TRIAL

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Background: We compared the safety and virologic efficacy of dolutegravir (DTG) + emtricitabine (FTC)/tenofovir alafenamide fumarate (TAF) vs. DTG + FTC/tenofovir disoproxil fumarate (TDF) vs. efavirenz (EFV)/FTC/TDF in pregnant women.

Methods: Pregnant women with HIV-1 in 9 countries were randomized 1:1:1 to start open-label DTG+FTC/TAF, DTG+FTC/TDF, or EFV/FTC/TDF at 14-28 weeks gestational age (GA). Up to 14 days' pre-entry antiretroviral treatment (ART) was permitted. In primary efficacy analysis, we compared the combined DTG-containing arms to the EFV arm for non-inferiority (-10% margin), then superiority, with regard to delivery HIV RNA<200 cp/mL. Safety outcomes compared between all arms were a) composite adverse pregnancy outcome (preterm delivery [PTD]<37 weeks, small for GA [SGA]<10th centile, stillbirth [SB] or spontaneous abortion [SAB]); b) maternal grade>3 adverse event (AE) through 14 days postpartum; and c) infant grade>3 AE through 28 days. Neonatal death (NND, <28 days) was also evaluated.

Results: We randomized 643 women: 217 to DTG+FTC/TAF, 215 to DTG+FTC/TDF, and 211 to EFV/FTC/TDF. Baseline medians were: GA 21.9 weeks, HIV RNA 903 cp/mL, CD4 count 466 cells/uL; 83% took ART prior to entry (median 6 days). Median antepartum follow-up was 17.4 weeks. Delivery HIV RNA, available for 605 (94.1%) women, was <200 cp/mL in 395 of 405 (97.5%) in the combined DTG arms vs 182 of 200 (91.0%) in the EFV/FTC/TDF arm (difference 6.5% [95%CI 2.0%, 10.7%]; p=0.005). Pregnancy outcomes were available for 640 (99.5%). Fewer women in the DTG+FTC/TAF arm (24.1%) had an adverse pregnancy outcome than in DTG+FTC/TDF (32.9%, p=0.043) or EFV/FTC/TDF (32.7%, p=0.047) arms. Although SB was more frequent with DTG+FTC/TAF (3.7%) and DTG+FTC/TDF (5.2%) than EFV/FTC/TDF (1.9%) (all by-arm p-values ≥0.05; post-hoc), NND was more frequent with EFV+FTC/TDF (4.8%) than DTG+FTC/TAF (1.0%, p=0.019) or DTG+FTC/TDF (1.5%, p=0.053). Combined SB or NND rates were similar by arm (post-hoc analysis). At least one grade>3 AE occurred in 148 (23.0%) women and 105 (17.0%) infants (all by-arm p-values ≥0.05). Two babies were diagnosed with HIV at <14 days, one each in DTG+FTC/TAF and DTG+FTC/TDF arms (maternal delivery HIV-1 RNA 58,590 and <40 cp/mL, respectively).

Conclusion: DTG-containing ART started at GA 14-28 weeks had superior virologic efficacy at delivery to EFV/FTC/TDF. DTG+FTC/TAF had the lowest composite frequency of adverse pregnancy outcomes. Maternal and infant AE outcomes were similar by arm.

Table: IMPAACT 2010 maternal virologic efficacy outcomes and pregnancy and maternal/infant safety outcomes

	Combined DTG Arms n/N (%)	EFV/FTC/TDF n/N (%)	Estimated risk difference (95% CI) [9]	P-value[9,10]
Delivery HIV-1 RNA <200, ITT[1,2]	395/405 (97.5%)	182/200 (91.0%)	6.5% (2.0%, 10.7%)	0.005
Delivery HIV-1 RNA <200, per-protocol[1,2]	389/399 (97.5%)	171/187 (91.4%)	6.0% (1.6%, 10.3%)	0.008

	Treatment Arm Estimates			P-value		
	DTG+FTC/TAF n/N (%)	DTG+FTC/TDF n/N (%)	EFV/FTC/TDF n/N (%)	DTG+FTC/TAF vs. DTG+FTC/TDF	DTG+FTC/TDF vs. EFV/FTC/TDF	DTG+FTC/TAF vs. EFV/FTC/TDF
Any adverse pregnancy outcome[1,2]	52/216 (24.1%)	70/213(32.9%)	69/211 (32.7%)	0.043	0.97	0.047
PTD (<37 wks)[2,3,4]	12/208 (5.8%)	19/202 (9.4%)	25/207 (12.1%)	0.16	0.38	0.023
SGA (<10th %ile)[2,4]	33/202 (16.3%)	45/200(22.5%)	41/200 (20.5%)	0.12	0.63	0.28
Stillbirth(≥20wks)[2,5,6]	8/216 (3.7%)	11/213 (5.2%)	4/211 (1.9%)	0.46	0.067	0.26
SAB (<20 wks)	0	0	0			
Maternal grade ≥3 adverse event[6,7]	45/217 (20.7%)	56/215(26.0%)	47/211 (22.3%)	0.27	0.59	0.58
Neonatal grade ≥3 adverse event[6,7]	29/208 (13.9%)	33/202(16.3%)	43/207 (20.8%)	0.51	0.25	0.069
Neonatal death[6,7]	2/208 (1.0%)	3/202 (1.5%)	10/207 (4.8%)	0.63	0.053	0.019
Ave. maternal weight gain per week, kg[6,8]	0.378	0.319	0.291	0.011	0.19	<0.001

[1]Primary pre-specified outcome for non-inferiority analysis;[2]Two-sample test of the difference in binomial proportions;[3]Preterm births in liveborn babies;[4]Secondary outcome;[5]Post-hoc test;[6]Log-rank test;[7]Partial follow-up for primary or secondary safety outcome;[8]Generalized Estimating Equations;[9]Adjusted for multiple interim analyses; [10]Test of superiority for secondary analysis.

131LB DIFFERENTIATED CARE FOR POSTPARTUM ART IN SOUTH AFRICAN WOMEN LIVING WITH HIV: AN RCT

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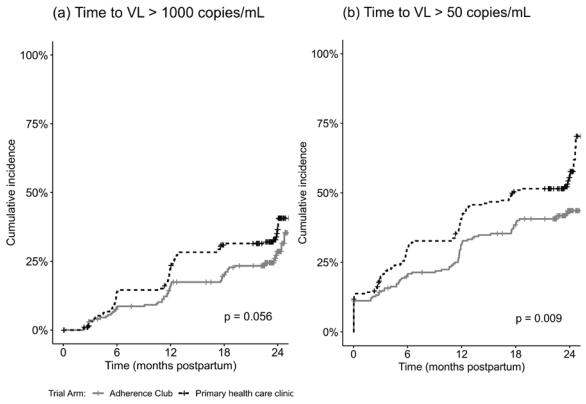
Background: Differentiated service delivery (DSD) models are used increasingly to deliver ART in high-burden settings but there are few data on DSD models for postpartum women, who are at high risk of non-adherence and elevated viral load (VL).

Methods: From Jan'16 to Sept'17 we enrolled consecutive postpartum women who initiated ART (TFV+XTC+EFV) during pregnancy and met local DSD eligibility (clinically stable with VL<400 c/mL) at a large urban primary care antenatal clinic (NCT03200054). Women were randomised to be referred to (i) a community-based "Adherence Club" (AC, the local DSD model: lay health worker-led groups of 20-30 patients with 2-4 monthly ART dispensing at a community venue) or (ii) routine primary health care clinics (PHC; the local standard with nurse/doctor-led care). Outcomes were measured through Nov'19 with study visits and batched VL separate from care in either arm at 3, 6, 12, 18 and 24m postpartum. Endpoints were time to VL>1000 c/mL (primary) and >50 c/mL (secondary) by intention-to-treat; per protocol analyses were restricted to women who attended the allocated service within 3m of referral.

Results: Overall 412 women were randomised at a median of 10d postpartum (IQR, 6-20d; at enrolment median age 27y; median duration of prenatal ART 21w; 100% VL<1000 and 88% <50 c/mL); baseline characteristics did not differ by arm. Attendance at the allocated service within 3m of referral per protocol was higher in AC (77%) vs PHC (68%); 90% completed the final study visit at 24m postpartum with no difference by arm. For the primary endpoint, 16% and 29% of women in AC experienced a cumulative incidence of VL>1000 c/mL by 12m and 24m, compared to 23% and 37% in PHC, respectively (HR=0.71; 95%CI=0.50-1.01; p=0.056; Figure). For the secondary endpoint, 32% and 44% of women in AC had VL>50 c/mL by 12m and 24m, compared to 42% and 56% in PHC, respectively (HR=0.69; 95%CI=0.52-0.92; p=0.009). Findings were unchanged in per protocol analyses and across a priori demographic and clinical subgroups. Infant HIV testing, MTCT, breastfeeding duration, family planning use, and other outcomes were similar between AC and PHC arms.

Conclusion: Postpartum referral to DSD models such as "Adherence Clubs" is associated with an approximately 30% reduction in elevated VL and may be an important part of strategies to improve women's virologic outcomes on ART.

Figure. Time to (a) VL>1000 copies/mL and (b) VL>50 copies/mL, among postpartum women on ART randomised to Adherence Clubs versus Primary Health Care clinics, by intention to treat



132 POC EID VS CENTRAL LAB TESTING: RESULTS FROM A STEP-WEDGE RCT IN KENYA AND ZIMBABWE

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Background: Despite WHO recommendations for early infant virologic diagnostic testing (EID) of HIV-exposed infants (HEI), in 2017, only 50% of HEI in 21 high-priority countries received an EID test in the first 2 months of life. This study builds on a Unitaid-funded, 9-country point-of-care (POC) EID implementation project that sought to improve access to EID and reduce turnaround time from sample collection to results availability.

Methods: This randomized stepped-wedge trial evaluated the effect of POC EID compared to standard-of-care conventional central lab-based testing on timely receipt of results in HEI. The study was conducted over two years, in two countries, Kenya and Zimbabwe. In each country, 18 health facilities were randomly selected from the list of project sites to serve as study sites. Study sites were randomized to one of four time points to transition from conventional EID testing to POC EID testing. HIV-exposed infants were eligible for inclusion if they presented for EID testing at the 4-8 week time-point recommended by the WHO. The study was powered to detect at least a 50% increase in the proportion of caregivers receiving HIV test results by 12 weeks of infant age after introduction of POC, assuming a design effect of 2.

Results: In Zimbabwe, caregivers with infants tested under POC EID were 4.56 (95% CI: 4.5, 4.6) times more likely to receive the infant HIV test results by 12 weeks of age compared to conventional EID. In Kenya, caregivers with infants tested under POC EID were 1.29 (95% CI: 1.27, 1.3) times more likely to receive the infant HIV test results within 12 weeks of age compared to conventional EID. POC EID significantly reduced the turn-around-time between sample collection and return of infant HIV test results to caregiver by an average of 8.41 weeks (95% CI: 8.87, 7.95) in Zimbabwe and 3.29 weeks (95% CI: 3.55, 3.03). For HIV-infected infants, POC EID significantly reduced the time between sample collection and infant antiretroviral therapy (ART) initiation by an average of 7.97 weeks (95% CI: 3.62, 12.32) in Zimbabwe and 2.43 weeks (95% CI: 1.34 , 3.52) in Kenya.

Conclusion: POC EID improved return of results by 12 weeks of age, turnaround time to receipt of results, as well as rapid initiation on ART for infected infants. Even where conventional lab-based EID systems had been strengthened, as in Kenya, POC EID had significant benefit in providing results to caregivers quickly.

Figure 1. Proportion of infant HIV test results returned to caregiver within 12 weeks of age for conventional standard of care (SOC) or point of care (POC), by time period (step).



133 A RANDOMIZED TRIAL OF POINT-OF-CARE EARLY INFANT HIV DIAGNOSIS IN ZAMBIA

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Background: Early infant HIV diagnosis (EID) requires molecular methods historically limited to central labs. As a result, many HIV-exposed infants either have no access to EID or must wait months for a result. Point of care (POC) EID offers a potential solution.

Methods: We conducted a POC EID trial at 6 clinics in Lusaka, Zambia. HIV-exposed infants were randomly allocated between 4-12 weeks of life to: (a) POC EID – same-day testing with Alere q or (b) Offsite EID – testing of dried heel prick samples at a central lab with Roche COBAS. The trial provided a safety net by testing an archived sample if off-site EID results did not return within 4 weeks. HIV-infected infants were referred for immediate antiretroviral therapy (ART). Our primary outcome was defined as being alive, in care, and virally suppressed (viral load <200 copies/mL) at 12 months.

Results: Between Mar 2016 and Nov 2018, we randomized 4,000 HIV-exposed infants at a median age of 6 (IQR 6-7) weeks to POC EID (1,989) or Offsite EID (2,011). Most mothers (94%) reported ART for PMTCT. Eighty-one (2.0%, 95%CI 1.6-2.5%) infants were diagnosed with HIV. Every infant in the POC arm received a same-day result, while the median time to diagnosis in the Offsite arm was 27 (IQR 22-30) days. The majority of infants randomized to Offsite EID relied upon the trial's diagnostic safety net (Fig. 1a). ART initiation was high in both arms (Fig. 1b), but adverse outcomes were common. Among 81 HIV-infected infants, there were 15 (19%) deaths, 15 (19%) follow-up losses, and 30 (38%) virologic failures (1 viral load result pending). By 12 months, only 20 (25%, 95%CI 16–34%) HIV-infected infants were alive, in care, and virally suppressed and this did not differ by study arm: 13 (30%, 95% CI 16-43%) infants in the POC arm vs. 7 (19%, 95% CI 7-32%) in the Offsite arm (RR 1.5, 95% CI 0.7-3.4).
Conclusion: Despite the success of Zambia's PMTCT program, adverse outcomes are high among HIV-infected infants. POC EID eliminated diagnostic delays and resulted in rapid ART initiation but this did not translate to treatment success at 12 months. As countries consider whether to adopt POC EID, they will need to weigh the costs of new technology against the costs of improving existing EID services. Most importantly, substantial investments are needed to strengthen pediatric HIV treatment programs.

Figure 1a: Time to Receipt of HIV results

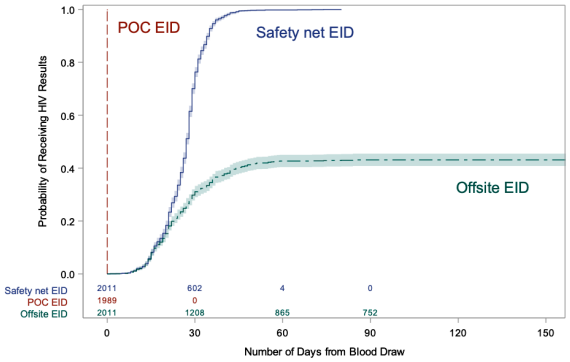
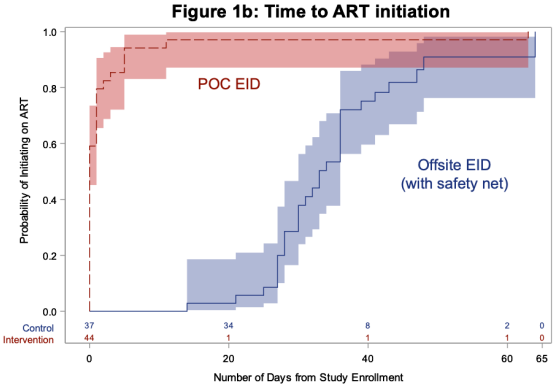


Figure 1b: Time to ART initiation



134LB POPULATION-LEVEL HIV-FREE INFANT SURVIVAL IN THE SEARCH TRIAL

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Background: Universal test and treat (UTT) strategies could reduce vertical transmission of HIV by diagnosing women living with HIV earlier and improving care delivery. We evaluated the effect of universal HIV testing and a patient-centered HIV care model on vertical transmission and HIV-free survival in the SEARCH Trial.
Methods: At baseline, 32 communities in rural Uganda and Kenya (total population ~350,000) received population level HIV testing (90% coverage) and were randomized to: 1) intervention: immediate ART, annual population level testing, and patient-centered HIV care (including welcoming staff, flexible hours, and facilitation between antenatal care and HIV clinic); or, 2) control: HIV-care per national guidelines. Pregnant women were offered immediate ART in both arms. After 3 years, we repeated population-level testing including children <3 years and ascertained births and deaths. In pre-specified analyses, we compared HIV-free survival (% of infants alive and HIV uninfected) and vertical transmission (% of living infants with HIV infection) between study arms among infants born to a) all women with known HIV+ status by year 3; and, b) the subset of women with known HIV+ status at baseline using cluster-level targeted maximum likelihood estimation.
Results: There were 1,417 births to 1,332 women with known HIV+ status by year 3; outcomes were ascertained in 76% of infants in intervention and 78% in control. The proportion (95%CI) with HIV-free survival was higher and vertical transmission was lower in the intervention versus control: 3.3% (1.0-5.6%) in the intervention died or became HIV-infected by year 3 versus 6.4% (4.7-8.0%) in the control (Relative risk:1.03; 95%CI:1.00, 1.06; p=0.04). Vertical transmission was 1.8% (0.2-3.3%) in the intervention versus 4.4% (2.7-6.1%) in the control (p=0.04). Of 1,230 births to 1,158 women with known HIV+ status at baseline, vertical transmission was 0.5%(0-1.3%) in the intervention, compared to 3.7% (2.4-5.1%; p<0.001) in the control.
Conclusion: Universal testing and a patient-centered care delivered via government clinics reduced 3 year population-level HIV infection/mortality among infants by over 50% and reduced vertical transmission to 0.5% among women with known HIV, progress toward the elimination of vertical transmission.

135 PREDICTORS OF THE PERSISTING VIRAL RESERVOIR IN VERY EARLY TREATED INFANTS

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Background: The size of the persisting viral reservoir while receiving antiretroviral therapy (ART) has consistently been shown to be smaller when ART is initiated at a younger age in perinatally-acquired HIV infection. However, there are only limited data on predictors of the proviral DNA reservoir in very early treated infants.
Methods: Sixty-three confirmed HIV-infected neonates recruited at Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa, who had been identified <48 hours after birth were included. Viably- preserved PBMCs collected pre-treatment, and at 1, 3, 6 and 12 months after ART initiation, were tested if sufficient sample was available. To quantify the proviral DNA reservoir, a semi-nested real-time quantitative hydrolysis probe (TaqMan) PCR assay was designed to detect and quantify total HIV-1 subtype C proviral DNA. The assay was designed to target the integrase gene of HIV-1 subtype C. We conducted six replicates to allow detection to a level of one copy/9.1x105 cells. Multivariable Generalized Estimating Equation (GEE) regression models were used for statistical analysis.
Results: Thirty-one (49.0%) infants initiated ART <48 hours of birth and the remaining 32 infants at median of 7 days (all received daily nevirapine prophylaxis prior to ART start). Three-quarters were infected despite their mothers having received ART during pregnancy and, for 25%, mothers had received no ART prior to delivery. At all post-ART time points, infant HIV-1 DNA was significantly associated with concurrent HIV-1 RNA levels (viral load [VL]) (Spearman correlation=0.645, p<0.0001). If VL was target not detected, the median HIV-1 DNA was 1.56 log copies and 23.1% had <10 DNA copies detected. Whereas, at VL <50, 51-399, 400-999 and >1000 RNA copies/ml, median DNA log copies (and % with <10 copies) were 1.83 (17.7%), 2.38 (10.8%), 2.83 (10.0) and 3.15 (0%), respectively. In multivariable analysis, starting ART <48 hours after birth (p=0.03), having been born to a mother who did not receive ART during pregnancy (p<0.0001), and pre-treatment infant CD4+ T-cell percentage >30 (p<0.0001) predicted lower HIV-1 DNA log copies in the first year post-treatment (Table).

Conclusion: Age at starting ART, combined with other maternal and infant factors, predict the size of the pool of proviral DNA in very early-treated infants during the first year of ART.

	Multivariable GEE regression model predicting HIV-1 DNA (log copies/10^6 cells) in the first 48 weeks after ART start		
	Parameter co-efficient	95% Confidence Interval	p-value
Start ART < 48 hours after birth vs later (median 7 days) [ref]	-0.488	-0.938, -0.037	0.033
Pre-ART CD4+ T-cell percentage > 30 vs. < 30 [ref]	-1.286	-1.79, -0.778	<0.0001
Mother had no ART prior to delivery vs Had ART [ref]	-1.124	-1.594, -0.654	<0.0001
Months after ART start	-0.033	-0.064, -0.003	0.031

136 LONG-TERM TREATMENT OUTCOMES: EARLY VERSUS DEFERRED ART IN CHILDREN LIVING WITH HIV

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Background: WHO antiretroviral treatment (ART) guidelines currently recommend initiating ART in HIV infected children at any CD4 count, as soon as possible after diagnosis. The objective of this study was to describe long term treatment outcomes after a decade of follow up, among children in the PREDICT study who did not have rapidly progressive HIV, and were randomized to early versus deferred treatment strategies.

Methods: The PREDICT study was a multicentre, randomisedtrial in Thailand and Cambodia. ART-naïve HIV-infected children aged 1-12 years with CD4 15-24% and no advanced HIV symptoms were randomly assigned (1:1) to start ART at study entry (early treatment) or when CD4 < 15% (deferred treatment, standard of care at that time). The long-term endpoints were virological suppression, cumulative probability of virological treatment failure,defined as plasma HIV RNA> 1000 copies/mL, and immunological status. Cumulative failure probability was calculated using the Kaplan-Meier method; formal comparisons between group were made using chi-square, log rank test, Mann_Whitney U tests.

Results: From March 2006 to September 2008, 300 Thai and Cambodian children were enrolled, with a median age of 6•4 (IQR 3•9-8•4) years, and median baseline CD4 of 19% (IQR 16-22). As of July 2019, 230 (77%) participants remained in the study (132 Thai, 98 Cambodian), 19 withdrew, 2 died and 47 were lost or referred out at median age of 12.9 (10.4-15.4) years.
The median age at last visit was 16.7 years (IQR 14.3-18.6). Current antiretroviral regimens were 75.2% NNRTI-based, 20.4% PI-based and 4.4% others. Among adolescents with HIV, 86.3% in the early arm and 77.9% in the deferred arm had plasma HIV RNA <50 copies/mL (p=0.09); 88.9% in the early arm and 76.1% in the deferred arm had CD4 > 500 cells/mm_3 (p=0.01). However, the 10 year cumulative probability of virologic failure was higher among adolescents in the deferred (34.3(95%CI 24.8-46.1)) versus early treatment group 22.8(95%CI 16.1-31.7) [P=0.07].

Conclusion: Leveraging this randomized study conducted when early ART was not the standard of care, it demonstrates that amongst children with slow progressor, a decade of ART could not overcome the lower CD4 count at ART start. The long lasting poorer CD4 recovery and higher virological failure mandates prompt diagnosis and ART initiation in children.

Table: Long term outcomes among HIV infected adolescents with early or deferred antiretroviral treatment initiation strategies

Characteristic Median (IQR) or n(%)	Total (N=230)	Early (N=117)	Deferred (N=113)	P value
Age at enrollment (years)	6.7 (3.8- 8.1)	6.4 (3.6-7.9)	6.4 (4.2-8.6)	0.21
CD4 % at enrollment	21 (18-23)	20 (17-22)	21 (18-23)	0.18
Age at ART initiation (years)	7.6 (4.9-10.1)	6.4 (3.6-7.7)	9.7 (7.0-12.1)	<0.001
At last visit				
Age (years)	16.7 (14.3-18.6)	16.5 (14.2-18.2)	16.8 (14.8-19.0)	0.40
Duration of ART (years)	9.6 (7.6-10.7)	10.6 (9.9-11.2)	7.9 (5-9.2)	<0.001
On first line ART regimen	178 (77%)	91 (78%)	87 (77%)	0.89
CD4 %	30 (254-34)	31 (27-35)	27 (22-32)	<0.001
CD4 cell count (cells/mm^3)	725 (538- 952)	801 (618 -999)	672 (511-896)	0.002
HIV-RNA <50 copies/mL	189 (82%)	101 (86%)	88 (78%)	0.24
10 year probability of virologic failure	27.7(22.0-34.7)	22.8(16.1-31.7)	34.3(24.8-46.1)	0.07

137 ANTIMICROBIAL PROPHYLAXIS AMONG AFRICAN ADULTS ON ART: RESULTS OF A RANDOMIZED TRIAL

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Background: Before widespread antiretroviral therapy (ART) use in sub-Saharan Africa, studies demonstrated that daily trimethoprim-sulfamethoxazole (TS) prophylaxis reduced morbidity and mortality among HIV-infected adults, predominantly by preventing malaria and diarrhea in this population. Routine administration of TS prophylaxis has continued with expanded access to ART throughout sub-Saharan Africa. However, the public health benefit has not been definitively evaluated. We designed a clinical trial to evaluate the impact of TS prophylaxis on morbidity and mortality among HIV-infected Malawian adults following good response to ART. If beneficial, we also aimed to determine if this is due to TS antibacterial and/or antimalarial properties

Methods: We conducted a randomized, controlled, open label, phase 3 trial of continued standard of care prophylaxis with daily TS compared to discontinuation of TS and starting weekly chloroquine (CQ) prophylaxis or discontinuation of TS prophylaxis. The study randomized 1,499 HIV-infected adults (1:1:1 ratio) with nondetectable viral load and CD4 count >250/mm_3. The primary endpoint events were death and WHO Stage 3 and 4 events. We compared virologic, immunologic and clinical responses to ART among study arms.

Results: Among 2219 persons screened, 1499 were enrolled. 4958 pyo were accrued, and 1249 (83%) completed the study. 24 deaths were reported, 10 in TS group, 6 in CQ group, and 8 in no prophylaxis group. The primary endpoint rate was lower in TS group compared to no prophylaxis, but this result was not significant (Table 1). When WHO Stage 2 events are added to the primary endpoint rate per 100 pyo for each group, TS group had a lower rate of events compared to no prophylaxis and to CQ. Groups did not differ regarding secondary endpoints of virologic failure, low CD4 cell count, or adverse events. Participants on TS prophylaxis experienced fewer malaria episodes than those on no prophylaxis and equivalent episodes compared to CQ prophylaxis. Participants on TS experienced fewer suspected or confirmed bacterial infections than those on no prophylaxis or CQ.

Conclusion: Following immune reconstitution, TS prophylaxis continued to provide benefit in terms of prevention of non-severe bacterial infections and malaria, and was safe and well tolerated. Continuation of TS prophylaxis should be considered based on comprehensive analyses of cost and risk/benefit alongside other public health interventions aimed to improve outcomes in this population.

Table 1. Event counts and analysis by Poisson regression for efficacy endpoints

				Poisson			
				Rate ratio (95% CI)		P-value	
Endpoint	TS N=500 pyo=1654 n (rate per 100 pyo)	CQ N=500 pyo=1646 n (rate per 100 py0)	No prophylaxis N=499 pyo=1658 n (rate per 100 pyo)	CQ vs TS	No prophylaxis vs. TS	CQ vs. TS	No prophylaxis vs. TS
WHO Stage 3+ event or death (primary endpoint)	54 (3.3)	69 (4.2)	69 (4.2)	1.28 (0.90, 1.83)	1.27 (0.89, 1.82)	0.17	0.18
WHO Stage 2+ event or death	66 (4.0)	94 (5.7)	97 (5.8)	1.43 (1.04, 1.96)	1.47 (1.07, 2.00)	0.026	0.017
P. falciparum clinical malaria	63 (3.8)	49 (3.0)	465 (28.0)	0.78 (0.30, 2.03)	7.40 (3.77, 14.50)	0.61	<0.001
Grade 3+ adverse event	2.9 (12.6)	244 (14.8)	239 (14.4)	1.17 (0.91, 1.51)	1.14 (0.89, 1.47)	0.21	0.31

pyo=person-years of observation

138 ISONIAZID TO PREVENT MTB INFECTION IN HIV-EXPOSED UNINFECTED INFANTS

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Background: HIV-exposed uninfected infants (HEU) in TB endemic settings are at high risk of *Mycobacterium tuberculosis* (Mtb) infection and TB disease, even in the absence of known Mtb exposure. For infants, progression from primary infection to TB disease can be rapid; whether isoniazid (INH) prevents primary Mtb infection in HEU is unknown.

Methods: We conducted a non-blinded RCT comparing 12 months daily INH (10 mg/kg) vs. no INH to prevent Mtb infection among HEU infants enrolled at 6 weeks of age in Kenya between August 2016-September 2019. Initially Mtb infection was assessed by interferon gamma release assay (IGRA, QFT-Plus) at 12 months. After February 2018, tuberculin skin test (TST, >10 mm) was added as a composite primary endpoint per DSMB recommendations.

Results: Three-hundred HEU infants were enrolled (150 in each arm). Median age was 6 weeks (IQR 6.0-6.6), 158 (52.7%) were male, and 282 (94.0%) received BCG. All mothers were on antiretroviral (ARV) therapy; 297 (99.0%) infants received ARVs for HIV prevention. Two-hundred twenty-four (74.7%) mothers had received programmatic isoniazid preventive therapy (IPT) and 32 (10.7%) mothers reported history of TB. Excluding two HIV-infected children, retention was 96.0% with 286 participants completing the study (1 withdrew, 1 died, 10 were lost-to-follow up). Of 263 (88.3%) with available QFT and/or TST results, 3/246 (1.3%) were QFT-positive and 25/186 (13.4%) were TST-positive. Prevalence of Mtb infection (by QFT or TST) was 7.7% (10) in the INH and 13.5% (18) in the no INH arm (7.0 vs. 13.5 per 100PY, HR 0.55 [95% 0.25-1.17], p=.118). There was a trend for decreased risk of positive TST among children randomized to INH (8.9% vs. 18.3%, 5.6 vs. 12.7 per 100PY, HR 0.48 [95% 0.20-1.06], p=.06). Severe adverse events (primarily non-TB hospitalizations) were similar between arms (INH 12.7% [19] vs. no INH 10.0% [15], p=.72). There were no INH-related serious adverse events. One child was diagnosed with TB (INH arm), and one died of non-TB related causes (No INH arm).

Conclusion: Rates of primary Mtb infection were approximately 2-fold lower in children randomized to INH, though this did not reach statistical significance, with a stronger trend of reduced TST-positivity. Secondary endpoint analyses including IFN-γ-independent immune markers in QFT-Plus supernatants to indicate Mtb infection are ongoing.

139 PREDICTORS OF TUBERCULOSIS INFECTION IN MDR-TB HOUSEHOLD CONTACTS ≥15 YEARS OLD

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Background: Few multinational, multisite studies have evaluated predictors of TB infection in MDR-TB household contacts (HHC).

Methods: From 10/2015-4/2016, ACTG and IMPAACT networks conducted A5300/I2003, a cross-sectional observational study of adults with pulmonary MDR-TB and their HHCs, in high TB-burden countries in preparation for a randomized trial. Among HHCs≥15 years of age without TB disease, index case (IC), household (HH), HHCs, and TB exposure characteristics were evaluated for association with TB infection based on interferon gamma release assay (IGRA) status (QuantiFERON Gold/Gold-in-Tube). HHCs<15 years have previously been reported on. Logistic regression using generalized estimating equations was used for testing.

Results: 278 ICs enrolled at 16 sites in 8 countries had 712 HHCs≥15 years of age. 36% of ICs were HIV-infected and 10% had unknown HIV status. 59 (8%) HHCs age≥15 years were HIV-infected and 436 (64%) female (16 pregnant). 686 had determinate, 4 indeterminate, and 22 no IGRA results. Factors independently predictive (p≤0.05) in multivariable models are shown in the Table. Of 686 HHCs with determinate results, 471 (69%, 95% confidence interval: 65-73%) were positive; prevalence varied with age: 59% in 15-<25, 76% in 25-<50, and 68% in ≥50 years (p<0.001). Cavitations on CXR, smear status, and duration of IC TB treatment were not associated with HHC TB infection prevalence. TB infection prevalence increased when a HHC had self-reported or a medical history of COPD/asthma (83% vs 69%, p=0.039), spent more nights/week with the IC (61%, 68%, 70% for 0-2, 3-5, 6-7 nights, respectively, p=0.05) but not by sleeping proximity. Compared to HHCs never incarcerated and not substance or alcohol users (66%), HHCs previously incarcerated had the highest prevalence of TB infection (95%); HHCs never incarcerated using substances or alcohol were also more likely to have TB infection (84%)(p<0.001). Smoking in the household (77% vs 64%, p=0.02) and lower quality exterior wall materials (see definition in Table) were associated with increased TBI prevalence (77% vs 67%, p=0.009).

Conclusion: Over 2/3rd of HHCs age≥15 in HHs of adult MDR-TB patients had evidence of TB infection, confirming the importance of household contact investigation. HHs with poorer quality homes and HHCs highly exposed to IC, ever incarcerated or currently using substances or alcohol, or with COPD/asthma require particular attention to identify all TB infected HHCs.

Table: Logistic Regression Modeling Results*

			Univariable		Multivariable	
Characteristic		n/N (%)	Odds Ratio [95%CI]	P value	Odds Ratio [95%CI]	P value
HHC age	15-<25 years	108/184 (59%)	0.7 [0.4,1.03]	<0.001	0.6 [0.4, 1.01]	<0.001
	25-<50 years	252/334 (75%)	1.5 [1.01, 2.3]		1.6 [1.04, 2.4]	
	≥50 years	111/168 (66%)	1.0 (ref)		1.0 (ref)	
HHC history of COPD/ asthma	Yes	24/29 (83%)	1.9 [0.8, 4.8]	0.11	2.1 [1.2, 3.4]	0.039
	No	437/637 (69%)	1.0 (ref)		1.0 (ref)	
Nights/week with IC, past 6 months	0-2	58/95 (61%)	1.0 (ref)	0.14	1.0 (ref)	0.05
	3-5	48/71 (68%)	1.5 [0.8, 2.9]		1.8 [0.9, 3.9]	
	6-7	364/519 (70%)	1.7 [1.1, 2.7]		2.1 [1.2, 3.4]	
Incarceration, substance and alcohol use composite†	Ever incarcerated	19/20 (95%)	6.7 [1.9, 24.4]	<0.001	7.1 [1.5, 33.6]	<0.001
	Never incarcerated, substance &/or alcohol user	67/80 (84%)	2.3 [1.3, 4.2]		2.5 [1.3, 5.1]	
	Never incarcerated, not substance or alcohol user	380/578 (66%)	1.0 (ref)		1.0 (ref)	
Smokers in household‡	Any	205/267 (77%)	1.8 [1.2, 2.6]	0.005	1.6 [1.1, 2.5]	0.020
	None	264/410 (64%)	1.0 (ref)		1.0 (ref)	
Home primary exterior wall material	Brick/cinderblock/stone with mortar	356/534 (67%)	1.0 (ref)	0.022	1.0 (ref)	0.009
	Adobe/rammed earth/ sticks or stones & mud/ wood/straw/tin/other	114/148 (77%)	1.6 [1.1, 2.5]		1.8 [1.2, 2.8]	

IC, index case, HHC, household contacts; n, number of HHCs who are IGRA-positive; N, number of HHCs with determinate IGRA results (positive or negative); CI, confidence interval.
*Models were fit using an exchangeable working correlation. Univariable models include the one characteristic only. The multivariable model included all characteristics shown in the table. The p values are from score tests.
†Incarceration is defined as having spent a night in jail/prison/youth detention center, alcohol use as alcoholic beverages almost every day, and substance use as marijuana, cocaine, etc. all in the past 12 months.
‡Smoking is defined as currently smoke tobacco products, ongoing or having quit within the past 6 months.

140 DIAGNOSTIC AND THERAPEUTIC CHALLENGES ARISE WITH EARLY HIV INFECTION ON PrEP

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Background: The impact of PrEP during HIV acquisition may alter reservoir establishment, viral load set points, and immune responses. Some individuals on PrEP may remain negative by screening assays while still becoming infected. Characterization of such individuals is needed to define how to diagnose early infection in this context.

Methods: Working with the San Francisco Department of Public Health, we identified individuals with early HIV infection, many of whom were on PrEP. The estimated date of detected infection (EDDI) was calculated; standard diagnostic and resistance testing was performed.
Results: 58 participants (all men) with early HIV enrolled from 2015-2019. Most had sex with men (87%); median (IQR) age was 30 (25-37) years; pre-ART CD4 508 (355-680); log plasma HIV RNA 5.1 (4.1-5.7); time between EDDI and ART 29 (20-91) days. Among 24 with PrEP exposure, 13 (54%) reported prior use (>10 days pre-diagnosis), 6 (25%) active use (≤10 days pre-diagnosis), and 5 (21%) were found to have HIV on the day of PrEP initiation. The 6 reporting active PrEP at diagnosis had lower initial log plasma HIV RNA (2.8 vs 5.3, p=0.001) and higher CD4 (768 vs 488, p=0.03) than the 52 not on PrEP. The remaining analyses focus on those on active PrEP and those positive at PrEP initiation (n=11, Table). HIV Ab screening was positive in only 4/11 (36%). HIV RNA was detected in all cases, although <100 copies/mL in one and <20 copies/mL in two. Of these two, one had a newly positive Ab/Ag test, with cell-associated (CA)-DNA not detected and CA-RNA 117 copies/10^6 cells. The second had a negative Ab/Ag test and analysis of 25M PBMCs did not show CA-DNA or CA-RNA despite transiently detectable HIV RNA on clinical assays. Of the 8/11 who could have genotypic resistance testing, three had M184V/I mutations, with two transmitted and one emerging after 5 days on PrEP.
Conclusion: Increasingly widespread PrEP use may result in distinct and challenging presentations of HIV infection. We present the largest case series of early (or pre-existing) HIV on PrEP, with resultant blunting of immune responses and viral loads. Those presenting with delayed evidence of infection may be continued on PrEP, resulting in suboptimal treatment and development of resistance. In some cases, diagnostic uncertainty will arise regarding whether infection was prevented or established with a more limited reservoir. Further characterization of infections during PrEP is needed.

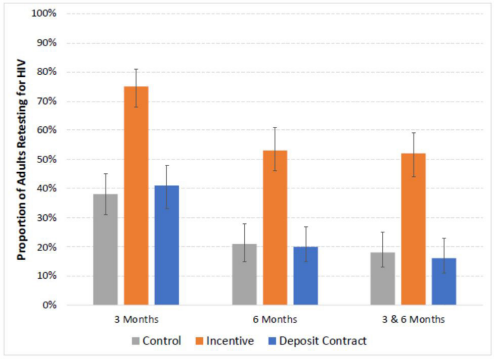
Age	Race	Initial Ab Screening	Pooled RNA	Plasma HIV RNA (copies/mL)	Baseline CD4	Genotype Information	Other Information
Participants reporting active PrEP use at the time of suspected HIV acquisition							
28	White	Positive	Not done	49	518	Too few copies	
24	White	Positive	Not done	Detected, <20	768	Too few copies	CA-DNA no copies detected CA-RNA 117 copies detected
26	Latinx	Negative	Positive	33,123	573	M184I	
21	Latinx	Negative	Positive	529	983	M184V,L74V, L100I, K103N	Previously reported[1]
47	Black	Positive	Not done	722	788	Wild type	
34	White	Positive	Not done	4,807	543	Minor mutations	
Participants presenting for PrEP initiation found to have existing infection							
33	Asian	Negative	Positive	247,583	346	M184I	Prior wild type virus confirmed; M184I developed after 5 days of PrEP
25	Asian	Negative	Positive	400,924	702	Wild type	
35	White	Negative	Positive	>10,000,000	568	Wild type	
40	White	Negative	Positive	4,194	324	Minor mutations	
54	Latinx	Negative	Not done	Detected, <20	527	Too few copies	CA-DNA no copies detected CA-RNA no copies detected

Abbreviations: Ab, antibody; CA, cell-associated. [1]Cohen *et al* Lancet HIV 2019.

141 A RANDOMIZED TRIAL OF INCENTIVES AND DEPOSIT CONTRACTS TO PROMOTE HIV RETESTING

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Background: Retesting for HIV in high-risk populations is critical for identifying newly infected persons and promoting prevention services. Whether standard financial standard incentives and less costly deposit contracts can increase retesting for HIV among at-risk adults is unknown.
Methods: In a peri-urban Ugandan community, we recruited persons at-risk for HIV from selected venues (bars, sites of commercial sex work, and transport hubs) and referred them for clinic-based HIV testing. HIV-negative adults (18-59 years old) with self-reported risk (either >1 partner, HIV-infected partner, sexually transmitted infection, or payment/receipt of compensation for sex) were enrolled. Participants were randomized to either: (1) no incentive (control); (2) cash incentives (US$7) for retesting at 3 and 6 months (total $14); or (3) deposit contracts that leveraged loss aversion: participants could voluntarily deposit $5.50 at baseline and at 3 months that would be returned with interest (total US$7) upon retesting at 3 and 6 months respectively (total $14) or lost if participants failed to retest. The primary outcome was retesting for HIV at both 3 and 6 months.
Results: A total of 524 participants were randomized to either no incentive (N=180), incentives (N=172), or deposit contracts (N=172). Participants' median age was 25 years (IQR: 22-30), 44% were women, and median weekly income was US$13.60 (IQR: $8.16-21.76). Baseline characteristics were similar across arms. Among participants randomized to deposit contracts, 24 (14%) made a baseline deposit, and 2 (1%) made a 3-month deposit. In intent-to-treat analyses, the proportion of participants who retested for HIV at both 3 and 6 months was higher in the incentive arm (52%) than either the control arm (18%, p<0.001) or the deposit contract arm (16%, p<0.001; Figure). Among those in the deposit contract arm who made a baseline deposit, 83% retested at 3 months, and 46% retested at both 3 and 6 months. Those who made baseline deposits were significantly more likely to retest at 3 and 6 months than those who declined (46% vs. 11%, p<0.001). Seven participants seroconverted during the trial and were immediately referred for antiretroviral therapy
Conclusion: Offering financial incentives to high-risk adults in Uganda resulted in significantly higher HIV retesting. Deposit contracts to help individuals follow through on a commitment to retesting had low uptake and overall did not increase retesting rates.



142 COMMUNITY-BASED HIV TESTING IN URBAN KENYA: A STRATEGY TO REACH MEN AND YOUTH

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Background: Some countries are struggling to reach the UNAIDS testing target, especially among men and youth. Randomized controlled trials and HIV testing services (HTS) have successfully conducted community-based hybrid HIV testing in rural settings in East Africa to identify persons unaware of their HIV-positive status and achieve testing saturation. We implemented a hybrid HIV testing approach in an urban slum setting in Kisumu, Kenya.
Methods: The Community Health Initiative (CHI) conducted community mapping, household census, multi-disease community health campaigns (CHCs) and home-based tracking in Obunga in 2018. To encourage participation by men and youth, health and counseling services tailored for them were provided. HTS eligibility (not previously diagnosed HIV-positive, aged >=15 years, sexually-active <15 years) and antiretroviral therapy (ART) initiation were based on 2018 national guidelines. We calculated the previously unidentified fraction (PUF), a new metric, as the proportion of newly identified PLWH out of all previously identified and newly identified PLWH.
Results: CHI reached a total of 23,584 persons: 21,364 enumerated residents and 2,220 nonresidents. There were 22,685 persons engaged through CHCs and tracking. Of 12,768 HTS-eligible persons, 12,407 (97%) accepted testing, of whom 3,917 (32%) were first-time testers. First-time testers were more likely to be men (AOR=1.1; p<0.03) and adolescents aged 15-19 years (AOR=2.8; p<0.01). There were 100 newly identified PLWH out of 1,247 total HIV-positive persons, representing an 8.0% PUF. The PUF was higher among men (9.8%) and youth aged 15-24 years (13.1%). Ninety-four percent of newly diagnosed persons initiated same-day ART.
Conclusion: The community-based hybrid HIV testing approach was implemented successfully for the first time in an urban setting characterized by a high risk, impoverished and highly mobile population. CHI identified persons previously unaware of their HIV-positive status, thereby enabling linkage to care and same-day treatment and reducing onward transmission risk. Innovative approaches that make HIV testing more accessible and acceptable to the

community, in particular men and youth, are critical for reaching individuals who might otherwise be reticent to take up standard facility-based testing services. An approach focused on identifying persons unaware of their HIV-positive status in combination with monitoring the PUF has the potential to achieve the UNAIDS 90-90-90 target.

143LB EFFECTIVENESS OF 3HP ANNUALLY VS ONCE FOR HIV-POSITIVE PEOPLE: THE WHIP3TB TRIAL

Gavin Churchyard[1], Vicky Cardenas[2], Violet Chihota[2], Kathryn Mngadi[2], Modulakgotla Sebe[1], William L. Brumskine[3], Salome Charalambous[1], Neil A. Martinson[4], Getnet Yimer[5], Alberto L. Garcia-Basteiro[6], Leeanne Masilela[2], Susan Van Den Hof[7], Richard E. Chaisson[8], Alison Grant[9], Katherine Fielding[9]
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Background: Weekly isoniazid (900mg) and rifapentine (900mg) for 12 weeks (3HP) has similar efficacy to 6 months of daily isoniazid (6H) as TB preventive therapy. We compared treatment completion rates and effectiveness of 3HP vs. 6H and the effectiveness of 3HP given annually vs. once among HIV-positive people. (NCT02980016)

Methods: HIV-positive people in South Africa, Ethiopia and Mozambique aged ≥2 years, without active TB and on antiretroviral therapy (ART) for ≥3 months or ineligible were randomized 9:9:2 to periodic (annual) 3HP (p3HP), 3HP, or 6H. Participants in the 3HP/p3HP and 6H arms were followed for 24 and 12months, respectively; all were seen monthly for the first three months of each participation year. Medication doses were directly observed at dispensing visits and otherwise self-administered. Participants in the 6H arm were dispensed 3 months treatment at month 3. Participants were screened for TB with symptoms, chest X-ray and sputum culture after 12 and 24 months. Completion of the initial treatment course in the combined 3HP/p3HP arms vs. 6H was compared using pill counts. TB incidence and all-cause mortality over 12 months was compared in the 3HP and 6H arms, and TB incidence, all-cause mortality, and permanent discontinuation of 3HP for adverse events over 24 months was compared in the p3HP and 3HP arms.

Results: Between November 2016 and November 2017, 4593 participants were screened, 4027 enrolled and 4014 analysed. The median age was 41 years (19 (0.5%) <18 years), all were on ART, 70% were female, 38% were QuantiFERON-TB GOLD Plus positive; 63%, 22% and 15% were from South Africa, Ethiopia and Mozambique, respectively. Treatment completion in the combined 3HP (n=3610) and 6H (n=404) arms was 90.4% versus 50.5% (risk ratio: 1.79; 95%CI:1.62-1.79). TB incidence and mortality by study arm are shown in the table. TB incidence and mortality from month 0 to month 12 was similar in the 3HP and 6H arms. TB incidence over 24 months and from month 12 to month 24 was similar in the p3HP (n=1808) and 3HP (n=1802) arms. Over 24 months, TB incidence among QuantiFERON Plus positive participants, incidence of rifampicin resistant TB, and mortality were similar in the p3HP and 3HP arms. Treatment discontinuation in the p3HP and 3HP arms was 1.2% vs. 0.6% (OR2.11, 95%CI:0.95-5.02).

Conclusion: Treatment completion was higher in the 3HP arms vs. 6H. In high TB transmission settings, annual 3HP did not provide additional benefit to people receiving ART.

Table. TB and mortality incidence by study arm

Outcome	Time period (Months)	3HP: events/py Rate/100py	6H: events/py Rate/100py	HR (3HP vs 6H) 95% CI	P-value
TB incidence	0-12	55/3808 1.44	4/372 1.07	1.06 (0.38-2.95)	0.91
Mortality incidence	0-12	16/3838 0.42	1/430 0.23	1.79 (0.24-13.5)	0.57
Outcome	**Time period (Months)**	**p3HP: events/py Rate/100py**	**3HP: events/py Rate/100py**	**HR (p3HP vs 3HP) 95% CI**	**P-value**
TB incidence	0-24	37/3141 1.18	39/3149 1.24	0.95 (0.61-1.49)	0.83
TB incidence	12-24	14/1463 0.96	14/1471 0.95	1.01 (0.48, 2.12)	0.98
TB incidence, among quantiferon-positives	0-24	19/1142 1.66	18/1113 1.62	0.99 (0.52-1.89)	0.98
Rifampicin-resistant TB incidence	0-24	4/3141 0.13	4/3149 0.13	1.00 (0.25, 4.01)	>0.99
Mortality incidence	0-24	29/3238 0.90	19/3239 0.59	1.55 (0.87-2.76)	0.14

py=person years, HR=hazard ratio, CI=confidence interval. Quantiferon positive=QuantiFERON Gold Plus positive

144LB RIFAPENTINE PHARMACOKINETICS AND SAFETY IN PREGNANT WOMEN WITH AND WITHOUT HIV ON 3HP

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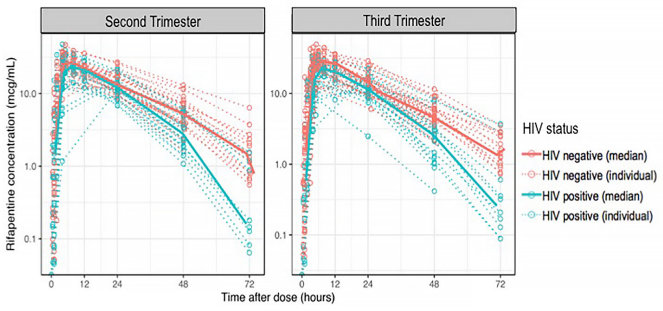
Background: Pregnancy increases the risk of progressing from latent tuberculosis infection (LTBI) to active TB. A 3-month TB-prevention regimen of weekly isoniazid and rifapentine (3HP) shows excellent safety and adherence in non-pregnant people, including those with HIV. We hypothesized that the pharmacokinetics (PK) of rifapentine (RPT) in pregnant women taking 3HP would be comparable to non-pregnant adults and well-tolerated.

Methods: IMPAACT 2001 is a Phase I/II study evaluating the PK and safety of 3HP among pregnant women with or without HIV, who had LTBI or a household contact with active pulmonary TB (NCT02651259). Sites were in Haiti, Kenya, Malawi, Thailand, and Zimbabwe. Cohort 1 had dosing and PK sampling in the 2nd and 3rd trimesters; Cohort 2 in the 3rd trimester and postpartum. Isoniazid and RPT were provided at standard doses of 900mg weekly. PK samples were collected with the 1st (predose, 0.5h, 1h, 2h, 4h, 5h, 8h, 12h, 24h, 48h, 72h post-dose) and 12th doses (predose, 1h, 4h, 24h, 48h post-dose). Primary objectives were to estimate the population PK of RPT during pregnancy and post-partum using non-linear mixed effects modeling, and to describe maternal-infant safety outcomes.

Results: We enrolled 50 pregnant women, 25 per cohort. Twenty women had HIV; all were taking efavirenz (EFV)-based antiretroviral therapy (median CD4:510 cells/mm$_3$). All women completed the 3HP regimen. There were no drug-related SAE and no cases of active TB in women or their infants. There was one maternal and fetal death by abruptio placentae from trauma. Among women without HIV, oral clearance (CL/F) of RPT was 36% lower during pregnancy (1.24 L/h) than post-partum (1.68 L/h), with an area under the concentration-time curve (AUC) of 736 and 618 mg*hr/L, similar to historical non-pregnant controls. In women with HIV, CL/F was the same during pregnancy and postpartum (1.60 vs.1.61 L/hr), which was 34% higher (p<0.001) compared to pregnant women without HIV, resulting in a lower AUC of 512 mg*h/L.

Conclusion: Pregnancy does not appear to increase RPT clearance; thus, there is no need for dose adjustment of 3HP in pregnancy. Among women with HIV taking EFV, however, clearance of RPT was higher than expected during pregnancy. Exposures remained in the expected therapeutic range. Initial tolerability and safety results from this small trial are encouraging, given limited options for TB prophylaxis in pregnancy, but larger studies will be needed to characterize its safety in pregnancy definitively.

Figure 1: Increased clearance of RPT in HIV-infected vs. HIV-uninfected pregnant women



145 NO HIV INCIDENCE INCREASE IN FIRST-TIME BLOOD DONORS WITH 12-MONTH DEFERRAL FOR MSM

Eduard Grebe[1], Edward P. Notari[2], Roberta Bruhn[1], Claire Quiner[1], Mars Stone[1], Sonia Bakkour[1], Hong Yang[3], Debra Kessler[4], Rita Reik[5], Michael P. Busch[1], Susan Stramer[2], Simone Glynn[6], Alan Williams[3], Brian Custer[1], for the U.S. FDA Transfusion Transmissible Infections Monitoring System

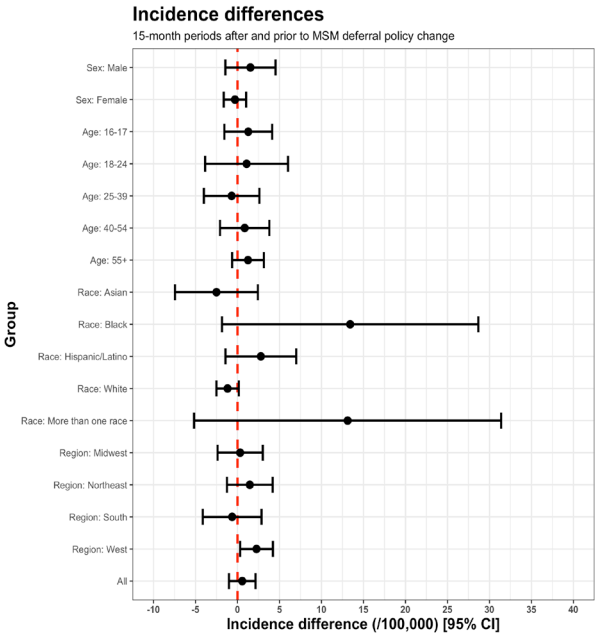
[1]Vitalant Research Institute, San Francisco, CA, USA, [2]American Red Cross, Washington, DC, USA, [3]FDA, Silver Spring, MD, USA, [4]New York Blood Center, New York, NY, USA, [5]OneBlood, St Petersburg, FL, USA, [6]National Heart, Lung, and Blood Institute, Bethesda, MD, USA

Background: In 2015, the FDA published revised guidance that recommended a change in donor deferral policy for men who have sex with men (MSM) from indefinite to one year. The Transfusion Transmissible Infections Monitoring System (TTIMS) has monitored HIV, HBV and HCV infections in four blood collection organizations since 2015, representing approximately 60% of the US blood supply. We evaluated HIV-1 incidence changes in first-time blood donors following the implementation of the new MSM deferral policy using biomarkers of recent infection.

Methods: We utilized an algorithm to identify recent HIV infections amongst 5.7 million first-time donors (NAT-positive/Ab-negative or by applying the LAg Avidity EIA and viral load testing to seropositive donations). We derived a context-specific mean duration of recent infection using a novel Bayesian method and a false-recent rate, and utilized these parameters to estimate incidence rates and incidence rate differences in first-time donors during the 15-month periods preceding and following the deferral policy implementation, as well the entire post-implementation period through end 2018. We used Poisson regression models to identify demographic covariates of incidence.

Results: Overall HIV incidence in first-time donors in the 15 months prior to the MSM deferral policy implementation was estimated at 2.63 cases/100,000PY (95% CI: 1.44–3.81), in the 15 months after at 3.19 (1.94–4.43) and in the entire period after at 2.59 (1.71–3.48). Incidence differences were not statistically significant for either comparison. The figure shows incidence difference estimates by sex, age group, race/ethnicity and public health region. Of these, only the Western region showed a marginally significant increase, which becomes non-significant when the post period is expanded to include all available data. Bivariable and multivariable Poisson regression models using data from the entire TTIMS period showed that MSM deferral policy was not a significant correlate of incidence, although male sex (risk ratio 5.0, 95% CI: 2.8–9.5), age 18-24 (RR: 4.3, 1.5–18.3), black race (RR: 10.1, 5.8–17.9), Hispanic ethnicity (RR: 2.6, 1.3–5.0) and Southern region (RR: 2.0, 1.4–7.9) were significant.

Conclusion: There is no evidence that the implementation of a 12-month MSM deferral policy resulted in increased HIV incidence in, and therefore transfusion transmission risk from, first-time blood donors in the United States.



146 EXPLAINING RACIAL DISPARITIES IN VIRAL SUPPRESSION AMONG MSM LIVING WITH HIV

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[1]Columbia University Medical Center, New York, NY, USA, [2]Emory University, Atlanta, GA, USA, [3]State University of New York at Albany, Rensselaer, NY, USA

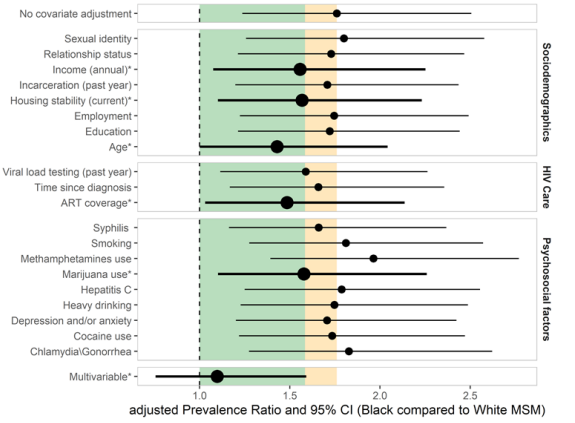
Background: National surveillance has documented consistent racial disparities at each step of the HIV treatment cascade, culminating in HIV-infected black men who have sex with men (MSM) having a 30% lower level of viral suppression compared to white MSM. Modifiable reasons for these racial disparities remain unclear. Nearly all supporting data for these findings are from clinical cohorts. Community-based studies that sample people living with HIV are not subject to the bias of selecting on those more likely to be engaged in HIV care, and thus are critical to understand causes of these disparities and to identify targets for interventions. We examined factors associated with racial disparities in baseline viral suppression in a community-based cohort of black and white MSM living with HIV in Atlanta, GA.

Methods: Baseline visits occurred from June 2016-July 2017 when laboratory and behavioral survey data were collected. Explanatory factors for racial disparities in viral suppression that were assessed included: sociodemographics, psychosocial variables and biological factors. Poisson regression models with robust error variance were used to estimate prevalence ratios (PR). We first estimated the unadjusted black/white PR for lack of viral suppression. Factors were individually added to that model and those that diminished the adjusted PR for race by ≥10%, were considered to meaningfully attenuate the racial disparity. All variables that met this criterion were included in a multivariable model.

Results: Overall, 26% (104/398) of participants were not virally suppressed at baseline. Lack of viral suppression was significantly more prevalent (PR=1.62; 95% CI: 1.05–2.50; p<0.001) among black MSM (33%; 69/206) than among white MSM (19%; 36/192). Adjustment for the following explanatory factors diminished the adjusted PR for race: age (-19%), ART coverage (through health insurance, a government program or a pharmaceutical company drug program) (-16%), income (-12%), housing stability (-11%), and marijuana use (-10%). In a multivariable model, these factors cumulatively diminished the PR for race by 38%, and it was no longer statistically significant (adjusted PR=1.10 [95% CI: 0.76–1.59]).

Conclusion: Relative to white MSM, black MSM living with HIV in Atlanta were less likely to be virally suppressed. However, this disparity was attenuated when accounting for explanatory factors, many of which can be targeted or modified by policy and individual-level interventions to help reduce racial disparities.

Figure. Adjusted black-white prevalence ratios for lack of viral suppression from multivariable models in a community-based sample of 398 black and white non-Hispanic MSM living with HIV, Atlanta, 2016–2017



a. Yellow region indicates covariate-adjusted PR for race that are between 0% and 10% less than the PR for race without covariate adjustment, whereas green region indicates covariate-adjusted PR that are more than 10% less, indicating meaningful attenuation of the race disparity in lack of viral suppression. b. Multivariable adjustment included the five variables that meaningfully attenuated the race disparity in lack of viral suppression (income, housing stability, age, ART coverage, marijuana use), which are indicated with asterisks after their labels.

147 EXPLOSIVE HIV AND HCV EPIDEMICS DRIVEN BY NETWORK VIREMIA AMONG PWID

Steven J. Clipman[1], Shruti H. Mehta[1], Aylur K. Srikrishnan[2], Katie J. Zook[3], Priya Duggal[1], Shobha Mohapatra[2], Shanmugam Saravanan[2], Nandagopal Paneerselvam[2], Muniratnam S. Kumar[2], Elizabeth Ogburn[1], Allison M. McFall[1], Gregory M. Lucas[3], Carl A. Latkin[1], Sunil S. Solomon[3]

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Background: While much attention has focused on the US opioid crisis, misuse of opioids is rapidly becoming a global epidemic with >80% of drug seizures in Africa/Asia in part due to increased use of opioids to manage pain and expansion of heroin trafficking routes. Little is known about the drug using networks in these settings which contribute to HIV/HCV transmission.

Methods: 2512 people who inject drugs (PWID) in New Delhi, India were recruited (2017-19) into a cohort by a chain referral approach. Index participants were asked to name and recruit people they injected with in the past month (egocentric network of the index). Each recruit was asked to name and recruit their recent injection network members (egocentric network of recruit; sociometric network of index). Biometrics were used to identify duplicates and cross-network linkages. Participants underwent a survey and blood draw semi-annually. Blood was tested for HIV and HCV antibodies, HIV RNA and HCV RNA. Network viral load was calculated as the number of egocentric network members with HIV RNA>150 copies/ml. Poisson regression was used to identify predictors of incident HIV.

Results: At baseline, 36.9% had HIV infection of whom only 7.4% were virologically suppressed; HCV prevalence was 65.1%; recent heroin and other opioid use were 26.6% and 95.3%, respectively. Among 1,066 with at least one follow-up as of 9/1/19, 96 seroconversions were observed in 370 person-years (p-y) (HIV incidence: 25.9 per 100 p-y); 64 HCV antibody seroconversions were observed in 188 p-y (primary HCV incidence: 34.0 per 100 p-y). Of 96 incident HIV cases, 74% were directly connected to at least one viremic person in their egocentric network (Figure). In multivariable analysis adjusting for recent needle sharing and injection frequency, HIV incidence increased by 23% per unit increase in egocentric network member with detectable HIV RNA (incidence rate ratio [IRR]: 1.23; p<0.01); further, every increased step in the path between a participant and a sociometric network member with detectable HIV RNA decreased HIV incidence by 37% (IRR: 0.63; p<0.01).

Conclusion: We observed explosive HIV and HCV epidemics among PWID in New Delhi, largely driven by exposure to viremic individuals in both egocentric and sociometric networks, highlighting the importance of achieving broad viral suppression in order to curb transmission. Expanding treatment and prevention efforts in such disenfranchised populations will be critical for epidemic control.

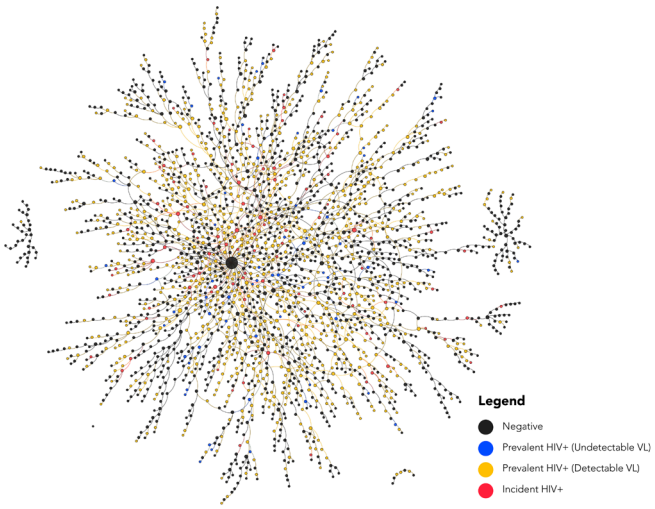


Figure. Sociometric injection network of 2,512 people who inject drugs in New Delhi, India. Nodes are colored based on HIV status and viral load (VL); HIV RNA<150 copies/ml was classified as undetectable.

148 THE AGING OF HIV-1 INCIDENCE IN HYPERENDEMIC RURAL SOUTH AFRICA

Adam N. Akullian[1], Alain Vandormael[2], Joel Miller[3], Anna Bershteyn[4], Edward Wenger[1], Diego F. Cuadros[5], Frank Tanser[6]

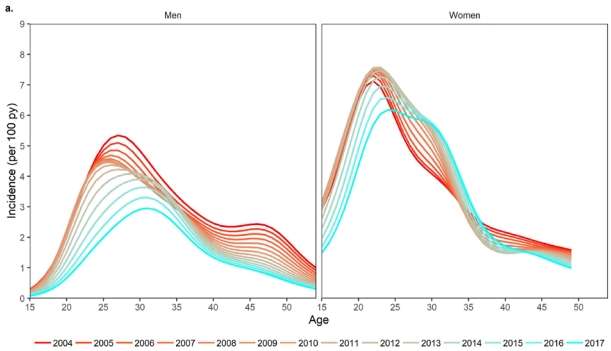
[1]Institute for Disease Modeling, Bellevue, WA, USA, [2]University of KwaZulu-Natal, Durban, South Africa, [3]Monash University, Melbourne, VIC, Australia, [4]New York University Langone Medical Center, New York, NY, USA, [5]University of Cincinnati, Cincinnati, OH, USA, [6]Africa Health Research Institute, Mtubatuba, South Africa

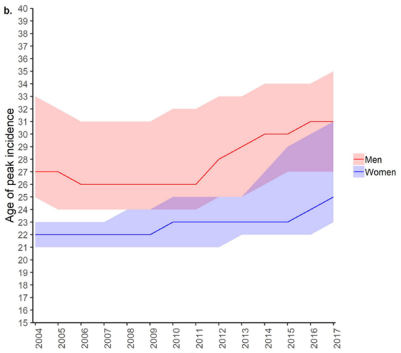
Background: The burden of HIV in sub-Saharan Africa has aged substantially over the last decade, yet little is known about age-specific shifts in HIV incidence.

Methods: Between 2004 and 2017, data were collected from individuals enrolled in the Africa Health Research Institute's population-based HIV cohort in rural South Africa. A population-based cohort study was conducted to quantify changes in age-specific incidence among men 15-54 and women 15-49. Poisson generalized additive models were used to test changes in the age-distribution of HIV incidence and explore potential drivers.

Results: We observed 3,144 HIV seroconversions among 20,388 HIV negative individuals contributing 87,882 person-years of observation from 2004-2017 (incidence rate of 3.5 per 100 person-years). The age-distribution of HIV incidence shifted older in both men (p=0.021) and women (p<0.001). Age of peak incidence increased by four years among men, from 27 (95% CI, 25-33) to 31 (95% CI, 28-34); and by three years among women, from 22 (95% CI, 21-23) to 25 (95% CI, 23-31). Incidence declined by 50% among men 15-19, IRR = 0.53 (0.33-0.82). Age-specific incidence relative to 15-19 year-olds doubled among men 30-34 years, IRR=2.30, 95% CI, 1.24 - 4.26; and increased by 50% among women 30-34 years, IRR=1.51, 95% CI, (1.09-2.05).

Conclusion: HIV-1 incidence shifted older over a 14-year period during scale-up of HIV treatment and prevention in a hyperepidemic South African cohort. The aging risk of HIV acquisition will require expanding demographic targets for HIV prevention beyond the youngest cohorts in high burden settings.





149 HIGH HIV INCIDENCE IN YOUNG WOMEN IN THE BOTSWANA COMBINATION PREVENTION PROJECT

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Background: The Botswana Combination Prevention Project (BCPP) demonstrated a 30% reduction in community HIV incidence through expanded HIV testing, enhanced linkage to care, and universal antiretroviral treatment and exceeded the UNAIDS 90-90-90 targets. In this analysis we report rates and characteristics of incident HIV infections occurring during the study, using data from repeat HIV testing performed over time in the intervention arm.

Methods: BCPP was a community-randomized control trial in 30 rural/peri-urban Botswana communities. Community-wide home-based and mobile HIV test campaigns were conducted in 15 intervention communities from 2013-2017. Although campaigns did not specifically aim to re-test the same individuals, 30% of residents received HIV testing at least twice. We assessed the HIV incidence rate (IR) among these repeat testers. The IR was estimated as the number of new HIV infections occurring per 100 person-years (py) at risk (time to last HIV-negative test or midpoint between last HIV-negative test and first HIV-positive status). HIV infection risk factors were evaluated with right-censored Cox proportional hazards models.
Results: During 27,517 person-years at risk, 195 of 18,597 residents (females=54.9%;males=45.1%) from the selected sample became HIV-infected (IR=0.71/100py). Of the 195 seroconversions, 153 (78.5%) were in females and 42 (21.5%) in males; females had a higher IR (1.01) compared to males (0.35). The highest IR was observed among females aged 16-24 years (1.87) with IRs ranging from 0.65 to 5.73 (median=1.74) across 15 communities. Females aged 25-34 years were observed with an IR of 1.24. Among males, the highest IR was in the 25-34 year age group (0.56). The lowest IRs were observed in the older age group (35-64) in both females and males (0.41 and 0.20, respectively). Gender and age were both significantly associated with the HIV incidence (both p<0.0001). The hazard of incident infection was highest among females aged 16-24 (HR=7.05; 95%CI:3.83,14.68).
Conclusion: Despite demonstrating an overall reduction in HIV incidence and surpassing the UNAIDS 90-90-90 targets in a community-randomized control trial, high HIV incidence was observed in adolescent girls and young women in the intervention communities. These findings highlight the current urgency for additional prevention services, e.g. PrEP, to achieve epidemic control in this population.

150 RAPIDLY DECLINING HIV INCIDENCE AMONG MEN AND WOMEN IN RAKAI, UGANDA

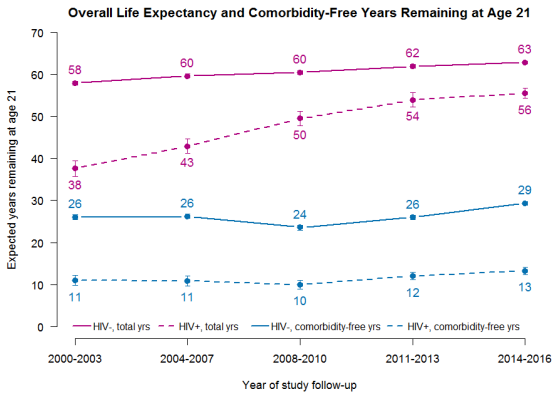
Gertrude Nakigozi[1], Larry W. Chang[2], Steven J. Reynolds[3], Fred Nalugoda[1], Godfrey Kigozi[1], Thomas C. Quinn[3], Ronald H. Gray[4], Alice Kisakye[1], Anthony Ndyanabo[1], Robert Ssekubugu[1], David Serwadda[1], Maria Wawer[4], Joseph Kagaayi[1], Mary K. Grabowski[2], for the Rakai Health Sciences Program
[1]Rakai Health Sciences Program, Kalisizo, Uganda, [2]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [3]NIAID, Baltimore, MD, USA, [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Background: We previously reported on declines in HIV incidence associated with the scale-up of voluntary medical male circumcision (VMMC) and antiretroviral therapy (ART) at CD4 counts of <500 in 30 communities continuously surveyed between 1994 and 2016 in the Rakai Community Cohort Study (RCCS). Prior analyses showed a 42% reduction in HIV incidence by 2016 relative to the period prior to VMMC and ART availability with greater declines observed among men than women (54% vs. 32%). We report here on HIV incidence following the implementation of universal test and treat in 2016.
Methods: Population-level trends in HIV incidence among RCCS study communities were assessed between April 1999 and May 2018. Trends in HIV incidence based on observed seroconversion, self-reported male circumcision, and self-reported ART use were assessed using data collected over 13 surveys. Viral loads among all HIV-positive persons were assessed at three surveys, including the two most recent surveys. Relative changes in HIV incidence at each survey after 2006 was compared to the mean HIV incidence before 2006 (i.e., before scale-up of VMMC and ART) using multivariate Poisson regression models and are reported as adjusted incidence rate ratios (adjIRR) with 95% confidence intervals (CI).
Results: 37,283 individuals participated, including 19,645 initially HIV-negative persons who contributed at least one-follow-up visit. There were 992 HIV incident cases detected over 107,297 person-years of follow-up. By 2018, HIV incidence was 0.43 per 100 person years (py), a decline of 58% relative to the period prior to VMMC and ART availability (adjIRR=0.42; 95CI: 0.31-0.57). Recent incidence declines were most pronounced among women whose incidence fell from 0.83 per 100 py to 0.48 per 100 py between the final two surveys (adjIRR=0.63; 95%CI: 0.41-0.98) and by 59% since the period prior to VMMC and ART availability (adjIRR=0.41; 95CI:0.28-0.60). Viral load suppression levels in 2018 improved modestly compared to the prior survey, increasing from 76% to 80% overall, from 79% to 85% among women, and from 67% to 71% among men. Prevalence of male circumcision continued to increase with 65% coverage among all men in 2018.
Conclusion: HIV incidence is rapidly declining among women and men with the continued scale-up of ART and VMMC in Rakai. Sustained investment and targeted efforts to achieve increased levels of viral load suppression and male circumcision coverage could potentially eliminate transmission in this African setting.

151 INCREASED OVERALL LIFE EXPECTANCY BUT NOT COMORBIDITY-FREE YEARS FOR PEOPLE WITH HIV

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Background: Combination antiretroviral therapy (ART) has dramatically improved life expectancy for people with HIV (PWH), but recent data comparing overall lifespan and comorbidity-free years by HIV status are lacking.
Methods: We conducted a cohort study of adult (aged ≥21) members of Kaiser Permanente in Northern or Southern California, or Mid-Atlantic States (DC, MD, VA), during 2000-2016. PWH were frequency-matched 1:10 to uninfected adults on age (2-year groups), sex, race/ethnicity, medical center, and calendar year. We used abridged life tables to estimate the average number of total and comorbidity-free years of life remaining at age 21 by calendar era. Comorbidity-free years were prior to diagnosis of any of 6 common comorbidities: cardiovascular disease, respiratory disease, renal disease, liver disease, cancer, or diabetes. For 2014-2016, we also estimated life expectancy for PWH with early ART initiation (i.e., with CD4 ≥500).
Results: Among 39,000 PWH and 387,785 matched uninfected adults, there were 2,661 and 9,147 deaths, with mortality rates of 1,303 and 390 per 100,000 person-years, respectively. In 2000-2003, overall life expectancy at age 21 was 37.6 and 57.9 years for PWH and uninfected adults, respectively, corresponding with a gap of 20.3 years (95% CI: 18.4-22.1; Figure). Overall life expectancy for PWH increased to 55.5 years in 2014-2016, narrowing the gap to 7.3 years (6.1-8.6). PWH with early ART initiation had a life expectancy at age 21 of 59.4 years in 2014-2016, further narrowing the gap compared with uninfected adults to 3.4 years (0.9-5.8). In 2000-2003, the expected number of comorbidity-free years remaining at age 21 was 11.0 and 26.1 years for PWH and uninfected adults, respectively, with PWH being diagnosed with comorbidities 15.1 years (13.7-16.4) earlier than uninfected adults. This gap persisted in 2014-2016, with comorbidity-free life expectancy at age 21 of 13.3 and 29.3 years for PWH and uninfected adults, respectively (16.1-year gap, 15.1-17.1), and no improvement for PWH with early ART initiation.
Conclusion: Overall lifespan has continued to increase for PWH in care, and only a 3-year gap remains relative to uninfected adults. However, PWH have 16 fewer healthy years than uninfected adults, with diagnoses of common comorbidities beginning at age 34, and no improvement over time or with early ART initiation. Greater attention to comorbidity prevention for PWH is warranted.



152 LOW-LEVEL VIREMIA DURING ART AND THE RISK OF DEATH, AIDS, AND SERIOUS NON-AIDS EVENTS

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Background: The impact of low-level viremia (LLV) during ART is unclear. We explored the associations between LLV and mortality, AIDS, and serious non-AIDS events (SNAE) using a population-based cohort.

Methods: All adults in the nationwide Swedish InfCare HIV register who started combination ART (cART) 1996-2017 were included if ≥2 viral load results (VL) were available ≥6 months after cART initiation. Participants were grouped into 3 categories: virologic suppression (<50 c/mL), LLV (50-999 c/mL), and high-level viremia (HLV, ≥1000 c/mL). Viremia was handled as a time-varying covariate; reclassification was only possible to a higher viremia stratum. In a separate analysis, LLV was divided into 2 subcategories: LLV 50-199 c/mL and 200-999 c/mL. Cox proportional-hazard models were fitted to determine the associations between viremia category and all-cause death, first AIDS condition, and first SNAE (cardiovascular disease, non-AIDS cancer, thromboembolism, pulmonary hypertension, renal and liver disease). The multivariable analysis included sex, age at start of cART, CD4 count and VL before ART, country of birth, injection drug use, exposure to mono and/or dual ART prior to cART, treatment interruptions, and an interaction term between viremia category and time.

Results: In total, 6,956 participants were included, with a median follow-up of 5.7 years (49,986 person years). LLV occurred in 953 (14%) subjects; at the end of follow-up, 4,177 (60%) had virologic suppression, 339 (5%) had LLV 50-199 c/mL, 258 (4%) had LLV 200-999 c/mL, and 2,182 (31%) had HLV. LLV was associated with increased all-cause mortality compared to virological suppression, adjusted hazard ratio (aHR) 2.2 (95% confidence interval [CI] 1.3-3.6). When analyzed separately, LLV 50-199 c/mL had an aHR of 2.2 (95% CI 1.3-3.8) and LLV 200-999 c/mL of 2.1 (95% CI 0.95-4.7). All-cause mortality was also independently associated with higher age, male sex, lower CD4 counts, injection drug use, and treatment interruptions. Overall, LLV was not linked to increased risk of AIDS and SNAE, but in a subanalysis, LLV 200-999 c/mL was significantly associated with SNAE, aHR 2.1 (95% CI 1.2-3.8).

Conclusion: In conclusion, patients with LLV during cART were at increased risk of death. LLV 200-999 c/mL was associated with SNAE when compared to virologic suppression. Our study adds to mounting evidence that persistent LLV may be associated with increased risk of adverse events.

Table 1. Cox regression models for all-cause mortality, AIDS, and serious non-AIDS events by viremia category. Results are presented with virologic suppression <50 copies/mL as reference group.

	Unadjusted model	Unadjusted model with time-interaction	Fully adjusted model*
All-cause mortality	*n* = 6,956	*n* = 6,956	*n* = 4,541
LLV 50–999 copies/mL	1.7 (1.2–2.4)	2.6 (1.8–3.7)	2.2 (1.3–3.6)
Viremia ≥1000 copies/mL	2.5 (2.0–3.1)	6.6 (4.2–10.6)	7.7 (3.8–15.7)
AIDS	*n* = 6,823	*n* = 6,823	*n* = 4,440
LLV 50–999 copies/mL	0.45 (0.11–1.9)	0.84 (0.19–3.7)	no event
Viremia ≥1000 copies/mL	4.6 (2.9–7.3)	20.1 (8.3–48.6)	23.9 (6.3–90.1)
Serious non-AIDS events	*n* = 6,885	*n* = 6,885	*n* = 4,486
LLV 50–999 copies/mL	1.2 (0.92–1.6)	1.6 (1.2–2.2)	1.2 (0.81–1.9)
Viremia ≥1000 copies/mL	1.5 (1.3–1.8)	3.0 (2.0–4.6)	3.1 (1.7–5.7)

Values are hazard ratio with 95% confidence interval.
*Adjusted for age, sex, CD4 count and VL before start of ART, injection drug use, born in Sweden, treatment experience, and treatment interruptions.
Abbreviations: LLV, low-level viremia; VL, viral load.

153 USING SYSTEMS BIOLOGY TO UNDERSTAND THE MECHANISMS OF VACCINE EFFICACY

Bali Pulendran, *Emory University, Atlanta, GA, USA*

For more than a century, immunologists and vaccinologists have existed in parallel universes. Immunologists have for long reveled in using 'model antigens', such as chicken egg ovalbumin or nitrophenyl haptens, to study immune responses in model organisms such as mice. Such studies have yielded many seminal insights about the mechanisms of immune regulation, but their relevance to humans has been questioned. In another universe, vaccinologists have relied on human clinical trials to assess vaccine efficacy, but have done little to take advantage of such trials for studying the nature of immune responses to vaccination. The human model provides a nexus between these two universes, and recent studies have begun to use systems biological approaches to study the molecular profile of innate and adaptive responses to vaccination in the human model. Such 'systems vaccinology' studies are beginning to provide mechanistic insights about innate and adaptive immunity in humans. Here, we present an overview of such studies, with particular examples from studies with the yellow fever and the seasonal influenza vaccines. Vaccination with the yellow fever vaccine causes a systemic acute viral infection and thus provides an attractive model to study innate and adaptive responses to a primary viral challenge. Vaccination with the live attenuated influenza vaccine causes a localized acute viral infection in mucosal tissues and induces a recall response, since most vaccines have had prior exposure to influenza, and thus provides a unique opportunity to study innate and antigen-specific memory responses in mucosal tissues and in the blood. Vaccination with the inactivated influenza vaccine offers a model to study immune responses to an inactivated immunogen. Studies with these and other vaccines are beginning to reunite the estranged fields of immunology and vaccinology, yielding unexpected insights about fundamental mechanisms of immune regulation.

154 DECODING THE TRANSCRIPTIONAL INFLAMMATORY CASCADES THAT MAINTAIN HIV RESERVOIR

Susan Pereira Ribeiro, *Case Western Reserve University, Cleveland, OH, USA*

Antiretroviral therapy (ART) has improved the quality of life of HIV-infected subjects. However, the persistence of long-lasting viral reservoir poses a major obstacle for viral eradication. Early HIV infection is characterized by a cascade of inflammatory cytokines followed by a negative feedback loop of anti-inflammatory cytokines, such as IL10, in order to reestablish homeostasis. Interestingly, viruses have evolved mechanisms that exploit the immunoregulatory function of IL10 for immune evasion, suppression, and tolerance to promote their own survival. As a result, some viruses, as HIV, can persist for life in infected hosts. HIV persists in a small pool of long-lived latently infected quiescent CD4 T cells and molecular mechanisms that maintain the survival of productively infected cells is not completely understood.

In a cohort of ART-treated HIV aviremic subjects, IL10 was increased in blood and lymph nodes as compared to healthy controls. IL10 producing cells, including T cells, macrophages and B cells were in close proximity to cells with viral DNA in lymph nodes of infected subjects. Importantly IL10 triggered several cellular processes that promoted HIV persistence including the survival of infected cells, the upregulation of several co-inhibitory receptors (Co-IRs) which are involved in the establishment of HIV latency and immune dysfunction; confirming the ex vivo and in vitro gene signatures we also have shown that IL-10 is a potent regulator of TFH differentiation, a major HIV reservoir. Genetic manipulation i.e in vitro knockout of STAT3, the transcription factor downstream of IL10/IL10R engagement, or functional inactivation of this pathway through the use of a neutralizing antibody to IL10, led to decreased T cell survival, downmodulation of Co-IRs expression and decreased TFH frequencies, and consequently led to a significantly lower frequency of HIV infected cells in vitro. These data confirm the role of IL-10 as a trigger for HIV persistence.

In vivo blockade of the IL10 pathway in aviremic chronically infected Rhesus macaques, using an anti-IL10 antibody, led to reversion of all the pathways observed in humans as associated to HIV reservoir maintenance, and resulted in significant decrease on SIV provirus. The NHP pre-clinical data confirmed the safety of this intervention which could be targeted for HIV Cure in humans.

155 DISSECTING THE DRIVERS OF CHRONIC INFLAMMATION

Krystelle Nganou, *NIH, Bethesda, MD, USA*

Immune recovery during HIV infection is profoundly influenced by inflammation, with chronic inflammation being consistently associated to disease progression and poor prognosis. In addition, numerous studies have shown that antiretroviral therapy (ART) does not resolve inflammation. Therefore, understanding the drivers of chronic inflammation is of considerable interest. This presentation will review current knowledge on the factors known to influence inflammation during ART; such as the HIV reservoir, microbial translocation and co-infections with other viruses. Recent studies on the microbiome will be presented in an effort to clarify whether changes in the microbiome are a cause or consequence of chronic inflammation. Moreover, we will describe how metabolic factors and health risk behaviors also contribute to chronic inflammation in persons living with HIV. Finally, the use of multi-omics approaches and state-of-the-art methodologies will be highlighted as means to unravel the mechanisms underlying chronic inflammation in HIV infection and, ultimately, to identify optimal therapeutic targets.

156 DEFINING TREATABLE PATHWAYS IN INFLAMMAGING: IS IT NICE TO FOOL WITH MOTHER NATURE?

Michael M. Lederman, *Case Western Reserve University, Cleveland, OH, USA*

Our host defenses have evolved over millions of years and in general they work pretty well, except when they don't. In HIV infection, defenses are broadly dysregulated resulting in both a heightened risk of infection and a systemic proinflammatory environment. Thus host defenses and the immune activation and inflammation that mediate these defenses cannot be viewed on a simple two-dimensional scale. These perturbations are improved with antiretroviral therapy, but they are not completely normalized and in particular, inflammatory morbidities persist as does a reservoir of replication-competent virus. If properly monitored, targeted interventions to alter this environment can provide insight as to how immune and inflammatory pathways interact but we should be prepared to expect the unexpected as these pathways are complex, dynamic and difficult to orchestrate smoothly with the simple yet blunt interventions that we possess.

157 NOVEL ANTIRETROVIRAL AGENTS: TRANSFORMING THE CARE OF PEOPLE WITH HIV

Rajesh T. Gandhi, *Massachusetts General Hospital, Boston, MA, USA*

In this state-of-the art overview, we will discuss new approaches to treating HIV, including agents with novel mechanisms of action; long-acting medications; and innnovative delivery systems. We will review novel options for optimizing treatment of HIV for a broad array of patients, including those initiating therapy for the first time and those who have multi-drug resistant virus. And we will highlight treatments that are on the horizon but that have the potential to transform the care of people with HIV.

158 PEDIATRIC AND ADOLESCENT ART: A ROAD LESS TRAVELLED

Carolyn Bolton Moore, *Centre for Infectious Disease Research in Zambia, Lusaka, Zambia*

Over the last three decades, advances in antiretroviral therapy and improvements in overall clinical management and service provision have dramatically reduced both morbidity and mortality in children with HIV across the globe. However, in general, outcomes remain much poorer than those seen in adults and data from both the developing and developed world show that children have consistently lower rates of viral suppression than adults. Adherence to ART is critical for optimal treatment outcomes. Proper adherence to treatment results in viral suppression, improved symptoms, fewer opportunistic infections and less chance of viral resistance. Barriers to poor adherence are diverse and those affecting young children may differ significantly from those largely affecting older children and adolescents. Developing more palatable, child-friendly formulations of ART which do not require specialized cold chain management is likely to significantly increase adherence amongst younger children. But improving treatment outcomes in older children and adolescents likely requires a multi-pronged approach combining innovative behavioral interventions, stigma reduction strategies and simplification of treatment regimens. Several strategies for reducing and simplifying antiretroviral therapy for adolescents and children are currently under investigation and aim to maximize adherence, reduce toxicity, preserve future treatment options, and reduce costs. Development of pediatric formulations of antiretroviral drugs have historically lagged 10-15 years behind that of adult versions of the drugs, partly as a result of diminishing markets for these drugs in wealthier countries and partly due to the complexity of the physiological and developmental changes associated with childhood and adolescence. Over the past few years, various efforts have enabled better alignment and agreement on key principles in pediatric drug development and research including defining dosing by weight bands, applying innovative study designs, synergizing work across research networks to achieve common goals, including adolescents in adult trials and the establishment of a global prioritized research agenda. However, despite these advances, accelerating the pediatric agenda and prioritizing new/ more effective agents and formulations remains a priority. Keeping up the momentum, and finding new momentum, is key to ending the epidemic and allowing our children and adolescents to be happy, healthy and free of HIV.

159 METABOLIC COMPLICATIONS OF HIV AND ITS THERAPIES

Jordan E. Lake, *University of Texas at Houston, Houston, TX, USA*

This talk will discuss the contributions of current ART agents and combinations to metabolic disease, including the potential impact of weight gain on co-morbid conditions, and possible interventions to mitigate metabolic complications of ART.

160 GETTING IT RIGHT: PRACTICAL APPROACHES TO ADHERENCE WITH MODERN ARVs

Jose R. Castillo-Mancilla, *University of Colorado Denver, Denver, CO, USA*

Along with the remarkable advancements in antiretroviral therapy (ART), new paradigms have emerged on the importance of adherence. Early studies with older antiretrovirals (ARVs) proposed that >95% adherence was required to achieve and maintain virologic suppression, which led to the concept that an undetectable HIV viral load (VL) was equivalent to full adherence. However, the potency and favorable pharmacology of the new ARVs have allowed for more forgiveness to missed doses, with recent studies demonstrating that the "minimal" level of ART adherence required to sustain viral suppression may range between 80-85% (and as low as 75%). While advantageous, achieving viral suppression despite variable ART adherence has de-emphasized the focus on adherence in clinical practice, limiting our understanding of its consequences at the individual (i.e., biological, virological) and population (i.e., transmission) levels. This is essential to maximizing the benefit of ART and controlling the HIV epidemic, since maintaining an undetectable HIV VL (mainly driven by adherence) is indispensable for the U=U (Undetectable=Untransmittable) strategy to be effective, and because adherence remains a lifelong challenge. However, despite its critical importance, we currently lack a gold-standard measure to quantify ART adherence. In response to this gap, several innovative methods and strategies to objectively measure ART adherence have emerged in recent years. These include: a) pharmacologic methods that inform about cumulative adherence and recent dosing by quantifying drug concentrations in plasma, urine, hair and dried blood spots; b) advances in electronic medication dispensers that monitor pill-taking behavior, and; c) digital pills that confirm medication ingestion. These novel methods have proven more accurate than self-report, can predict adverse clinical outcomes (i.e., viremia), and provide real-time adherence information that can lead to actionable interventions during a routine clinical visit. Moreover, pharmacologic methods can assess inter-individual pharmacokinetic differences not captured by HIV VL monitoring or other adherence measures. This symposium talk will address these and other questions by exploring the benefits and potential risks of forgiveness of modern ARVs (including long-acting agents), evaluating the pearls and pitfalls of existing and new ART adherence measures, and providing the audience with some practical strategies for integrating these tools into clinical practice.

161 GLOBAL EPIDEMIOLOGY OF HEPATITIS C

Yvan J. Hutin, *WHO, Geneva, Switzerland*

In 2017, WHO published its Global Hepatitis Report, which described the status of the viral hepatitis epidemic in 2015, at the baseline of the Global Health Sector Strategy (GHSS)on viral hepatitis that aims for elimination. In 2020, 4 years into the strategy, we can reflect on what is known and what is unclear in terms of incidence, prevalence, and mortality of HCV infection. With respect to incidence, using a model from the Centre for Data Analysis (CDA), WHO estimated that in 2015, 1.75 million new infections occurred. Surveillance for acute hepatitis C and age-specific seroprevalence suggests that in most countries, the incidence has been on the decline. However, a recrudescence of transmission because of injection drug use, unsafe health care or unsafe practices among men who have sex with men is always possible. This calls for enhanced case reporting of acute hepatitis to describe trends and risk factors for infection. With respect to prevalence, on the basis of a CDA systematic review of biomarker surveys adjusted with modeling, WHO estimated that 71 million persons were living with HCV in 2015. This number is decreasing because of curative treatments. Also, the heterogeneity of prevalence needs to be better characterized so that testing and treatment policies can be adapted. A limited number of high-prevalence countries (> 2-5%) faced substantial morbidity and mortality that require testing in the general population. However, most infections are located in settings where prevalence is under 2% and where focused testing may be more cost-effective. Given this heterogeneity, local biomarker surveys and data on the prevalence of HCV infection in subgroups being tested are needed to guide testing and treatment policies. Finally, on the basis of death certificates and attributable fractions, WHO estimated that in 2015, about 400,000 persons died from the sequelae of HCV infection, including cirrhosis and hepatocellular carcinoma. While on average HCV-associated mortality is increasing worldwide, there are differences. In countries where transmission occurred many decades ago, mortality already started to decrease. In countries where transmission took place more recently, mortality is still increasing or in some cases, may not even have started to increase. Therefore,

sequelae surveillance is needed to describe baseline mortality trends so that we can better predict the impact of testing and treatment.

162 MODELING AND EXAMPLES OF HCV ELIMINATION: POSSIBILITIES, ACHIEVEMENTS, AND NEXT STEPS

Natasha Martin, *University of California San Diego, San Diego, CA, USA*

The WHO viral hepatitis elimination strategy set ambitious targets for reducing HCV incidence and mortality by 2030. Modeling indicated these targets could be achieved at global, national, and local levels through scaling-up interventions to prevent and treat HCV. However, differences in transmission risks and historical or on-going epidemiology highlight the need for setting-specific strategies, and local data to understand these differences. Indeed, a recent modeling study indicated unsafe injecting practices among people who inject drugs will contribute to ~43% of incident HCV infections globally from 2018-2030, but varying considerably by country. In Pakistan, where transmission is highly disseminated the contribution is low, whereas in the U.S. the contribution is high due to the ongoing opioid crisis thus requiring combination harm reduction and treatment strategies.

Where are we now? Several countries are implementing ambitious national elimination strategies, with interim evaluations occurring. In Egypt, from 2014 to 2018, >2.5 million people were treated, yet an even greater number were undiagnosed. In 2018, Egypt initiated the world's largest HCV screening program, aiming to screen the entire population (101 million); 50 million were screened in the first 6 months. In Georgia, >54,000 people were treated between 2015 and February 2019 and a recent interim dynamic modeling analysis predicted the country was on track to achieve both WHO targets by 2030. In Australia, unrestricted access to direct-acting antivirals since 2016 led to widespread treatment uptake, with modeling indicating the country is on track for elimination.

What is still needed? Despite progress in a few countries, the vast majority are not on track to achieve elimination. Political commitment and funding for harm reduction interventions, which additionally prevent HIV and overdose, are urgently needed. Interventions to increase diagnoses will be required as the diagnosed and untreated pool dwindles. Strategies to reduce cost are still required and will be setting-specific. For example, in Pakistan, modeling indicates elimination requires a national screening program, which could require annual expenditure of 9% of the health budget even with a simplified treatment algorithm and low DAA costs. Integration strategies could reduce costs. Robust local data systems will enable modeling to inform efficient elimination strategies and evaluation of elimination progress across the next decade.

163 VERTICAL HEPATITIS C TRANSMISSION: DÉJÀ VU ALL OVER AGAIN?

Ali Judd, *University College London, London, UK*

Vertical transmission of HIV and hepatitis B virus (HBV) is preventable, and risk is reduced through routine antenatal screening coupled with treatment during pregnancy for all women with HIV and those with high HBV viral loads. This approach is a "double dividend" for HIV, as it provides the opportunity for pregnant women to receive treatment for their own health, while at the same time preventing vertical transmission. The number of new HIV infections in children is declining, but the global incidence of chronic hepatitis B is still largely driven by vertical and early childhood infections, and challenges remain in implementing HIV and HBV prevention and treatment strategies in pregnant women and infants in some high burden countries.

There are important differences between vertical transmission of HCV, and HIV and HBV, most notably that HCV is not associated with high infant mortality (unlike HIV), there is no vaccine (unlike HBV), and HCV is curable (unlike HIV and HBV). Efforts are being made to scale up HCV treatment worldwide, and there are ambitious HCV elimination goals. However, pregnant and breastfeeding women and their infants have been left behind in the HCV elimination agenda, as no direct acting antivirals are licensed for use in these groups. This is partly due to uncertainty regarding optimal test and treat strategies, with a weak evidence base, and many countries know little about the epidemiology of HCV in pregnant women due to the scarcity of universal antenatal HCV screening. In this talk the evidence for the effect of HCV on pregnancy and neonatal outcomes, risk of vertical transmission, potential interventions to prevent transmission, safety profiles of DAAs, screening and linkage to care for mothers and HCV diagnosis and treatment for children, will be reviewed. Key gaps in knowledge and areas for future research will be identified. There is a need to improve our understanding of the potential benefits associated with routine HCV screening and treatment in these vulnerable populations, to ensure that the double dividend approach of treatment and prevention is used in the most effective way. Fast-forwarding to the future, if we are serious about HCV elimination then we cannot neglect the potential opportunities of universal antenatal screening to treat mothers and prevent vertical transmission. We need to learn from our experience with HIV and HBV and accelerate our response. Otherwise, will it be déjà vu all over again?

164 HEPATITIS C TREATMENT ON A SHOESTRING

Isabelle Andrieux-Meyer, *Drugs for Neglected Diseases Initiative, Geneva, Switzerland*

Despite the effective diagnostic & therapeutic tools available to eliminate hepatitis C, WHO reported that only 5M people with HCV, out of 71 million infected, had received treatment by the end of 2017. Of these, 2.5M people were treated in Egypt, 1.8M in high-income countries, and a tiny fraction (0.7M) in the rest of the world. In Egypt, a 2018 campaign aimed to screen 53M people and treat 2.2M HCV patients. This is facilitated by locally produced DAAs priced below 1% of the US price, following government rejection of DAA patents. After agreements signed between DAA patent holders and generic manufacturers, DAA prices decreased spectacularly by over 99%, from $120,000 in 2013 to $20 for 12 weeks of the same curative treatment. However, most low- and middle-income countries eligible for the lowest generic DAA prices end up paying $ 750-1,000, which does not support test and treat strategies. High and middle-income countries excluded from licensing agreements used different strategies to decrease DAA prices and implement elimination programs. In Brazil, the threat of patent rejection and local DAA production initiatives supported government pricing negotiations, resulting in the lowest prices offered by originator companies. The Malaysian government opted to grant a compulsory license to import affordable generic sofosbuvir at $237 per course, compared to $11,200 with sofosbuvir. Australia paved the way with "Netflix" type agreements aimed at reduced prices based on volumes to support test and treat programs. As demonstrated by countries on track for HCV elimination, the main challenges are detecting the 80% of people unaware of their status and providing universal access to DAAs, essential to halt HCV transmission. Simplification of HCV models of care and DAA affordability are key determinants for countries to launch elimination programs.

POSTER ABSTRACTS

165 HIV-1 CAPSID-NUCLEAR ENVELOPE INTERACTIONS THAT FACILITATE NUCLEAR IMPORT

Mohamed Husen Munshi[1], *Ryan C. Burdick*[1], *Wei-Shau Hu*[1], *Vinay K. Pathak*[1]
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Background: HIV-1 must enter the nucleus and integrate its DNA into host genome for successful infection. However, the mechanism by which the viral complex docks at the nuclear envelope (NE) and enters the nucleus is not well understood. Although CA is known to play a critical role in nuclear import, the CA determinants that influence NE docking and viral complex translocation through the nuclear pore have not been defined. To identify the critical CA determinants, we developed quantitative live-cell imaging assays to study the NE docking and nuclear import of single viral complexes.

Methods: A high-throughput live-cell imaging assay was developed to study NE docking and residence times of single viral complexes labeled with either HIV-1 integrase-superfolder green fluorescent protein (sfGFP), APOBEC3F-yellow fluorescent protein (A3F-YFP) or Cyclophilin A-red fluorescent protein (CypA-DsRed). The amount of CA associated with viral complexes was quantified using a newly developed direct CA label (GFP-CA); CA was also detected by immunostaining with anti-CA antibody. Infectivity was determined in HeLa cells, and the CEM-SS and MT4 T cell lines.

Results: Using high-throughput live-cell imaging, we identified CA mutants M10I, M10V and I15V that exhibited longer NE residence times compared to wild-type viral complexes in a CypA-dependent manner. Additionally, the M10 mutant complexes that entered the nucleus had longer NE residence times compared to WT, but only for the CypA-dependent nuclear import pathway. Analysis of virions labeled with CypA-DsRed also indicated that most viral complexes lost CypA-DsRed prior to nuclear import. CA mutants did not show infectivity defects in HeLa cells but were defective in T cell lines. Direct labeling of CA (GFP-CA) indicated that the CA levels of WT and mutant viral complexes were similar; however, CA detection using anti-CA antibody suggested differences in mutant viral complexes that reduced anti-CA antibody binding as a result of differences in conformation or host protein binding.

Conclusion: We have identified CA determinants that play a critical role in NE docking and nuclear import in a CypA-dependent manner. We propose a model in which CypA stabilizes the initial interaction of the viral core with NE but does not enter the nucleus with the viral core. These studies provide valuable insights into the interactions between the viral complex and the NE that result in stable docking and nuclear import.

166 REPORTER VIRUSES WITH PROTEIN BARCODES TO ANALYZE HIV LATENCY ESTABLISHMENT

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Background: Studies of HIV latency establishment at the single cell level have been hampered by difficulties to identify CD4+ T cells that harbor transcriptionally silent proviruses. HIV molecular clones encoding reporter proteins, whose expression is either dependent or independent of HIV LTR promoter, have been powerful tools to dissect mechanisms of HIV persistence. To better support multi-dimensional analyses such as those carried out by Mass Cytometry (CyTOF), we have generated HIV dual reporter viruses that carry cell membrane expressed protein barcodes.

Methods: To detect the LTR independent expression of affinity tags such as chimeric protein V5-NGFR or the GFP reporter protein, a PGK promoter driven reporter cassette was cloned into the envelope frame of HIV molecular clone pLAI2. In addition, for the assessment LTR-dependent expression, reporters HSA-mCherry were cloned upstream of an internal ribosomal site followed by nef. V5-NGFR and HSA, in contrast to GFP or mCherry, are both expressed at the plasma membrane of the cell making the reporters easily accessible to membrane probes and magnetic bead enrichment approaches.

Results: Primary human CD4+ T cells from six different donors were stimulated with IL-2, IL-15 or CD3/CD28 and infected with the different dual reporter viruses. Cells were analyzed by flow cytometry after 3, 4 and 5 days to determine the optimal conditions and select the most informative time points and donors. The reporter virus HIV-GKO previously described by the Verdin lab was used as reference. Mock infected and HIV infected cells were analyzed by CyTOF. We used a customized CyTOF antibody panel, which captures 30 different markers allowing the discrimination of five different CD4+ T populations including CD4+ T memory cells with stem cell like properties (CD4+ Tscm) and CD4+ Tregs. Markers for determining cellular features such as proliferation, activation and cell cycle were also included. CyTOF experiments were performed at the Human Immune Monitoring Center of the Icahn School of Medicine.

Conclusion: Our preliminary data indicate that our dual reporter viruses allow accurate detection of both LTR silent and LTR active proviruses with minimal promoter interference. We will expand on the existing viruses to generate panels of barcoded reporter viruses to test the influence that viral genes, such as integrase and Vpr, have on latency establishment and maintenance in specific primary human CD4+ T cell populations.

167 Gag DETERMINANTS OF SPECIFIC GENOME PACKAGING IN HIV-1 AND HIV-2

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Background: HIV packages a dimer of its RNA genome into virus particles. The viral protein Gag drives this process by binding to the packaging signal in the 5′ untranslated region of genomic RNA. However, Gag also binds cellular RNAs, and the mechanism by which Gag selectively packages the viral genome remains poorly understood. It was previously observed that HIV-1 and HIV-2 exhibit a striking difference: HIV-1 Gag efficiently packages HIV-2 RNA, but HIV-2 Gag does not package HIV-1 RNA. We hypothesized that studies of these non-reciprocal interactions would lead to the identification of novel HIV packaging determinants.

Methods: HIV-1-based Gag chimeras were constructed that contained the entire HIV-2 nucleocapsid (NC) domain or just the two zinc fingers of HIV-2 NC. The chimeras were transfected into 293T cells, and Gag expression, particle release, and maturation were examined. Single virion analysis, a technique in which individual particles are analyzed by fluorescence microscopy, was performed to determine packaging efficiencies for HIV-1 or HIV-2 RNA. Spreading infections were conducted in MT-4 T cells to determine replication competence and to select for adaptive mutations.

Results: The chimeras did not affect Gag expression or particle release but did slightly impair Gag processing. Surprisingly, both chimeras packaged HIV-1 RNA into ~70% of particles, a modest reduction relative to wild-type (WT) HIV-1 (~95%). However, when HIV-1 and HIV-2 RNAs were co-expressed and competed for packaging, both chimeras strongly preferred to package HIV-2 RNA. In contrast, WT HIV-1 Gag packaged HIV-1 and HIV-2 RNAs with similar efficiencies. We further found that the chimeras replicated in MT-4 cells, although with delayed kinetics compared to WT HIV-1. When re-passaged, the chimeras replicated significantly faster, indicative of adaptation. Putative adaptive mutations in Gag were identified by PCR and sequencing. One single amino acid substitution was found in the first zinc finger of HIV-2 NC and represents a switch from an HIV-2 to an HIV-1 residue at this position. This mutation alone significantly improved chimera replication.

Conclusion: Our findings provide new insights into the mechanistic basis of selective genome packaging in HIV-1 and HIV-2. These studies may inform future efforts to develop antivirals targeting RNA packaging and have implications for the possible emergence of HIV-1/HIV-2 recombinants in co-infected individuals.

168 EXPLORING THE REQUIREMENTS FOR HIV-1 GENOME PACKAGING THROUGH A NONVIRAL RNA BINDING

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Background: HIV-1 efficiently selects and packages its RNA genome into assembling virus particles at the plasma membrane. The main viral structural component, Gag, orchestrates the complex interactions that occur during this stage. In the cytoplasm, Gag shows only a slight preference for binding HIV-1 RNA over cellular mRNA. Therefore, we hypothesized that in addition to RNA binding, Gag must use other mechanisms to ensure selective HIV-1 RNA genome packaging. To better define the mechanism of HIV-1 RNA packaging specificity, we designed an experimental system to study Gag:RNA interactions.
Methods: To separate the specific and nonspecific Gag:RNA interactions, we created morphologically normal, empty, virus-like particles by replacing the NC domain of Gag with a leucine zipper (LZ). To package RNA, we fused a bacterial RNA binding protein, BglG, to an internally mCherry-labeled GagLZ (GagLZiC-Bgl). BglG specifically binds to a stem loop RNA structure, BSL. Gag-expressing constructs contained two sets of stems-loops: BSL and sequences recognized by bacterial phage PP7 coat protein. Viral RNA was detected by coexpressed YFP fused to PP7 coat protein (PP7-YFP). To examine whether GagLZ, GagLZ-CFP fusion protein, and GagLZiC-Bgl proteins coassemble to generate viral particles with RNA, the constructs were cotransfected with PP7-YFP into human 293T cells. Harvested viral particles were imaged using fluorescence microscopy.
Results: Most particles were CFP+ and iC+; thus, these Gag proteins coassembled into the same virus. Additionally, ~40% of the particles were also YFP+, indicating they contained viral RNA. To determine trans-acting requirements for RNA packaging, we created a series of GagLZiC-Bgl truncation mutants. RNA was efficiently packaged by mutants lacking the LZ motif or p6 domain. However, RNA packaging was significantly reduced when regions important for Gag oligomerization were deleted or when GagLZiC-Bgl myristylation was inhibited by a G1A mutation. These results reveal the importance of the Gag:RNA and Gag:Gag interactions at the plasma membrane for genome packaging. All mutant Gag constructs coassembled with GagLZ-CFP.
Conclusion: Overall, we developed an experimental assay to identify properties of Gag required for RNA packaging during HIV-1 assembly. In an NC-independent system as well as in the presence of NC, the multimerization of RNA-bound Gag is needed for efficient RNA packaging.

169LB MULTI-OMICS ANALYSES REVEAL IMMUNOMETABOLIC REPROGRAMMING-DEPENDENT HIV-1 REPLICATION

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Background: Human Immunodeficiency Virus type-1 (HIV-1)-infected individuals show metabolic alterations of CD4 T cells through unclear mechanisms. The nucleotide-binding, leucine-rich-repeat-containing protein NLRX1 is a novel host factor required for HIV-1 infection. Whether NLRX1 has an interaction with the immunometabolism to promote HIV-1 infection of CD4 T cells is an intriguing question.
Methods: First, we silenced NLRX1 expression in human primary CD4 T cells by short hairpin RNA and assessed HIV-1 replication in those cells compared with the control cells. Second, we used quantitative mass spectrometry to profile the altered protein expression resulted from HIV-1 infection of Jurkat T cells, followed by an analysis of differentially expressed proteins between NLRX1-silenced cells and the control cells. Third, we conducted metabolic assays to compare the differentially induced oxidative phosphorylation (OXPHOS) and glycolysis by HIV-1 infection in NLRX1-silenced T cells vs the control cells. Fourth, we used the inhibitor and activator of OXPHOS to modulate HIV-1 replication in both primary CD4 T cell culture and human CD4 T cell-reconstituted mouse model. Finally, we analyzed the RV217 transcriptomic study of HIV-1 patients to search the association between immunometabolic pathways and HIV-1 viremia.
Results: LRX1 facilitates HIV-1 replication in both human primary CD4 T cells and human CD4 T cells-reconstituted mice Quantitative proteomics and metabolic analyses reveal that NLRX1 enhances OXPHOS and glycolysis during HIV-1-infection of CD4 T cells to promote viral replication. Inhibition of OXPHOS by an FDA-approved drug, metformin, suppresses HIV-1 replication in primary CD4 T cells and in humanized mice. Potentiating OXPHOS by resveratrol restored the deficiency of HIV-1 replication in NLRX1-silenced T cells. The role of OXPHOS during HIV-I infection in patients is supported by the transcriptome profiling of CD4 T cells from 22 male and 15 female HIV-1 patients residing in Asia and Africa. HIV-1 viremia positively correlates with NLRX1 expression and poor outcomes are associated with elevated OXPHOS.
Conclusion: NLRX1 promotes HIV-1 replication in CD4 T cells by inducing immunometabolism OXPHOS and glycolysis. Inhibition of OXPHOS by metformin suppressed HIV-1 replication in both primary human CD4 T cells and humanized mice. OXPHOS is positively correlated with HIV-1 viremia in HIV-1 patients. This study uncovers a T cell OXPHOS pathway as an unappreciated target for HIV-1 therapy.

170LB HIGH-RESOLUTION PARTICLE STRUCTURE OF IMMATURE HIV-2

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Background: Immature retroviruses like human immunodeficiency virus type 1 (HIV-1) are known to possess an unusual degree of irregularity, with Gag proteins forming a hexagonal lattice that drives assembly and release of particles lacking icosahedral symmetry, and creating a lattice this is substantially incomplete. Immature virus particle structure can provide important clues to the nature of virus particle assembly in cells.
Methods: In this study, we sought to decipher key structural details of immature retroviral morphology of HIV-1 and the less pathogenic HIV-2 by obtaining high-resolution structures using cryo-electron microscopy (cryo-EM). In particular, we sought to identify a structural basis for our preliminary observations indicating that distinct differences in immature particle morphology are observed between HIV-1 and the less pathogenic HIV-2. In particular, key phenotypic features that distinguish HIV-2 immature particles include a larger average particle size as well as a nearly complete Gag lattice.
Results: Structural comparison at 5.5 Å resolution between published HIV-1 and that of our HIV-2 cryo-EM reconstructions emphasizes the importance of the capsid (CA) C-terminal domain (CTD) and spacer peptide 1 (SP1) regions in forming hexameric assemblies of CA in the intermolecular contacts of the overall lattice structure (including critical residues at the dimeric and trimeric intermolecular interfaces). In conjunction to the cryo-EM analyses, we solved a 1.98Å crystal structure of HIV-2 CACTD and found a unique extra alpha helix (H12) at the C-terminal region, which was not previously observed in the domain structures of HIV-1 or other retrovirus CA proteins. Fitting of the HIV-2 CACTD into the reconstruction map confirmed critical contact interfaces of Gag proteins, and emphasized the importance of the co-factor inositol hexakisphosphate (IP6) at the six-fold symmetry interface. The presence of H12 in CA may contribute the stability of the hexametric interactions in the HIV-2 immature Gag lattice.
Conclusion: Taken together, our observations provide important clues for explaining the observed morphological differences between immature HIV-1 and HIV-2 particles. These differences may help explain differences virus virulence.

171 B CELLS DIRECT R5-TROPIC HIV INFECTION OF CCR5^{NEG} NAIVE CD4+ T CELLS

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Background: Naive CD4 T (TN) cells are an important reservoir of latent, replication-competent HIV. CD4 TN isolated from peripheral blood are resistant to direct infection with R5-tropic HIV in vitro because there is negligible expression of CCR5 on the cell surface. Paradoxically, R5-tropic virus has been isolated from TN cells from HIV-infected individuals on antiretroviral therapy. We assessed whether antigen presenting cells (APCs) - B cells and dendritic cells (DCs) - mediate trans infection of R5-tropic HIV to TN cells in the absence of global T cell activation.
Methods: Total CD4 T cells, CD4 TN cells, B cells and monocytes were purified from PBMCs of seronegative donors by magnetic microbead separation. B cells were activated by CD40L and IL4, and DCs were differentiated from monocytes by GM-CSF and IL4. B cells and DCs were pulsed with 10-3 moi R5-tropic HIVBaL and cultured with TN or total CD4+ T cells at a 1:10 ratio. As a control, we exposed TN or total CD4 T cells to 10-1 moi of HIVBaL in the absence of B cells or

DC (i.e., cis infection). Cell phenotype was assessed by flow cytometry and viral replication by HIVp24 production before and after stimulation with anti-CD3/CD28 Ab or PMA/PHA. We quantified total HIV DNA in the TN and total CD4 T cell populations from 2 HIV nonprogressors (NPs).
Results: After 12 days of incubation, there were low levels of p24 in the B cell-TN co-cultures (n=10), indicative of productive infection, but not in the DC-TN co-cultures. In contrast, both B cells and DC could efficiently HIV trans infect total CD4 T cells. As expected, TN were refractory to direct, cis infection with HIVBaL. Phenotypic analysis of the TN cells revealed that they maintained a CCR5neg phenotype. B cell-TN co-cultures exposed to anti-CD3/CD28 Ab or PHA/PMA resulted in high-levels of p24 production, whereas no virus expression was recovered from the DC-TN co-cultures. We previously demonstrated that APCs derived from NPs cannot trans infect CD4 T cells, which prompted us to quantify the HIV DNA reservoir in TN and total CD4 T cells isolated from 2 NPs. We detected HIV DNA in the total CD4 T cells but not in the TN of both NPs.
Conclusion: B cells, but not DCs, efficiently trans infect CCR5neg TN cells with R5-tropic HIVBaL. No HIV DNA was detected in CD4 TN cells from NPs, consistent with the notion that APCs derived from NPs cannot trans infect CD4 T cells. B cell-mediated HIV trans infection of CD4 TN cells could be a key mode to establish early HIV reservoir.

172 TFR REDUCE HIV-1 INFECTED TFH IN VITRO IN AN IL-2 DEPENDENT MANNER

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Background: Follicular CD4+ T cells (TFH) are highly permissive to HIV-1 infection and a major reservoir of HIV-1 in lymphoid tissues. Follicular regulatory CD4+ T cells (TFR) limit TFH numbers and function in vitro and in vivo. We hypothesized that TFR inhibit HIV-1 replication in TFH.
Methods: TFH (CD3+CD8-CXCR5+CD25-) isolated from tonsils of individuals at low risk for HIV were spinoculated with the GFP reporter virus NLENG1, labeled with the proliferation dye VPD450, and co-cultured 1:1 with autologous TFR (CD3+CD8-CXCR5+CD25+) or TFH (control) for 5 days in Advanced R-10 media and 10 IU/ml IL-2. Percent GFP+VPD450+ TFH were determined by flow cytometry. Live VPD450+ TFH were isolated on a cell sorter, and total and integrated HIV DNA were quantified using QPCR. Cell counts were measured using counting beads. In some experiments, 0, 10, 30, or 100 IU/ml of IL-2, or blocking antibodies to TGF-beta, CD39, or IL-10 at 10 µg/ml were added. IL-2 supernatant concentrations were measured by ELISA. Statistical analyses were performed using non-parametric Wilcoxon matched-pairs test and Spearman's correlation.
Results: In comparison to control co-cultures, TFR reduced TFH numbers (p=0.023; n=14), %GFP+ TFH (p=0.001; n=14), total HIV DNA (p=0.016; n=7), and integrated HIV DNA (p=0.016; n=7). Blocking TGF-beta, CD39, and IL-10 did not reverse TFR inhibition of %GFP+ TFH. IL-2 increased TFH viability in a dose dependent manner (r= 0.946 p=<0.0001), but did not promote TFH proliferation. Compared to control co-cultures, %GFP+ TFH were reduced in TFR co-cultures with 10 IU/ml and 30 IU/ml IL-2, while no inhibition was detected in TFR co-cultures without IL-2 or with 100 IU/ml IL-2 (See Figure). TFH cell counts followed the same pattern. IL-2 supernatant concentrations were lower in TFR co-cultures compared to control co-cultures with 10 IU/ml (median, 1.0 vs 5.0 ng/ml; p= 0.031) and with 30 IU/ml (median, 5.3 vs 12.1 ng/ml; p= 0.156), but not with no IL-2 (median, 0 vs 0; p=0.999) or 100 IU/ml IL-2 (median, 67.39 vs 56.0 ng/ml; p=0.813).
Conclusion: IL-2 promoted TFH viability and HIV-1 associated GFP expression in vitro. TFR reduced HIV-1 producing TFH at low, but not high or absent concentrations of IL-2. Consumption of IL-2 in B cell follicles may be one mechanism by which TFR reduce HIV-expressing TFH in vivo.

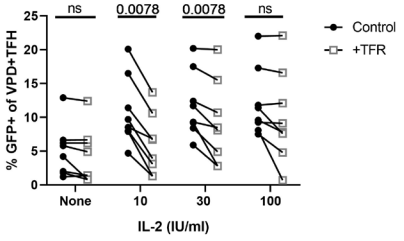


Figure: TFR mediated inhibition of %GFP+ TFH is IL-2 concentration dependent.

173 INCREASED BIRC2 AND BIRC3 TRANSCRIPTION ARE ASSOCIATED WITH INCREASED HIV PRODUCTION

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Background: ACH-2 cells are A3.01 cells containing a single proviral HIV genome. Unstimulated ACH-2 cells produce low levels of HIV. Prior to stimulation, surface staining of HIV Env identifies two ACH-2 populations, one that stains for Env and p24 and one that does not. With TNF stimulation >90% of virus production is from the Envbrt population while an Envdim population arises from the Env- population. We compared the cellular transcriptome of Envbrt to Envdim and A3.01 cells before and after stimulation with TNF.
Methods: ACH-2 cells were dual stained with PG9 and VRC07 to identify the envelope bright, dim and null populations and bulk sorted at 0, 3, 6, 9 and 24h post-stimulation. A3.01 cells were sorted similarly. Cells were lysed and then frozen. Total RNA was extracted, poly-adenylated RNA purified, fragmented and then reversed transcribed using random hexamers. Illumina ready libraries were generated and sequenced by paired-end HiSeq 4000 2x75 reads. Changes that were 2-fold different with a P<0.005 were defined as significant. Individual protein levels were determined using chemiluminescent antibody arrays.
Results: ACH2 and A3.01 transcriptomes were similar post-stimulation in many ways. In both ACH2 and A3.01 cells RELA and NFKB1 message were elevated prior to, and did not change with TNF stimulation. Increased NFKB2 and NFKBIA in both A3.01 and ACH2 cells 3h after stimulation and increased RELB and CD82 suggested rapid activation and transport of NFkB to the nucleus and early NFkB driven phosphorylation and transport of AP-1 to the nucleus. There were also differences. HIV RNA read frequency was significantly higher in ACH2 bright than in ACH2 dim cells and absent in A3.01 cells at all times. These changes were associated with differences in NFkB associated gene transcription. Most strikingly BIRC3 transcripts, which plays an important role in NFkB activation, were significantly increased in Envbrt compared to A3.01 cells post-stimulation. This change was not observed in the Envdim population. Increases in BIRC-3 protein at 1 hour and phosphorylation of AP-1 at 30m were confirmed by protein array.
Conclusion: These data indicate low level transcription of HIV RNA prior to stimulation in Envbrt cells are associated with higher level BIRC3 after stimulation. Increased transcription of BIRC3 may contribute to increased HIV production in these cells.

174 THE ARYL HYDROCARBON RECEPTOR NEGATIVELY REGULATES HIV REPLICATION IN TH17/TH22 CELLS

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Background ART fails to restore the depletion of Th17-polarized CCR6+CD4+ T-cells in PLWH. Novel Th17-targeted HIV remission/cure strategies are needed to restore Th17-mediated mucosal immunity. Autoimmunity studies demonstrated the existence of pathogenic and non-pathogenic Th17 cells and identified the aryl hydrocarbon receptor (AhR) as a marker of non-pathogenic Th17 cells. AhR is a ligand-dependent transcription factor that regulates the expression of several genes (IL-22, IL-10, integrin B7) and is involved in proteasomal degradation via its E3 ubiquitin ligase activity. We hypothesized that AhR negatively regulates HIV replication in non-pathogenic Th17 cells.
Methods: PBMC of ART-treated PLWH (n=8; median CD4 counts: 598, plasma viral load < 40 HIV-RNA copies/ml) and uninfected controls (n=5) were used in this study. Total/CCR6+/CCR6- memory CD4+ T-cells were isolated by magnetic/flow cytometry sorting. Cells of uninfected donors were stimulated via CD3/CD28, exposed to HIV, and cultured 9 days. Viral outgrowth assay (VOA) was performed with cells of ART-treated PLWH. AhR silencing was performed using CRISPR/cas9, with efficacy evaluated by T7 endonuclease assay and Western blotting. AhR agonist (FICZ) and antagonist (CH223191) were used. Cell viability/proliferation, HIV replication, cytokines, and gene expression were quantified by ELISA, flow cytometry and/or real-time PCR.
Results: AhR mRNA/protein expression was induced by T-cell receptor triggering. CRISPR/cas9-mediated AhR silencing significantly inhibited IL-22, IL-17A, IL-10 and integrin beta7 expression (p<0.01) and increased viral

replication upon infection in vitro (n=3; p=0.0084). Similarly, CH223191 significantly down regulated IL-22, IL-17A, IL-10, production (p<0.0001); increased wild type HIV replication (p=0.0016), as well as HIV-DNA integration/transcription upon single-round infection with HIV-VSVG pseudotyped viruses (n=5; p=0.001); and increased >2-fold HIV reactivation in VOA (n=7). At the opposite, FICZ significantly increased IL-22 and IL-10 production and inhibited viral replication in vitro and reactivation in VOA.

Conclusion: Our results identify the AhR as a novel negative regulator of HIV replication in Th17/Th22-polarized cells thus raising the interest in testing natural/synthetic AhR agonists/antagonists for HIV remission/cure strategies.

175 ANTI-HIV ACTIVITIES OF THE 12 INTERFERON-ALPHA SUBTYPES

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Background: The human genome encodes for 12 different interferon (IFN)-alpha subtypes, which share a common receptor on target cells, and trigger similar signaling cascades through Jak-STAT pathways. Several studies have collectively shown that this apparent redundancy may be justified by specific properties of the different IFN subtypes. Accordingly, the sets of genes induced by different IFN subtypes do not completely overlap, and different viruses, including HIV, are differently sensitive to individual subtypes.

Methods: We have measured the inhibition of HIV replication by the 12 IFN-alpha subtypes in primary T-lymphocytes and in a T-cell line using a multiple cycle replication assay. We have then measured the efficacy of inhibition on specific steps of the HIV replication cycle, including viral entry, reverse transcription, integration and budding. In parallel, we have measured the impact of IFN-alpha subtypes on cell proliferation, whose modification could indirectly participate in the overall antiviral effect.

Results: Working with primary T-lymphocytes and a T-cell line, we have first confirmed the differential potencies of the 12 IFN-alpha subtypes on HIV replication. The order of potency was similar in the two experimental settings, suggesting the induction of similar sets of antiviral genes. Using dedicated assays, we found that some subtypes act more potently on the early steps of HIV replication, while others target more efficiently the late steps.

Conclusion: Our findings support the notion that different genes with anti-HIV potential are induced by the different IFN subtypes. They allow to identify those characterized by potent direct antiviral effect with minimal perturbation of cellular proliferation. Our study also prompts the search for new anti-HIV factors, targeting specific steps of virus replication.

176 LOOP 1 OF HUMAN APOBEC3C REGULATES THE ANTIVIRAL ACTIVITY AGAINST HIV-1

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Background: The APOBEC3 (A3) family of single stranded DNA deaminases defends hosts from Human immunodeficiency virus (HIV)-1 lacking viral infectivity factor (vif) (HIV-1Δvif). A3 catalyzes the dC to dU deamination in the viral DNA/genome, causing hypermutation that abrogates the virus. Human APOBEC3C (hA3C) is known as a strong restriction factor of Vif-deficient Simian immunodeficiency virus (SIVΔvif), but exhibits a weak inhibition against HIV-1Δvif. The reason for this specificity of A3C's antiviral function remains unknown.

Methods: Experiments were performed in cell culture using virus infections, expression of APOBEC3 proteins, biochemistry to study protein DNA interaction and enzyme activity, which were complemented with structural protein modelling and gene evolution studies.

Results: We report that residues in loop 1 of A3C govern their anti-HIV-1 activity to the level compared to that of A3G. We identified that exchanging WE to RK in loop 1 in A3C drastically enhances A3C's deamination activity. Molecular modeling and EMSA experiments demonstrated that A3C.WE-RK interacts with ssDNA substrate stronger than that of wild-type, which consecutively facilitates catalytic function. As the RK residues are naturally presenting in A3F at the equivalent position, we swapped them with WE and found a marginal decrease in HIV-1Δvif inhibition. The gain-of-function A3C variant also exhibited stronger LINE-1 restriction capacity but RK-WE exchange did not crucially disarm A3F.

Conclusion: Loop 1 of human A3C restriction factor was identified as a novel protein domain that binds DNA and thereby drastically gains in antiviral activity against HIV-1.

177LB IFITM3 REDUCES RETROVIRAL ENV FUNCTION AND IS COUNTERACTED BY GLYCOGAG

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Background: The interferon-induced transmembrane (IFITM) proteins are known for inhibiting the entry of a wide array of viruses into host cells. Furthermore, when IFITM3 is present in virus-producing cells, it reduces the fusion potential of HIV-1 virions, but the mechanism is poorly understood.

Methods: To describe the antiviral mechanism of IFITM3 and to discover modes of viral evasion, we took advantage of a murine leukemia virus (MLV)-based pseudotyping system. By controlling IFITM3 and envelope (Env) levels in virus-producing cells, we found that IFITM3 potently inhibits MLV infectivity when Env levels are limiting.

Results: Loss of infectivity was associated with defective proteolytic processing of Env and lysosomal degradation of the Env precursor. Ecotropic and xenotropic variants of MLV Env, as well as HIV-1 Env and vesicular stomatitis virus glycoprotein (VSV-G), are sensitive to IFITM3, whereas Ebola glycoprotein is resistant, suggesting that IFITM3 selectively inactivates certain viral glycoproteins. Furthermore, endogenous IFITM3 in human and murine cells negatively regulates MLV Env abundance. However, the negative impact of IFITM3 on virion infectivity is greater than its impact on Env incorporation into virions, suggesting that IFITM3 also impairs Env function. Finally, we demonstrate that the presence of glycosylated Gag (glycoGag), the only accessory protein encoded by MLV, confers resistance to the IFITM-mediated loss of infectivity. GlycoGag has previously been shown to counteract another antiviral transmembrane proteins known as SERINC. Importantly, glycoGag rescues virus infectivity in the presence of IFITM3 without enhancing Env incorporation, indicating that glycoGag counteracts the cryptic function of IFITM3 which acts on Env function. This represents the first description of a viral auxiliary protein displaying the capacity to antagonize or enable viral evasion of IFITM3.

Conclusion: Overall, we demonstrate that IFITM3: (i) impairs virion infectivity by decreasing Env quantity and Env function, (ii) glycoGag confers virions with resistance to IFITM3 and, (iii) the antiviral activities of IFITM3 and SERINC3/5 may be linked. We are now testing whether the antiviral function of IFITM3 is maintained in SERINC5 knockout cells and whether other retroviral accessory proteins, such as HIV-1 Nef and EIAV S2, also exhibit the capacity to counteract IFITM3.

178 SEQUENCE CHANGES CAUSING REV ACTIVITY DIFFERENCES IN HIV-1 PRIMARY ISOLATES

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Background: The HIV-1 Rev-Rev Response Element (RRE) regulatory axis is required for the nucleocytoplasmic export of intron-containing viral mRNAs, an essential step in viral replication. A viral protein, Rev, binds to the RRE, an RNA structure found on incompletely spliced viral mRNAs, multimerizes, and recruits cellular factors to export the transcript. We previously described two Revs from primary isolates which display markedly different levels of activity. The high-activity, 9-G, and low-activity, 8-G, Revs differ by a total of 29 amino acids spanning across all domains including the bipartite oligomerization domain (OD), arginine rich motif (ARM), and nuclear export site (NES) (see Figure). Here, we define key residues causing differential activity.

Methods: Chimeric Revs were generated by exchanging regions between 8-G and 9-G sequences. Rev activity was determined using a recently described assay. Two constructs were created: an HIV vector modified to produce two fluorescent proteins in a Rev-dependent or Rev-independent fashion, and a murine stem cell virus vector producing different Revs and a third fluorescent marker. Both constructs were packaged and used to co-transduce lymphoid cells. Rev activity was determined by measuring relative intensity of the fluorescent markers.

Results: 9-G Rev displayed about 4-fold greater activity than 8-G Rev (p=0.001). Chimeric Revs created by exchanging the turn or link, the c-terminus,

a block including the ARM and second OD, or the NES did not show changes in functional activity. However, exchanging a block including the n-terminus and the first OD with four amino acid changes (N-OD) was sufficient to determine activity, such that a 9-G N-OD in an 8-G background was as active as unmodified 9-G Rev (p=0.55), and vice versa. A single variation at position 24 was tested as this has been shown to affect activity in NL4-3. The 9-G Q24R mutant had a 50% reduction in activity (p=0.001) but the 8-G R24Q mutant did not show increased activity, demonstrating an additional role for the other three amino acid changes.

Conclusion: The large difference in Rev-RRE activity between these primary isolates is due to four amino acid changes. Some of these residues have been implicated in Rev monomer stabilization while others may affect dimer-dimer interaction. Rev activity changes in another lentivirus are associated with clinical disease progression. Activity variation in HIV Rev may also play a role in clinical disease, such as in the establishment of latency.

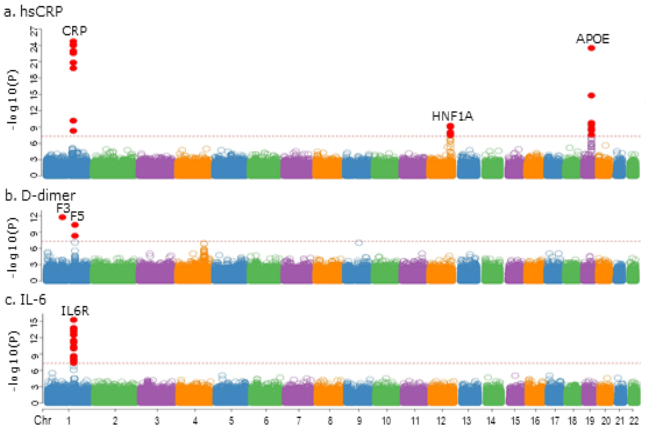


Figure. Manhattan plots of cross-cohort meta-analyses results for genetic associations with a. hsCRP, b. D-dimer, and c. IL-6 levels. Loci are labelled by the closest gene. Each point represents one SNP and is plotted by chromosomal location (x-axis) and -log10(P) (y-axis). The dashed red line represents genome-wide significance ($P = 5 \times 10^{-8}$) and SNPs meeting this threshold are colored red.

179 COMPLEMENTATION MAINTAINS QUASISPECIES OF DRUG-SENSITIVE AND -RESISTANT HIV WITH ART

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Background: HIV exists as multiple genotypes in a single infected individual, referred to as a quasispecies. How such sequence heterogeneity can be maintained in the same infection environment remains unclear.

Methods: We reproduced a quasispecies in vitro by using the antiretroviral drug efavirenz (EFV) as the selective pressure. The cell culture infection was performed over 18 days, with fresh uninfected cells and EFV replenished every two days. We determined the frequency of drug resistance mutations to EFV using deep sequencing both at the population and single cell level. For single cell sequencing of HIV DNA we sorted the infected cells into wells of a multi-well plate at 1 cell per well, then lysed the cells to extract DNA and amplified the reverse transcriptase region.

Results: We observed that while the frequency of genotypically EFV resistant virus increased with time, it never completely supplanted the drug sensitive genotype. Instead, the drug sensitive HIV genotype stabilized at approximately 20 percent of the total population. Single-cell sequencing of viral genotypes showed that the fraction of drug resistant virus in the population increased when most of the cells were infected with drug sensitive HIV but plateaued when cells were co-infected with drug sensitive and drug resistant genotypes. This suggested that in co-infected cells, drug sensitive virus may package drug resistant reverse transcriptase and become phenotypically resistant to the drug, known as phenotypic mixing or complementation. To verify that complementation can result in phenotypic drug resistance of EFV sensitive HIV, we transfected cells with CFP labelled wildtype and YFP labelled EFV resistant mutant HIV molecular viral clones, or co-transfected both. HIV from singly transfected cells followed the expected resistance pattern. However, virus from co-transfected cells was similarly resistant to EFV regardless of whether its genotype was drug sensitive or resistant.

Conclusion: These results indicate that complementation occuring between drug sensitive and drug resistant HIV is one mechanism which can drive and maintain an HIV quasispecies and account for the presence of drug sensitive virus in the face of ART.

180 DISRUPTION OF A RNA SECONDARY STRUCTURE IN HIV-1 gp41 INDUCES VIRAL LETHALITY

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Background: Synonymous genome recoding has been widely used to study different aspects of virus biology. Previous studies have demonstrated HIV-1 attenuation by reduction in protein expression after synonymous recoding. We aim here to explore the impact of synonymous codon usage on HIV-1 Env expression and virus replication capacity.

Methods: The 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. Different recoded envs were generated. Viral replication and viability was measured after transfection in MT-4 cells by quantifying HIV-1 p24 antigen production. Replication capacity assays were performed in MT-4 cells and PBMCs. WT, recoded env genes and HIV-1 rev were cloned in an expression vector (pcDNA3.1). Env expression plasmids were cotransfected with Rev expression plasmid in 293T cells. Immunoblot analyses and qPCR were performed to quantify protein expression and Env mRNA production. RNA secondary structures were obtained using Vienna RNA package.

Results: A recoded env variant containing 39 mutations was lethal for the virus. WB analysis of Env expression revealed that protein expression of the recoded variant was highly reduced. To further study the mutations responsible for this phenotype, new mutants were designed by reverting substitutions to WT or reducing the number of newly generated CpG dinucleotides. Most of the new virus variants were viable, although they showed different replication capacities. Interestingly, one variant that only reverted two nucleotides that belong to the same codon showed indistinguishable replication capacity when compared to WT. Moreover, after transfection, other virus variants generated compensatory mutations next to this codon or reverted this codon to WT. Computational analyses revealed a severe disruption in a RNA secondary structure of variants containing this mutated codon. Importantly, the disrupted RNA structure was restore when this codon was reverted to WT or new mutations were introduced in the proximity.

Conclusion: We show here that codon usage of the HIV-1 env strongly impact the replication capacity of the virus. Moreover, synonymous recoding of HIV-1 env gene has identified, in the gp41 coding region, an evolutionary conserved local RNA secondary structure that may be essential for virus viability. Disruption of this structure leads to severe reduction in mRNA translation and virus replication capacity.

181 GENETIC IDENTITY AND BIOLOGICAL PHENOTYPE OF EARLY TRANSMITTED FOUNDER HIV-1 VIRUSES

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Background: Among the repertoire of transmitted viral variants, only a small proportion of the viruses (transmitted founder (TF) viruses) are successful in establishing infection. It is widely believed that the early immune response to HIV infection is likely to be an essential factor in determining the clinical course of the disease. Thus, a better understanding of the characteristics of TF viruses and their role in early infection will throw light on the features that bestow these variants with the unique advantage of successfully establishing infection, and contribute significantly to the design and development of a protective HIV vaccine.

Methods: Patient-derived 250 envelope glycoprotein, gp120 were cloned in pMN-K7-Luc-IRESs-NefDgp120 to obtain chimeric viruses. Samples were obtained from eight infants who had recently infected with HIV through mother-to-child transmission and two adults who acquired infection through the heterosexual route and were in the chronic stage of the infection. 65 out of 250 clones tested were found infectious and analyzed for genetic identity and

biological phenotype of virus variants such as per-particle infectivity, response to neutralizing antibody (nAb), Maraviroc (MVC) and Interferon alpha (IFN-a).
Results: Based on the genotypic and phenotypic analysis, we identified 10 TF viruses from 8 infants. TF viruses were characterized by shorter V1V2 regions, reduced number of potential N-linked glycosylation sites and higher infectivity titer as compared to the non-transmitted (NT) variants. The sensitivity of the TF variants to MVC and a standard panel of nAbs (VRC01, PG09, PG16, and PGT121) were found to be much lower in TF than NT variants. IFN-a resistance by NT viruses were comparatively lower throughout the experiment when compared to TF viruses. Unexpectedly the productivity (amount of p24) of the NT viruses was found to be higher than TF viruses with the influence of IFN-a and MVC.
Conclusion: Despite small sample size, the study identified precise molecular and biological phenotype of the TF viral strains and its evolutionary dynamics on transmission-associated bottlenecks. In general, these studies improve our knowledge about the very diverse and highly adaptable nature of the TF virus, and hopefully takes us a few steps closer to addressing the challenges that come in the way of developing an effective vaccine or cure against HIV-1 infection.

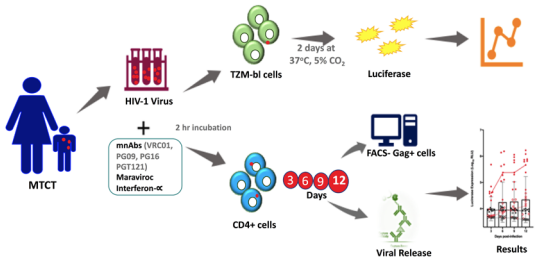


Figure 1. Schematic representation of the Study design

182 NEW HIV-1 CAPSID LABELING SYSTEM DOES NOT SUPPORT UNCOATING DURING NUCLEAR IMPORT

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Background: HIV-1 uncoating (capsid core disassembly) is a prerequisite for viral DNA integration into the host genome and a promising target for antiviral therapy. However, the timing and cellular location of uncoating remain elusive, in part because current methods are unable to directly and accurately measure the amount of capsid protein (CA) loss from the infectious viral complexes. Bulk measurement of CA loss by biochemical methods or imaging of viral complexes may not reflect the behavior of infectious viral complexes, since only a small fraction of the viral complexes in the cell lead to infection. Quantification of CA by immunostaining with anti-CA antibody or live-cell imaging of viral complexes labeled with fluorescently-tagged cyclophilin A (CypA) is confounded by loss of epitope accessibility to the antibody or loss of interactions to CypA.
Methods: We developed a method to directly label CA with green fluorescent protein (GFP) in infectious viral complexes, determined virus infectivity in HeLa and CEM-SS cells, characterized GFP-CA core incorporation and stability by sucrose gradient fractionation and Western blot, and quantified the core-associated CA during nuclear import using live-cell imaging.
Results: The GFP-CA labeling method is highly efficient and results in >96% of the virions being fluorescently labeled. Importantly, the GFP-CA labeling resulted in only a ~2-fold loss of virus infectivity in HeLa and CEM-SS T cells, indicating that GFP-CA-labeled viral complexes are infectious. Sucrose-gradient fractionation of virions indicated that GFP-CA was incorporated into viral cores and did not affect the core stability. Moreover, analysis of infected HeLa cells indicated that GFP-CA-labeled cores can efficiently associate with the nuclear envelope and enter the nucleus. We analyzed the amount of GFP-CA associated with viral cores docked at the nuclear envelope just before and after their translocation into the nucleus. No significant loss of GFP-CA was observed in the nuclear viral complexes compared to those at the nuclear envelope, indicating that uncoating does not occur during nuclear import.
Conclusion: These studies provide a new robust method for quantification of CA associated with viral complexes and will facilitate studies of HIV-1 post-entry events. Our results do not support the model that viral core uncoating occurs during nuclear import.

183 THE HIV ANTISENSE PROTEIN ASP IS A TRANSMEMBRANE PROTEIN OF THE VIRAL ENVELOPE

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Background: The negative strand of the HIV-1 genome encodes a highly hydrophobic antisense protein (ASP) with no known homologs. Humoral and cellular immune responses against ASP show that it is expressed in vivo, but its role remains unknown. We studied ASP expression in chronically infected myeloid and lymphoid cell lines, its impact on viral replication, and ASP sequence evolution during natural infection.
Methods: Flow cytometry was performed on Millipore Guava flow and analyzed with FlowJo. Confocal microscopy was performed with Zeiss LSM 800 and analyzed with Zen Blue. Fluorescence Correlation Spectroscopy (FCS) was performed with ISS Q2 confocal microscope and ISS VistaVision. Longitudinal sequences were downloaded from the Los Alamos HIV database and were aligned using GeneCutter.
Results: Using a monoclonal antibody (324.6) against an epitope mapping between two transmembrane domains of ASP, we detected ASP in the nuclei of all infected cell lines. Confocal microscopy showed a polarized nuclear distribution of ASP, and accumulation in areas containing actively transcribed chromatin. PMA treatment caused translocation of ASP to the cytoplasm and cell membrane. Cell surface detection of ASP without membrane permeabilization shows extracellular exposure of the 324.6 epitope. We found that ASP and gp120 co-localize on the membrane of PMA-treated cells (Manders overlap coefficient 76%), suggesting that ASP might be incorporated in the membrane of budding virions. Indeed, 324.6 captured HIV-1 particles with efficiency similar to anti-gp120 VRC01. Also, FCS showed that 324.6 binds single virions in solution with ~30% efficiency. Altogether, these two assays demonstrate the presence of ASP on the surface of HIV-1 virions. ASP-knockout HIV-1 particles displayed a ~50% reduction in replication rate compared to wildtype virus. Longitudinal sequence analysis shows that during natural infection viruses with intact ASP preserve the ORF, and viruses with early stop codons in ASP undergo deletion or recombination events that restore the ORF.
Conclusion: ASP is a transmembrane protein found on the surface of productively infected cells, and on the envelope of mature HIV-1 virions. Knocking out ASP expression reduced viral replication. Preservation or restoration of functional ASP ORF during natural infection indicates that ASP may provide a selective advantage to HIV-1.

184 HIV ADAPTATION FOLLOWING VERTICAL TRANSMISSION

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Background: Human immunodeficiency virus (HIV) can adapt to an individual's T cell immune response via genetic mutations that affect antigen recognition and impact disease outcome. In vaccine design, it is vital to understand this complex host-viral interaction including the mechanisms that underpin viral adaptations that subvert/alter the immune response. In this study, we assign the putative replicative cost and immune benefit of specific HIV adaptations in the unique setting of vertical HIV transmission. Single cell transcriptomics of antigen-specific T cells was also utilised to further delineate the dynamics of specific adaptations that may reflect a novel mechanism of adaptation. These results could be used to inform vaccine designs and cure strategies to combat the issue of immune adaptation.
Methods: Specifically, we utilised a deep sequencing approach to determine the HIV quasispecies in 26 mother/child transmission pairs where the potential for founder viruses to be pre-adapted is high. The resultant sequences and previously determined viral adaptations for specific host genotypes were used to generate adaptation scores for the transmitted virus. We used intra-cellular cytokine staining to assess specific antigen-specific T cell immune responses and single cell technologies to compare T cell receptor (TCR) repertoire and transcriptome data for a specific HIV epitope in which adaptation is associated with continued immune recognition.
Results: We showed that the dynamics of HIV adaptations following transmission provides insight into the in vivo replicative cost associated with

specific adaptations with limited evidence for reversion of adaptations in non-selective environments suggestive of extensive compensatory networks. The antigen-specific T cell responses in the child overall suggested the immune response to the heavily pre-adapted HIV strains may focus on sub-dominant T cell epitopes as evidenced by de novo adaptation following transmission. Interestingly, there was evidence of cross-reactive T cells to the adapted and non-adapted form of an epitope at the TCR family level for the mother/child pair, but this did not extend to the α/β CDR3. Unsupervised clustering of scRNAseq data separated cells stimulated by the adapted and non-adapted forms, with common differentially expressed genes upregulated in both the mother and child.

Conclusion: Such targets will be important in the development of a therapeutic vaccine for individuals that have an established reservoir of adapted virus.

185 DAILY IMMUNOLOGICAL/VIROLOGICAL VARIATIONS IN AVIREMIC ART-TREATED HIV PARTICIPANTS

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Background: Biological functions fluctuate in a circadian manner to align with environmental changes. In healthy uninfected individuals, variations in T-cell trafficking are documented in the blood, with nadir CD4 counts in the morning. Daily variations are also observed for plasma cortisol and melatonin, two regulators of immune functions. HIV infection is associated with profound alterations in CD4 T-cell homeostasis and chronic immune activation. HIV transcription is regulated by BMAL1, a circadian clock master regulator. However, daily variations in immunological/virological parameters during ART-treated HIV infection remain unknown.

Methods: Eleven ART-treated people living with HIV (PLWH; median CD4 counts: 606 cells/ml; age: 57 years; time since infection: 242 months; aviremia under ART: 216 months) were hospitalized at the CRCHUM Phase I Clinic a Friday afternoon for 40 hours. Starting the next morning, blood was collected/processed every 4 hours for 24 hours before food intake. Polychromatic flow cytometry allowed cell counting/phenotypic analysis on fresh blood. Plasma levels of cortisol/melatonin and markers of mucosal barrier impairment (FABP2, LBP) were measured by ELISA. PBMC were frozen. HIV DNA/RNA were quantified by PCR on sorted CD4+ T-cells.

Results: The memory/naive/regulatory T-cell counts showed daily variations, with maximal counts observed 20:00-4:00 (nadir 12:00). The expression of the HIV co-receptors CCR5/CXCR4, gut-homing molecules CCR6/integrin ß7, and the immune checkpoint PD-1 on memory T-cells showed similar maximal expression 20:00-4:00. Pro-inflammatory non-classical monocyte counts were similarly high 8:00-00:00 but dropped significantly at 4:00. Plasma FABP2 levels peaked at 4:00, while LBP levels significantly dropped at 4:00. Daily variations in plasma cortisol (peak 4:00-8:00) and melatonin (peak 4:00) levels were observed. HIV-DNA reservoirs were stable. HIV-RNA levels in CD4 T-cells collected at night were higher compared to morning.

Conclusion: Daily variations in the blood T-cell/myeloid compartments, mucosal permeability markers, HIV transcription, and melatonin/cortisol levels, were observed in a cohort of aviremic ART-treated PLWH. These findings provide a rationale for studying the role of the circadian clock machinery in regulating residual HIV transcription under ART.

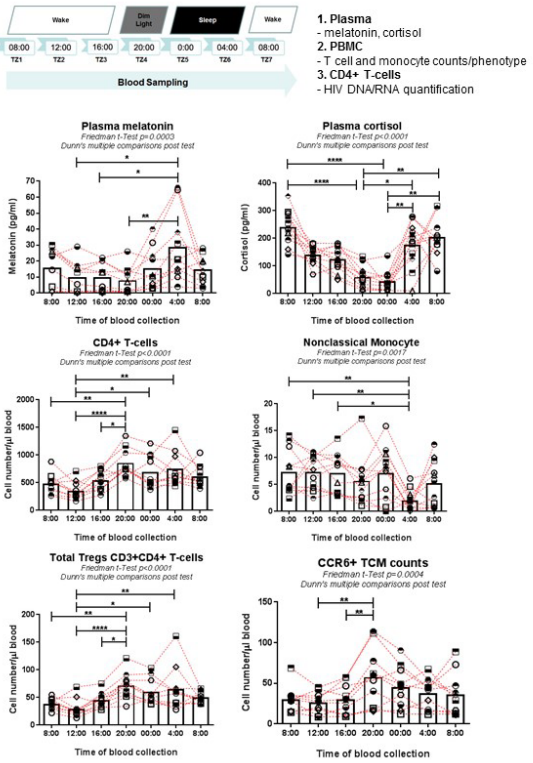


Figure 1: Daily variations in plasma and blood immune cell parameters in virologically suppressed ART-treated people living with HIV (PLWH)

186 Withdrawn

187 HIGH-THROUGHPUT SINGLE-MOLECULE SEQUENCING TO CHARACTERIZE AB-RESISTANT HIV/SHIV

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Background: Although HIV-specific broadly-neutralizing antibodies (bNAbs) can suppress viremia in ART-naïve people, clinical use of bNAbs is limited by neutralization-resistant viruses that may be too rare for detection before bNAb infusion. Novel assays to track the dynamics of rare viruses after bNAb infusion may inform future bNAb treatment approaches, and may also allow a better understanding of HIV evolution in response to humoral immune pressure.

Methods: We optimized high-throughput, single-copy HIV env sequencing methods to study samples taken in bNAb infusion trials. Virion RNAs were reverse-transcribed with or without the addition of 8-nucleotide unique molecule identifiers (UMIs), followed by PCR. Pacific BioSciences single-molecule, real-time (SMRT) technology was used to obtain full-length env sequences. Sequence data were analyzed using standard and custom software tools. Errors arising in the sequencing process were quantified using data obtained from HIV molecular clones and HIV-infected participant plasma virus samples.

Results: Initial studies demonstrated concordance of non-UMI-based SMRT sequence data with Sanger sequence data obtained in parallel from three HIV-infected participants. A non-UMI-based approach was then used to study samples from SHIV-infected macaques treated with bNAb VRC07-523LS. We observed pronounced changes in env sequences after VRC07-523LS infusion, with predominance of entirely new env clades and a relative loss of species clustering with pre-infusion virus. Selection of amino acid variants at several positions associated with resistance to CD4-binding-site antibodies was observed. Using plasmid HIV clones, we found that most of the error in the sequencing process was generated during the PCR and sequencing steps. We found that the use of UMIs reduced errors to a rate consistent with error rate of the RNA reverse transcription step alone. The number of unique sequences obtained after UMI-based analysis was comparable to the input template number, and reconstruction experiments showed that the use of UMIs substantially eliminated sequencing errors.

Conclusion: High-throughput, single-copy HIV env sequencing can reveal genetic changes that occur within large virus populations after bNAb infusion. The incorporation of UMIs in full-length env sequencing greatly improves accuracy, providing a robust method to study dynamics of Ab-resistant HIV.

188 ANALYSIS OF COMPARTMENTALIZATION OF HIV-1 IN BONE MARROW

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Background: HIV infection results in hematological disorders frequently observed in the late stages of disease. Little is known about the virus in the bone marrow (BM). We evaluated the compartmentalization of HIV in BM from participants not on antiretroviral therapy (ART).

Methods: Full HIV env was sequenced from BM and peripheral blood (PB) plasma using PacBio technologies. High-quality consensus sequences (FLEA software) were used to build phylogenetic trees (FastTree v.2.1.11) and assessed for compartmentalization by distance-based tests a) genetic diversity with the average pairwise distance (APD), b) divergence using a test for panmixia, c) Wright's measure of population subdivision (Fst), d) nearest-neighbor statistics and tree-based tests a) Simmonds Association Index, b) Slatkin-Maddison, c) correlation coefficients (MEGA7, HYPHY v.2.3.14). Viral tropism was determined at 2.5% of false-positive rate (https://coreceptor.geno2pheno.org/). Compartmentalization was established when results from phylogeny and compartmentalization analyses were concordant.

Results: Paired PB and BM samples were collected from 3 participants. Participant 1 was ART-naïve. Participants 2 and 3 were ART-experienced but stopped treatment 12 and 2 months before sample collection, respectively. Participant 3 self-discontinued his ART multiple times. The medians [IQR] log HIV-RNA (copies/mL) in BM (4.85 [4.06-4.97]) and in PB (4.84 [3.69-4.97]) were not statistically different (p = 0.25). The HIV populations had a low diversity (median APD of 1.29% in BM vs 0.94% in PB).
The APD was statistically different between BM and PB from participant 3 (1.78% in BM vs 2.65% in PB, p = 0.0005). Participant 3 had two viral populations with genetic distance of 22.44%, compartmentalized virus in BM (fig.1), and CXCR4-tropic virus present at 3.04% in BM and 7.27% in PB. CXCR4-tropic virus was also found in PB from participant 1 (6.59%). Neither participant 1 nor 2 had compartmentalized virus in BM.

Conclusion: We demonstrate viral compartmentalization and the presence of CXCR4-tropic virus in the BM. HIV-1 compartmentalization has been previously shown in the central nervous system and correlated with neurocognitive impairment suggesting that compartmentalization in other tissues might have pathogenic consequences.

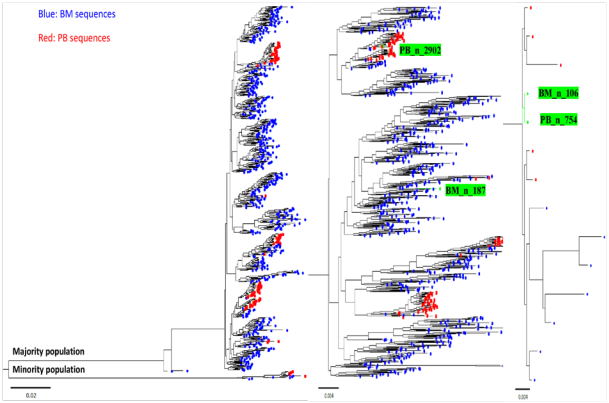


Figure 1: The phylogenetic tree (left) constructed from full *Env* sequences from bone marrow (BM) and peripheral blood (PB) plasma of the participant 3 with multiple periods of antiretroviral interruption. The patient harbored two distinct viral populations. Separate phylogenetic trees were constructed from sequences of the majority (middle) and minority populations (right). Phylogenetic trees reveal a clustering of BM and PB sequences into separate lineages, which is consistent with results from compartmentalization tests. In the majority viral population, the most predominant consensus sequences in BM and PB are shown in green, BM_n_187 and PB_n_2902 respectively, in which n represents the number of individual sequences assembled in each consensus. Similarly, in the minority population, the most predominant consensus sequences in each compartment are shown, BM_n_106 and PB_n_754. These two consensus sequences are identical, but the phylogenetic tree shows a compartmentalized and more diversified viral population in BM than in PB (average pairwise distance, APD = 1.38% in BM vs 0.94% in PB, p-value = 0.0118), suggesting a phenomenon in which HIV concomitantly migrates between BM and PB and distinctly replicates in BM.

189 INTRAHOST EVOLUTION OF HIV-2 p24 CORRELATES WITH PROGRESSION TO AIDS

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Background: HIV-2 infection will progress to AIDS in most patients without treatment, albeit at half the rate of HIV-1 infection. Prolines in p24 have been associated with low HIV-2 viral loads and enhanced processing of T cell epitopes. HIV-2 long-term non-progression has been linked to maintenance of Gag-specific CD8+ T cell responses. Lower evolutionary rates and positive selection on conserved residues in HIV-2 env have been associated with slower progression to AIDS. Here, we hypothesise that the intrahost evolution of HIV-2 p24 impacts on disease progression rates.
Specific aims: 1) To determine intrahost HIV-2 p24 sequence variation and evolution. 2) To determine site-specific selection pressure in HIV-2 p24 within hosts. 3) To determine how HIV-2 p24 evolution associates with disease progression

Methods: Twelve treatment-naïve patients from the Guinea-Bissau Police cohort with longitudinal CD4+ T cell data and clinical follow-up were included in the analysis. Gag amplicons of 735 nucleotides were amplified, cloned and sequenced from 25 blood plasma samples by nested PCR, TOPO-TA cloning, and Sanger sequencing. The sequences were analysed by Bayesian phylogenetics.

Results: In total, 371 heterochronous HIV-2 p24 sequences from 12 male patients with a median age of 29.5 years at enrolment were analysed. CD4+ T cell data was used to stratify patients into faster and slower disease progressor groups. Faster progressors had lower CD4% levels at the midpoint of follow-up and faster CD4% decline rates. The time to AIDS was approximately twice as fast among faster progressors than slower progressors (9.4 vs. 20.6 year, P<0.001). Slower progressors' p24 sequences were more likely to have the G6A, I12V and A119P variants (OR=4.2, P<0.001). P24 evolved under negative selection in both groups (dN/dS=0.13). Synonymous and nonsynonymous substitution rates were higher in faster than slower progressors (4.5x10-3 vs. 1.6x10-3 and 5.9x10-4 vs. 2.7x10-4 substitution/site/year, P<0.001). Viral evolutionary rates had a strong negative correlation with CD4% level (ρ=-0.78, P=0.02), but not decline rates.

Conclusion: Faster evolution in HIV-2 p24 was associated with lower CD4% level and faster time to AIDS

190 PLATELETS CARRY INFECTIOUS HIV IN cART-SUPPRESSED PATIENTS IN IMMUNOLOGICAL FAILURE

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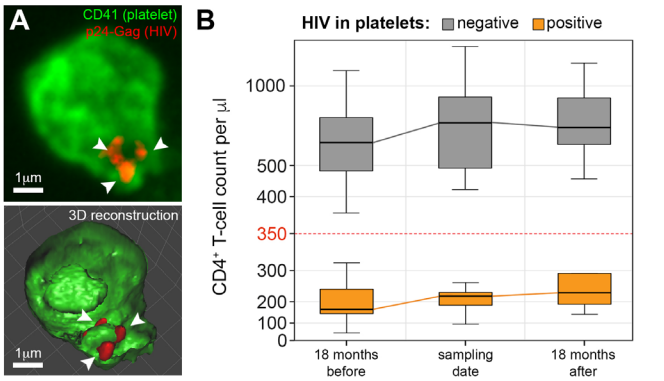
Background: Beside hemostasis, human platelets exert several immune functions and interact with infectious pathogens including HIV. We investigated whether platelets from cART-treated patients contain infectious HIV in vivo and addressed the significance and clinical implications of HIV sheltering by platelets in AIDS.

Methods: Infectious HIV content in platelets was quantified by qPCR, FISH-Flow, microscopy, and reporter cell assays using platelet-rich-plasma (PRP) from 78 HIV-infected cART-treated adult patients. The capacity of platelet containing HIV to propagate infection was evaluated by culturing human primary macrophages with PRP with or without the platelet activation-blocker Abciximab (anti-integrin alpha(IIb)/beta(3) Fab). The presence of HIV in platelets was correlated with patient clinical status and parameters over >3 years.

Results: We demonstrate that platelets from HIV-infected patients shelter infectious HIV in vivo, despite successful viral suppression by the combined antiretroviral therapy (cART) and in strong correlation with low blood CD4+T-cell counts (<350cells/microL). Patient platelets carrying HIV can propagate infection to macrophages in vitro in a process prevented by blocking platelet-macrophage interaction with Abciximab. Comparative phylogenetic analyses of virus found in peripheral blood and platelet samples prior to and > 1 year after cART initiation indicate that viruses contained in platelets do not originate from a latent reservoir established prior to therapy. Moreover, 88% of virally suppressed patients sheltering HIV in platelets are immunological nonresponders and fail to restore a proper immune status over > 1year of cART

with a >50-fold higher likelihood than patients without HIV in platelets (OR: 56, 95%CI: 4.3-719.2, p=0.002).

Conclusion: Altogether, our results reveal that platelets act as a neglected transient shelter for infectious HIV in the blood of HIV-infected cART-suppressed patient. Platelets carrying HIV establish an alternative pathway for HIV dissemination in correlation with immunological failure, thus opening new treatment strategies for immunological nonresponders, for whom no efficient treatment is available yet . Furthermore, HIV contained in platelets can potentially fuel the tissue-macrophage reservoir we recently described in cART-suppressed patients (Ganor, Real et al., Nat Microbiol, 2019) in a process inhibited by the therapeutical anti-platelet agents.



(A) HIV is detected in platelets from cART-treated patients: Platelet from HIV-infected cART-treated patient immunostained for CD41 (green) and p24-Gag (red), observed by confocal microscopy (top) and reconstructed in three-dimensions (bottom). Representative of n=11 different individuals. Bar=1µm.

(B) Presence of HIV in platelets is correlated with poor immunological recovery: CD4+ T-cell mean count of cART-suppressed patient positive (orange line) or negative (grey line) for the presence HIV in platelets, in a period of 18 months before and after the date of sampling. n=25 different individuals.

191 FOLICLE MORPHOLOGY AND HIV RNA DISTRIBUTION IN SPLEEN OF HIV+ HUMANIZED DRAGA MICE

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Background: The humanized DRAGA mouse model of HIV infection generates high viral loads, HIV-specific antibodies, and B cell follicles. Knowledge of follicle (F) morphology and HIV RNA distribution within secondary lymphoid tissues (SLT) of these mice is lacking. We assessed whether HIV+ DRAGA mice develop germinal centers (GC), whether F harbor high concentrations of HIV RNA+ cells, and whether follicular dendritic cells (FDCs) are present and trap HIV particles.

Methods: DRAGA (HLA-DR4.HLA-A2.Rag1KO.IL2RgcKO.NOD) mice (n=17) were infused with HLA-matched human hematopoietic stem cells (hHSCs) from cord blood and 7 were infected with HIV at 4-10 months post-hHSC infusion. Snap frozen spleens were stained with antibodies to human CD20, CD4, IgD, Ki67, FDC, and mouse FDC and analyzed by microscopy. HIV RNA was detected by RNAscope, %CD4 and %FDC by quantitative image analysis, plasma viral load by a modified Abbott RealTime HIV test and HIV-specific p24 and gp41 antibodies by ELISA. Non-parametric tests were used for analysis.

Results: No GC (IgD-Ki67+ regions) were seen in DRAGA spleen; IgD+ and Ki67+ cells were dispersed throughout F (CD20+ area). Human FDCs were not detected in any mice. Mouse FDCs were found throughout the F in contrast to normal mouse where FDCs localize in GC. %FDC+ area tended to be higher in HIV+ vs HIV- spleens (median 6% vs 2.9%; p=0.06). Many CD4+ cells localized within F (median, 70% in HIV- and 50% in HIV+; p=0.07). In 4 mice sacrificed at 4 months post HIV infection, more HIV RNA+ cells were located in F than extrafollicular regions (median, 128 vs 14 cells/mm_2), but differences disappeared when adjusted for CD4. In these mice, first HIV-specific IgM and then IgG antibodies were detected in plasma over time. HIV RNA particles colocalized with FDC in these animals, but not in 3 acutely infected animals (<16 days).

Conclusion: DRAGA mice lack canonical GC in spleen, possibly because of incompatible signaling between mouse FDCs and human lymphocytes. Despite this, they produce HIV-specific and class-switched antibody. In chronic infection, HIV RNA+ cells are concentrated in F (likely due to high numbers of CD4+ cells rather than heightened permissivity) and HIV RNA+ particles are associated with mouse FDC (likely bound via human antibody). Thus, the DRAGA model recapitulates some key aspects of HIV disease in SLT. This knowledge is important in the use of the DRAGA mouse model in HIV immunopathogenesis studies.

192 PERMANENT CONTROL OF HIV-1 PATHOGENESIS IN EXCEPTIONAL ELITE CONTROLLERS

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Background: Elite controllers (EC) represent a small subset of HIV-1-infected people able to spontaneously control viral replication. However, natural virological suppression and absence of immune dysfunction are not always long-term sustained. Exceptional EC (EEC) are HIV-1 subjects who maintain the EC characteristics without disease progression for more than 10 years.

Methods: We analyzed three EEC from the Sandoval Health Center in Madrid, diagnosed between 1988 and 1992, who without antiretroviral treatment have never shown signs of clinical progression. A comprehensive clinical, virological, and immunological study has been performed.

Results: The three EEC studied, diagnosed for more than 25 years, simultaneously exhibited previously described EC characteristics as ≥3 host protective alleles, low levels of total HIV-1 DNA (<20 copies/10^6 CD4+ T-cells), absence of viral transcription, without evidence of replication-competent viruses (<0.025 Infectious Units Per Million). This was consistent with high levels of defective genomes, and strong cellular HIV-1-specific immune response with a high poly-functionality index (>0.50). Inflammation levels of EEC (measured as plasma levels of hsPCR, β2-microglobulin, D-Dimer, IL-6 and sCD163) were similar to HIV-1 negative donors. Remarkably, they showed 8-fold lower genetic diversity (<0.01 s/n) in env gene than transient EC, and an exceptional lack of viral evolution.

Conclusion: We postulate that these EEC should be considered unique cases of spontaneous functional HIV-1 cure. Low genetic diversity and lack of viral evolution distinguish these individuals from other EC. The combined non-functional HIV-1 reservoir, extremely low viral diversity and an HIV-1-specific immune response seems to be key to mimic these cases of spontaneous functional cure in future eradication strategies.

193 LACK OF DONOR-DERIVED SUPERINFECTION IN HIV+ TO HIV+ KIDNEY & LIVER TRANSPLANTATION

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Background: HIV+ to HIV+ organ transplantation offers HIV-infected patients a unique treatment option for end-stage kidney and liver disease. One of the primary concerns for these surgeries, however is the risk of HIV superinfection (HIV-SI), which occurs when an HIV+ individual becomes infected with a new distinct HIV strain.

Methods: HIV+ to HIV+ kidney and liver transplant recipients were followed in a prospective observational study (NCT02602262). Peripheral blood mononuclear cells (PBMCs) were collected from recipients (14=kidney and 8=liver) and their respective donors (n=14) at the time of transplant (week 0) and followed post-transplant (spanning from weeks 13 to 104 post-transplant). Serum taken during a viremic episode from one recipient due to antiretroviral therapy (ART) non-adherence three years post-transplant was also evaluated. HIV proviral DNA from PBMC and viral RNA from the serum sample were extracted, amplified, and sequenced using a site-directed next generation sequencing (NGS) assay for both the reverse transcriptase region of pol and the gp41 portion of envelope with a sensitivity to detect minor variants at ≥1%. Neighbor-joining trees were constructed to examine for the presence of HIV-SI.

Results: Sequence data was obtained for 18 of the 22 recipients and 12 of the 14 matched donors (median amplicons analyzed: recipient gp41=54582, pol=74369; donor gp41=89304, pol=51715). Phylogenetic analyses of recipient HIV sequences from one or more time points post-transplant and/or with their corresponding donor sequences revealed the donor and recipient pol and gp41 sequences clustered separately, thereby indicating no evidence of HIV-SI in all patients examined (n=18). In the serum taken during the viremic episode (viral load=2,080,000), only recipient virus sequences could be detected (total

amplicons analyzed: gp41=128415, pol=74452; Figure) suggesting that the donor virus, if present, was not reactivated in spite of temporary withdrawal of ART.

Conclusion: This study monitoring recipient HIV sequences for up to two years post-transplant reveals no evidence of sustained donor-derived HIV-SI, even in one recipient following temporary ART non-adherence. These findings suggest that HIV-SI may not be a significant clinical concern in well-monitored ART suppressed recipients. Nevertheless, further monitoring of viral populations in a larger cohort of HIV+ transplant recipients is needed to investigate and fully assess the clinical and virologic significance of donor-derived HIV-SI.

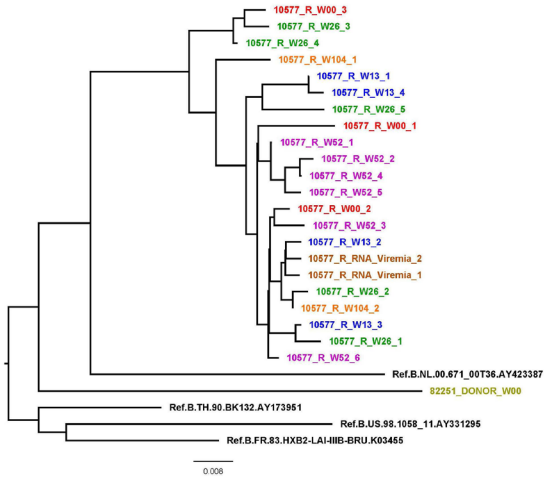


Figure: Neighbor-Joining tree of prominent gp41 sequences at the time of transplant obtained from donor (Gold) and longitudinal samples from liver transplant recipient who experienced viremia three years post-transplant due to ART non-adherence. Branch tips are color-coded based on time point and patient type (Day of Transplant W00= Red, W26=Green, W52=Purple, W104=Orange, serum RNA viremia sample=Brown). Scale of tree is shown

194 HIV SUPERINFECTION AMONG MSM AND TGW IN SUB-SAHARAN AFRICA: HPTN 075

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Background: HIV superinfection (SI) occurs when an infected person is infected with a new, distinct HIV strain. High rates of HIV SI have been reported among men who have sex with men (MSM). The HIV Prevention Trials Network (HPTN) 075 study evaluated the feasibility of recruiting and retaining MSM in sub-Saharan Africa in HIV clinical trials. We used next-generation sequencing (NGS) to assess SI among MSM and transgender women (TGW) enrolled in the HPTN 075 study.

Methods: HPTN 075 participants had quarterly visits with up to 12 months follow-up. The HPTN 075 study included 72 participants who were HIV-infected at enrollment (ENR+); 28 had a 12-month sample with a viral load >400 copies/mL. Twenty-one of 329 acquired HIV during the study (seroconverters); 17 (52.4%) had a sample from >30 days after the first HIV-positive visit (range: 38-316 days). HIV RNA was extracted using the ViroSeq HIV-1 Genotyping System. NGS was performed using the MiSeq System (env and pol regions). Phylogenetic analysis was used to identify and characterize SI events.

Results: Sequencing results were obtained for 27/28 ENR+ participants (one failed analysis) and for 11/17 seroconverters (6 failed analysis). Three cases of SI were identified; these included one (3.7%) of 27 ENR+ participants and two (18.2%) of 11 seroconverters. The incidence of SI among seroconverters (30.3/100 person-years [py]) was higher than among ENR+ participants (3.6/100 py; p=0.08) and was significantly higher than the rate of primary HIV infection in the HPTN 075 cohort (6.96/100 py; p=0.046). In one case, subtype C was present at enrollment and an inter-subtype recombinant strain was detected 369 days later (env subtype F2, pol subtype C); both strains were present at the follow-up visit. In the other two cases, the viral strain present at seroconversion shifted entirely to a new strain. In one case, the subtype C strain present at seroconversion was replaced with an inter-subtype recombinant strain 181 days later (env subtype A1, pol subtype C). In the other case, the subtype C strain present at seroconversion was replaced with a different subtype C strain 184 days later.

Conclusion: This study revealed a high incidence of SI in a cohort of MSM and TGW from sub-Saharan Africa. The incidence of SI was higher than the incidence of primary infection, and involved new infection with inter-subtype recombinant HIV strains in two of three cases.

195 GENETIC DETERMINANTS OF hsCRP, D-DIMER, AND IL-6 IN 3 MULTIETHNIC HIV COHORTS

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Background: Elevations in IL-6, D-dimer, and hsCRP, are associated with increased incidence of comorbid disease & mortality among HIV+ individuals (PLWH). Prior studies suggest a genetic basis for these biomarker elevations among certain ethnicities. We performed a genome-wide associated study (GWAS) using 3 HIV+ cohorts to identify single nucleotide polymorphisms (SNPs) associated with elevations in these 3 biomarkers in PLWH.

Methods: 7,192 participants across 3 established multi-ethnic HIV+ cohorts (START, SMART, ESPRIT) were studied. Baseline levels of hsCRP, D-dimer and IL-6 were measured & SNPs identified using a custom Affymetrix Axiom SNP array with 770,558 probes. Five ancestral ethnic groups were assigned (African, American, European, South and East Asian). Principal component (PC) analysis was used to account for population stratification, and single variant analysis was performed for each biomarker using multiple linear regression models incorporating the first 10 PCs, gender, age, CD4 count, HIV viral load, BMI, smoking (missing in ESPRIT) and biomarker related traits (CVD, diabetes, Hepatitis B & C) at baseline as covariates for combined and ethnicity-specific cohort samples. To increase power, a fixed-effects meta-analysis was conducted with inverse variance weighting for all samples, and those from the 3 largest ethnic ancestry groups (African, n=1732, American, n=645, European, n=4675).

Results: Allele frequencies varied by genotyped ethnicity, but associations between each biomarker and allele frequency did not, therefore results from the cross-cohort meta-analyses are cited. 22 SNPs within 3 gene loci (CRP, HNF1A and APOE) reached genome-wide significance (GWS, $P < 5 \times 10\text{-}8$) for hsCRP; 3 SNPs within 2 gene loci (coagulation factors F3 and F5) reached GWS for D-dimer; and 27 SNPS within 1 locus (IL6R) reached GWS for IL-6. (Fig.a,b,c). These loci have been previously described in non-HIV populations, mostly from studies of individuals of European descent.

Conclusion: Multiple SNPs were associated with elevations in hsCRP, D-dimer, and IL-6 in HIV+ individuals from 3 ethnically diverse cohorts. These findings support the hypothesis that host genetics partially contribute to chronic inflammation in this population and identify potential targets for intervention.

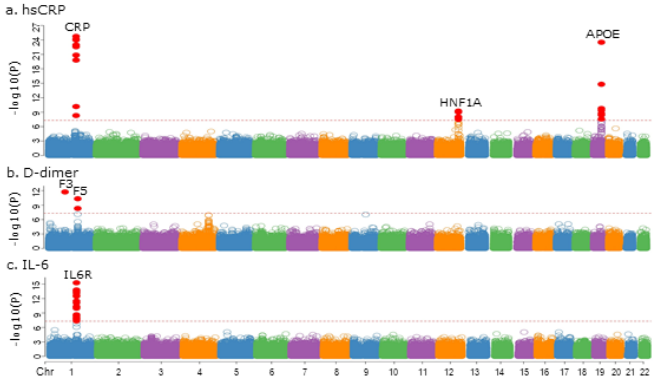


Figure. Manhattan plots of cross-cohort meta-analyses results for genetic associations with a. hsCRP, b. D-dimer, and c. IL-6 levels. Loci are labelled by the closest gene. Each point represents one SNP and is plotted by chromosomal location (x-axis) and -log10(P) (y-axis). The dashed red line represents genome-wide significance ($P = 5 \times 10^{-8}$) and SNPs meeting this threshold are colored red.

196 ABNORMAL IMMUNOMETABOLISM AND GENE ACCESSIBILITY IN ALVEOLAR MACROPHAGES IN HIV

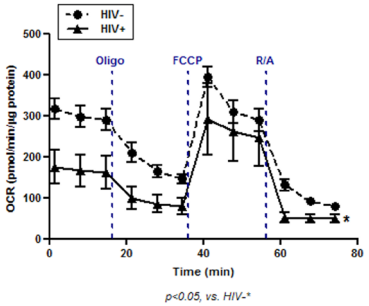
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Background: People with HIV, including those who are on antiretroviral therapy (ART) with an undetectable viral load, have an elevated risk of infectious and non-infectious pulmonary diseases, which persist even after immune reconstitution with ART. In the setting of HIV, alveolar macrophages serve as a viral reservoir and exhibit derangements in antioxidant balance and innate immune function. We sought to determine whether alterations in immunometabolism, which have been implicated in other pulmonary diseases, were associated with these observed immune defects in alveolar macrophages of people with HIV.

Methods: We enrolled 10 participants for a research bronchoscopy study in Atlanta, GA. Five participants with HIV were matched by age, sex, race and smoking status with five participants without HIV. Participants had no major medical comorbidities and those with HIV were on ART for ≥ 18 months with a CD4 count ≥ 350 cells/µl and undetectable viral load. Bronchoalveolar lavage was performed and alveolar macrophages were washed and isolated before plating for analysis of mitochondrial bioenergetics using Agilent Seahorse XFe96 and chromatin accessibility using ATAC-seq.

Results: Compared to participants without HIV, participants with well-controlled HIV demonstrated impaired alveolar macrophage oxygen consumption rates and mitochondrial bioenergetics across multiple domains, including basal and ATP-linked respiration (Figure). In parallel, ATAC-seq analysis identified 803 genes with significantly greater chromatin accessibility in participants with HIV than in those without HIV. Of those genes, 19 are known to have a critical impact on mitochondrial homeostasis, with functions ranging from mitochondrial RNA processing to free radical scavenging, including mitochondrial transcription termination factor-4 (MTERF4), superoxide dismutase 2 (SOD2), cathepsin B (CTSB), and Methionyl-TRNA Synthetase 2 (MARS2).

Conclusion: In people with HIV, we identified alterations in alveolar macrophage mitochondrial bioenergetics and chromatin accessibility for multiple genes associated with mitochondrial function. These alterations in alveolar macrophage function, in the face of ART and immune reconstitution, suggest that mitochondrial derangements may contribute to the elevated risk of pulmonary disease among people with HIV.



197 IMPACT OF EARLY ART ON CD8 T CELLS IN MESENTERIC LYMPH NODES DURING SIV INFECTION

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Background: CD8 T-cells play a pivotal role in clearance of HIV-infected cells, such that CD8 exhaustion contributes to their dysfunction and consequently, viral persistence. Mesenteric lymph nodes (MLNs), which drain the large and small intestine, are critical sites for the induction and maintenance of gut mucosal immunity. However, the dynamics of CD8 T-cells in MLNs is less known due to the lack of accessibility to these tissues in human. Thus, we assessed CD8 T-cell dynamics in MLNs vs blood in SIV-infected rhesus macaques (RMs) following early antiretroviral therapy (ART) initiation.

Methods: 32 female Chinese RMs were enrolled including 25 intravenously SIVmac251-infected animals. Nine monkeys were treated at day 4 post-infection with a cocktail of antiretroviral drugs. Furthermore, 5 RMs after ART interruption (8 weeks post-ART initiation) and 4 untreated chronically infected were also studied. Peripheral blood and mechanically isolated cells from MLNs were analyzed by flow cytometry.

Results: Acute SIV infection was associated with decreased CD4/CD8 ratio and increased memory CD8 T-cell immune-activation (CD39/HLA-DR), exhaustion (PD1) and immunosuppressive CTLA-4 expression in both blood and MLNs which were all normalized by early ART initiation. Notably, MLN CD8 T-cells had consistently higher levels of immunosuppressive CTLA-4 and CD39 expression compared to matched blood samples in acute phase. Furthermore, acute SIV infection resulted in the expansion of FoxP3+ CD8 Tregs in both blood and MLNs, while early ART decreased CD8 Tregs only in blood. Helios+ thymic CD8 Tregs were also increased in both tissues in acute infection which were normalized by ART. Analyzing the trafficking of CD8 T-cells by assessing the expression of chemokine receptors, we found that the acute SIV infection results in decreased of CCR6+ but not CXCR3-expressing CD8 T-cells in both MLNs and blood, which was recovered following early ART. ART interruption was associated with increased HLA-DR+ CD8 T-cells and decreased CCR6+ CD8 T-cells within MLNs.

Conclusion: Early ART initiation during acute infection normalized CD8 frequencies and their markers of immune activation and function in both MLNs and blood, but elevated levels of suppressive CD8 Tregs persists despite early ART in MLNs. This could be of great importance regarding immune surveillance of SIV persistence despite ART.

198 ENHANCED MUCOSAL IMMUNITY AND SIV SUPPRESSION AFTER MESENCHYMAL STEM-CELL TRANSFER

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Background: Despite the presence of HIV-specific responses, HIV reservoirs persist and pose obstacles for cure. Early pathogenic effects of HIV infection in secondary lymphoid tissues including the gut contribute to ineffective anti-viral immunity, which are not repaired by ART. MSC secrete immuno-modulatory molecules and have beneficial effects in clinical studies. Using the SIV model of AIDS, we tested the hypothesis that systemic MSC administration will modulate antigen presentation and enhance anti-viral immunity at mucosal sites and lead to better viral suppression and increased immune recovery.

Methods: Rhesus macaques with chronic SIV infection were administered with MSC by adoptive transfer and compared with SIV-infected and SIV-negative animals without MSC treatment. Virologic, immunologic, transcriptomic, metabolomic and microbiota (16s sequencing) analyses were performed. SIV RNA loads in plasma and tissue samples were determined by RTPCR and RNAscope. Changes in the T and B cell subset distribution and activation was measured by flow cytometry. SIV-specific cellular and humoral (SIV Env antibodies by ELISA) responses were measured and changes in the gene expression (RNAseq) were performed.

Results: MSC-treated animals had decreased SIV viral loads that correlated with increased levels of activated B cells, SIV-specific CD8+ T cells and SIV Env-specific antibodies in peripheral blood compared to untreated controls. In the gut and lymph nodes, SIV RNA-positive cells were relocated to germinal centers and majority of them were PD1+. In contrast, SIV+ cells were dispersed in lamina propria. Transcriptomic analysis revealed enhanced immune networks supporting anti-viral immunity. Increased prevalence of Lactobacillus and enhanced Linoleic acid metabolism was detected.

Conclusion: Collectively, our data support the hypothesis that MSCs enhance the virus-specific cellular and humoral immune responses by corralling SIV+ cells to the lymphoid follicles and improving antigen presentation and activating immune cell networks. Thus, MSC can be used for reviving or tooling mucosal immunity in HIV infection for viral clearance.

199 IDENTIFYING CENTRAL COMPONENTS OF THE HIV-1+ PREGNANCY IMMUNE NETWORK

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Background: Successful pregnancy is reliant on the acceptance of a semi-allogeneic fetus, meaning the systemic regulation of the immune system to maintain tolerance is important. In complicated pregnancies changes in both frequency and activation of peripheral leukocytes have been found. HIV-1 positive women have increased incidence of preterm labour suggesting HIV-1 infection disrupts immunological interactions relevant to the regulation of immunological balance in pregnancy, though this has not been explored in depth. We aimed to identify central leukocyte populations in HIV-1 positive and negative pregnancy immune networks that were shared or discordant which may impact on systemic immune regulation.
Methods: Freshly isolated peripheral blood mononuclear cells from uncomplicated ART treated HIV-1 positive pregnant (PP; n=21) and HIV-1 negative pregnant (NP; n=36) women were analysed using flow cytometry and ELISpot assays. Natural killer (NK) cells, monocytes (Mo), dendritic cells (DC), and both classical and non-classical T-cell subsets were identified, while IFNg, IL-2, IL-10 and granzyme B functional responses against Influenza, Epstein-Barr and Cytomegalovirus were quantified. Cytometer acquisition was optimised for longitudinal comparison between samples. Non-parametric correlation networks of the resulting 500+ parameter group datasets were generated and analysed to determine network centrality measures and compare group networks using R packages. The top 50 Strength (number of significant associations) and Betweenness (times passed through in shortest paths between all other interacting parameters) centrality measures were compared.
Results: Mo PD-L1 expression was identified as highly central by both measures in both groups, suggesting this pathway of interaction shapes the pregnant immune system. CD40-L expression on CD4 and CD8 T-cell subsets and PD-L1 on CD8 T cells had high Strength scores in both groups, while NKG2A and CD11b expression on NK cells as well as CD56bright NK subset frequency had high Betweenness scores in NP and PP women. However, the PP group had more high Strength scoring T-cell parameters, predominantly CD38 expressing T cells, suggesting these activated T cells are more influential in the HIV-1 positive pregnancy network.
Conclusion: Our work highlights shared immune components that may be key regulators of pregnancy tolerance and has identified parameters uniquely impacted by HIV-1 that may negatively influence the pregnancy immune network.

200 CXCR5+ NK CELLS IN THE LYMPH NODE ARE ASSOCIATED WITH CONTROL OF SHIV INFECTION

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Background: Natural killer cells (NKs) play an essential role in antiviral immunity; however, their function in Lymph nodes (LN) during chronic HIV/SIV infection is not fully elucidated. LN follicles constitute major reservoir sites for HIV/SIV persistence. Cure strategies could benefit from the characterization of CXCR5+ NK cells able to access/eliminate HIV-reservoirs.
Methods: Here we studied the phenotype, distribution and function of CXCR5+ NK cells in the LN of SHIV naïve and chronic SHIV1157ipd3N4-infected (>14 weeks PI) rhesus macaques (RM) and their association with plasma viral RNA levels. Flow cytometry was used for phenotypic analysis, function (IFN-g, TNF-a, CD107a) was assessed by intracellular staining and in vitro target cell killing experiments. Immunohistochemistry was performed to identify the location of NK cells in B cell follicles.
Results: We found that prior to infection, a significant proportion of NK cells (~15%) expressed CXCR5. Following infection, the frequency of CXCR5+ NK cells was significantly higher in chronic SHIV-infected RM. Phenotypically CXCR5+ NK cells express higher levels of FCgRIIa and FCgRIIIa compared to CXCR5- NK cells, which might be important for ADCC function. The CXCR5+ NK cells demonstrated enhanced polyfunctionality with higher production of IFN-g, TNF-a and CD107a when stimulated with mitogen. Immunohistochemistry analysis confirmed the presence of NK cells in LN follicles. Transcriptional profiling (RNA-seq) of sorted CXCR5+ and CXCR5- NK cells from SHIV-infected RM revealed that CXCR5+ NK cells are activated and express increased levels of cytolytic markers (perforin, granzyme-B, granulysin and CD107a), suggesting that these cells have a higher capacity to kill. Gene set enrichment analysis of CXCR5+ cells additionally showed elevated transcripts associated with cell activation, TNF-alpha, interferon signaling and apoptosis. Importantly, the frequency of CXCR5+ NK cells correlated inversely with plasma SHIV viral RNA levels and exhibited a significant negative association with germinal center Tfh cells
Conclusion: Chronic SHIV infection is characterized by accumulation of NK cells within LN follicles and suggest that CXCR5+ NK cells could play an important role in controlling SHIV infection. Cure strategies should focus on inducing these cells for sustained HIV remission

201LB THE ROLE OF CD101 IN HIV/SIV PATHOGENESIS AND MAINTENANCE OF THE VIRAL RESERVOIR

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Background: HIV infection results in depletion of CD4+ T cells, induction of systemic inflammation, and exhaustion of antiviral responses, all features that are not normalized during ART and implicated in promotion of viral persistence. CD101 is a surface glycoprotein that has been linked to highly suppressive TRegs and defining "terminally exhausted" CD8+ T cells during chronic infection. Here, we sought to understand implications of CD101 expression on CD4+ T cells during SIV infection and mechanisms leading to SIV persistence.
Methods: 28 rhesus macaques (RMs) were infected with SIVMac239 and started ART 42 d.p.i. Samples were collected longitudinally for flow cytometric and RNAseq analysis. Latency and Reversion Assay (LARA) was used for latency induction and integrated HIV was measured by qPCR.
Results: At 14 d.p.i. CD101+ CD4+ T cells were preferentially depleted, as compared to other CD4+ memory subsets ($p<0.0001$). CD101+ CD4+ T cells remained significantly lower than CD101- CD4+ T cells in blood and tissues up to 42 d.p.i. ($p<0.001$). Reconstitution of CD101+ CD4+ T cells was delayed compared to CD101- CD4+ T cells after ART. In SIV+ RMs on ART for >1 year, PD-1 and CTLA-4 were upregulated in CD101+ as compared to CD101- CD4+ T cells ($p=0.0156$ and $p=0.0078$, respectively). We also detected higher levels of cell cycling ($p=0.0078$) in the CD101+ CD4+ T cells, suggesting that these cells may persist through homeostatic proliferation and replenish the reservoir via clonal expansion. RNAseq showed that CD101+ CD4+ T cells were transcriptionally distinct and in a more terminally differentiated state, aligning with reports stating that CD101+PD-1+CD8+ T cells were "terminally differentiated". Using LARA, we detected similar levels of integrated HIV-DNA in CD101+ and CD101- CD4+ T cells. Interestingly, and consistent with their higher co-expression of PD-1/CTLA-4 and transcriptomic profile, p24 gag expression within CD101+ CD4+ T cells was significantly lower at 7 d.p.i., suggesting that HIV-infected CD101+ CD4+ T cells progress to a latent state more readily.
Conclusion: Altogether, these data identify CD101+ CD4+ T cells as a cell subset that (i) is preferentially depleted during early SIV infection, (ii) leads to the establishment of immune exhaustion, and (iii) preferentially enter latency. As such, CD101+ CD4+ T cells could be vital contributors to the HIV reservoir and targets of future therapeutic approaches.

202 IMMUNE CONTROL OF LIVE ATTENUATED-HIV INFECTION AND DISEASE IN BLTS-HUMANIZED MICE

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Background: We recently demonstrated the robust development of human lymphoid and myeloid cells in immunodeficient mice, achieved through co-transplantation of bone marrow-derived human hematopoietic stem cells (hHSCs), liver, thymus, and spleen (BLTS). Importantly, unlike other earlier mouse models, BLTS-humanized (hBLTS) mice exhibit lymphoid tissue with proper development of B cell follicles, a major site of the latent HIV reservoir. Therefore, we hypothesize that hBLTS mice with complete human immune cell repertoire and lymphoid tissue architecture will provide an improved model for studying HIV immunity.
Methods: To generate hBLTS mice, NSG mice were engrafted with autologous hHSCs via intravascular injection, and with human hematopoietic lymphoid tissues (fetal thymus, liver and spleen) via kidney capsule transplant. Reconstitution and characterization of human immune cells was determined by flow cytometry. Wild type and Nef-deleted HIV strains were used to infect the hBLTS mice. Blood samples were analyzed by flow cytometry and qRT-PCR to measure impact on the human immune cell populations and HIV viral load, respectively. Lymphoid tissue pathology was examined via immunohistochemistry.

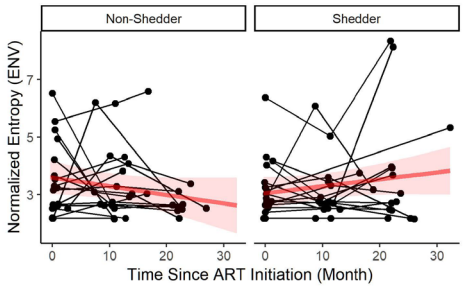
Results: We demonstrated successful reconstitution of functionally active T Cells (αβ and γδ T cells), NK cells, and antibody-secreting B cells in hBLTS mice, along with the formation B cell follicles within lymphatic tissues. We were also able to generate differentially matured and functionally polarized human dendritic cells from bone marrow of hBLTS mice. We found that the BLTS model also could successfully support HIV infection that could be controlled by antiretroviral therapy. Infection of hBLTS mice with live-attenuated (Nef-deleted) HIV resulted in the establishment of long-term aviremia (below detection limit). Moreover, CD4+ T cell counts were maintained in Nef-deleted HIV infected mice at levels similar to uninfected hBLTS mice. Viral control in these mice was concurrent with induction of human antiviral immune responses and reduced lymphoid tissue pathology compared to that found in hBLTS mice infected with wild type HIV.
Conclusion: The immune system of the hBLTS mouse effectively recapitulates that of the human immune system, and therefore provides a robust model for investigating human immunity to HIV. Furthermore, this model provides a means to evaluate novel HIV immunotherapeutic approaches in vivo.

203 FLT3L-MEDIATED EXPANSION OF PLASMACYTOID DCS CONTROLS HIV INFECTION IN HUMANIZED MICE

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Background: Plasmacytoid dendritic cells (pDCs) play a crucial role in host's immune responses through their ability to secrete high levels of IFN-I and other proinflammatory proteins. HIV infection affects pDCs although the nature of such modulation is less understood. It also remains unclear whether pDCs shape the outcome of early HIV infection. Thus, in this study, we directly assessed the role of pDCs in early phases of infection, evaluating whether modulating levels of pDCs could alter the course of viral replication.
Methods: Humanized (hu) NSG and BLT mice were treated with CDX-301 and infected with CCR5-tropic NL4.3-ADA HIV for up to 3 weeks. CDX-301 is a recombinant form of fms-like tyrosine kinase-3 ligand (Flt3L), which binds the Flt3 receptor on progenitor cells and enhances development and mobilization of DCs to tissues. Mice may be treated with pDC-depleting Ab or an Ab that blocks IFN-I signalling prior to HIV exposure. Levels of DCs and infected (p24+) CD4+ T cells were analyzed by flow cytometry (FC). Splenocytes from Flt3L-treated or untreated mice were co-cultured with HIV-infected T cells or treated with TLR7/8 agonist R848 and pDCs expressing IFNα were enumerated by FC.
Results: HIV infection led to systemic depletion of pDCs, but not conventional DCs, in various lymphoid organs of hu-NSG and hu-BLT mice. Flt3L treatment led to widespread expansion and mobilization of DCs to multiple tissues but had no discernable effects on levels of T cells or monocytes. Upon viral challenge, Flt3L-treated mice consistently displayed a meaningfully delayed infection and markedly reduced viremia compared to untreated mice. Levels of infected CD4+ T cells were globally reduced in the treated group. Ab-mediated depletion of pDCs abolished the protective effect by Flt3L, demonstrating that the Flt3L-mediated control of HIV was pDC-dependent. Functionally, pDCs from Flt3L-treated mice were more responsive to TLR7 stimulation, leading to a higher frequency of pDCs expressing IFNα relative to those from untreated animals. Lastly, the protective effect of Flt3L treatment was mediated through an enhanced IFN-I response as blocking IFN-I signalling early in Flt3L-treated animals restored viremia to the level of untreated mice.
Conclusion: Maintaining pDC levels and functions is key to early viral control and in this context, our findings provide a practical insight for novel anti-HIV strategies and vaccine design.

204 EFFECTS OF CMV ON HIV DNA DIVERSITY IN PERIPHERAL BLOOD CELLS DURING EARLY ART

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Background: We previously showed that detectable Cytomegalovirus (CMV) DNA was associated with increased activation of CD4+ T cells and with a slower decay of HIV DNA in people starting antiretroviral therapy (ART) during early HIV infection. Here, we investigate changes in HIV DNA molecular diversity associated with CMV DNA in the setting of early ART.
Methods: We obtained at least 3 longitudinal peripheral blood mononuclear cell (PBMC) samples from 37 individuals starting ART during early HIV infection and who reached virologic suppression (<50cp/ml, no viral blips) within a median of 3 months of the estimated date of HIV infection (IQR: 2.6-6.8). In each PBMC sample (N=120), levels of HIV, CMV and Epstein-Barr Virus (EBV) DNA were measured by digital droplet (dd)PCR. Deep Sequencing of HIV DNA C2-V3 env was performed using the MiSeq Illumina platform. Cleaned mapped reads were obtained after iterative read mapping and quality filtering using an in-house pipeline. The HIV DNA molecular diversity (Shannon Entropy) was computed for 99 samples. A linear mixed-effect regression model was used to analyze the effect of detectable CMV or EBV DNA on HIV DNA molecular diversity and its change from ART initiation (baseline) to the end of follow-up (approximately 30 months).
Results: Participants had a median of 515 (IQR: 363-732) CD4+ T cells/ul at baseline and were followed for a median of 29 months (IQR: 18-39) while on suppressive ART. Overall, 19 (51%) participants had detectable CMV DNA during follow up, while 18 did not. Entropy levels at the time of ART initiation did not differ by CMV status (p=0.2). However, entropy levels were more likely to increase during ART for participants who exhibited CMV shedding and to decrease for those who did not (see Figure), and this change in entropy was significantly different for the 2 groups (interaction p<0.05). Such a relationship was not found for EBV (EBV by time interaction; p=0.66).
Conclusion: In addition to slower HIV DNA decay and increased CD4+ T cell activation, we now observe increasing HIV DNA molecular diversity during early ART in the setting of subclinical CMV replication. Taken together, these observations suggest that subclinical CMV DNA shedding might affect HIV persistence by promoting HIV replication at low levels during early ART. Future studies with anti-CMV therapeutics could help determine the underlying mechanisms and if causal associations exist.



Legend: Thin lines and dots indicate individual patients and their entropy values. Thick red lines and shades indicate model-estimated means and their 95% confidence intervals.

205 GUT MICROBIOTA FACILITATES HIV ACQUISITION IN THE GUT

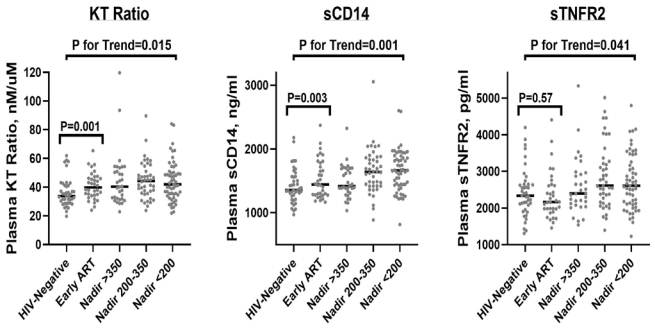
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Background: Resident microbiota protect the gut from pathogenic organisms. However, gut microbiota can facilitate the transmission and pathogenesis of viruses. The gut is a significant site of HIV acquisition in infants (via breastfeeding) and adults (via receptive anal intercourse) and a primary site of HIV replication and CD4+ T cell depletion. The effect of gut microbiota on HIV acquisition risk, pathogenesis, and disease progression is unknown.
Methods: It is not possible to perform the direct experimentation that is needed to establish gut microbiota's role in HIV acquisition and infection in humans. Bone marrow/liver/thymus (BLT) humanized mice have been extensively utilized to study HIV acquisition, pathogenesis and prevention strategies in vivo. To examine the role of gut microbiota in HIV acquisition risk, we constructed germ-free BLT mice and BLT mice colonized with gut microbiota. First, we rederived the immunodeficient NSG mouse strain germ-free. Next, germ-free NSG mice were implanted with human thymus/liver tissue and transplanted autologous stem cells in a germ-free surgical isolator. Germ-free BLT mice were housed in a gnotobiotic Trexler isolator. The germ-free status of

mice was monitored by the National Gnotobiotic Rodent Resource Center with Gram stain, culture and PCR. BLT mice colonized with gut microbiome were also constructed. To directly evaluate the effect of gut microbiota on HIV acquisition risk after oral exposure, germ-free BLT mice (n=8) and colonized BLT mice (n=10) were exposed to HIV via oral gavage. HIV-RNA levels were monitored longitudinally in the peripheral blood plasma of mice weekly by real-time PCR analysis. At necropsy, we also measured HIV-DNA levels in tissues.
Results: Following a single oral HIV exposure, HIV-RNA was detected in the plasma of 4/10 colonized BLT mice. Remarkably, no HIV-RNA was detected in the plasma of germ-free BLT mice. Given that breastfed infants are repeatedly exposed to HIV, we administered a second dose of HIV to BLT mice with a negative HIV viral load. Following a second HIV exposure, 5/6 colonized BLT mice became positive for HIV. In sharp contrast, only 2/8 germ-free BLT mice became positive for HIV. Overall, gut microbiota significantly increased oral HIV acquisition of colonized BLT mice (9/10 vs 2/8, p=0.01).
Conclusion: To our knowledge, these results provide the first direct evidence that gut microbiota facilitate HIV acquisition.

206 KYNURENINE PATHWAY ACTIVITY REMAINS ABNORMAL DESPITE VERY EARLY ART INITIATION

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Background: Despite early ART initiation, ART-suppressed people living with HIV (PLWH) remain at higher risk for tuberculosis (TB) and infection-related malignancies than the general population. The immunologic pathways that remain abnormal in this setting—and may plausibly drive these complications—are unclear.
Methods: PLWH maintaining ART-mediated viral suppression >1 year and HIV-negative controls, all CMV+ and enriched for HIV risk factors, were sampled from a study of influenza vaccine response. PLWH were stratified by timing of ART initiation (within 6 months of HIV infection [early ART] vs. later), and among later initiators, by nadir CD4 count (>350, 200-350, <200 cells/mm$_3$). Plasma kynurenine/tryptophan (KT) ratio (by LC-MS) and both sTNFR2 and sCD14 (by ELISA) were assessed before vaccination. Between-group differences adjusted for age, sex, # lifetime male sexual partners, and ART type were assessed by linear regression, transforming biomarkers as necessary.
Results: A total of 164 PLWH and 41 HIV-negative participants were enrolled. Median age was 54 years and 91% were men. Of HIV-negatives, 56% were MSM, 41% had >100 lifetime male sexual partners, and 15% had distant IDU. Of the PLWH, 34 were early ART initiators and the remainder had a range of nadir CD4 counts: >350 (n=32), 200-350 (n=43), and <200 cells/mm$_3$ (n=55). Median duration of viral suppression was 8 years (IQR 5-11 years). Compared to HIV-negatives, PLWH with later ART initiation had higher KT ratio, sCD14, and sTNFR2 after adjustment for age and sex, but only KT ratio and sCD14 remained abnormal in the early ART initiators (see figure). Both efavirenz use (P<0.001) and # lifetime male sex partners (P=0.03) were associated with higher sCD14, but not KT ratio or sTNFR2. After additional adjustment for EFV use and # male sex partners, early ART initiators continued to have a mean 22% higher KT ratio (P=0.001), but not sCD14 (+7%, P=0.11), than HIV-negative controls.
Conclusion: While PLWH initiating ART in the first 6 months of infection appear to restore near-normal levels of many immune activation markers that predict morbidity and mortality, the kynurenine pathway of tryptophan catabolism—a biomarker of indoleamine 2,3-dioxygenase-1 (IDO) activity—remains abnormal. As IDO confers adaptive immune defects and contributes to TB and cancer pathogenesis in animal models, the persistent induction of this pathway in PLWH with early ART initiation may plausibly contribute to persistent risks of these complications in this setting.



*P values reflect differences between groups after adjustment for age and sex

207 TREHALOSE INHIBITS HIV IN CD4+ LYMPHOCYTES AND MACROPHAGES BY 2 DISTINCT MECHANISMS

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Background: We previously showed that induction of autophagy through the inhibition of mTOR inhibits HIV replication. However, inhibition of mTOR may have cellular effects other than autophagy that could affect HIV infection. Here, we examined trehalose, a naturally occurring glucose mTOR-independent inducer of autophagy, to determine the effects on HIV replication.
Methods: Human macrophages (M0) and CD4+ T lymphocytes (T-cells) treated with trehalose with or without HIV infection were assessed for cytotoxicity by LDH release assay and viral replication by p24 ELISA. Autophagy proteins were assessed by immunoblotting, qRT-PCR and fluorescence microscopy combined with assessment of LC3B lipidation. Viral entry was measured by intracellular p24. Data were analyzed using the Student paired T-test and one-way Anova.
Results: Pretreatment of T-cells and M0 with trehalose resulted in a dose dependent inhibition of HIV reaching ~90% inhibition at 100mM in both cell types without cytotoxicity. Trehalose induced autophagic flux in T-cells and M0 as indicated by increased LC3B lipidation and LC3B-II accumulation following treatment with the autophagic flux inhibitor bafilomycin. Inhibition of HIV was at least partially dependent on induction of autophagy since knockdown of ATG5 by RNAi significantly increased p24 release by 42% and 47% in trehalose-treated HIV-infected T-cells and M0. Surprisingly, trehalose also decreased HIV entry into T-cells and M0 in a dose dependent manner reaching ~80% reduction of intracellular virus in both cell types. The inhibition of viral entry was associated with ~3-fold decrease in CD4 expression (p<0.001) and CCR5 expression (p<0.001) in T-cells, and a 4.6-fold decrease in CD4 expression (p=0.002) but no significant change in CCR5 expression in M0.
Conclusion: These data demonstrate that the naturally occurring sugar, trehalose, at doses safely achieved in humans inhibits HIV through two mechanisms: 1) decreased entry through the down-regulation of CCR5 in T-cells, and decreased CD4 expression in both T-cells and M0; and 2) degradation of intracellular HIV through the induction of mTOR independent autophagy. These findings demonstrate that cellular mechanisms can be modulated to inhibit HIV entry and intracellular replication using a naturally occurring, non-toxic sugar. Trehalose may be a useful adjunct in the maintenance of patients who achieve an HIV functional cure.

208 FECAL MICROVESICLES UNIQUELY INFLUENCE TRANSLOCATING BACTERIA AFTER SIV INFECTION

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Background: Microbial translocation contributes to persistent inflammation in both treated and untreated HIV infection. Although translocation is due in part to a disintegration of the intestinal epithelial barrier, there is a bias towards the translocation of Proteobacteria. In murine models, epithelial-derived microvesicles (MVs) have been shown to influence bacterial gene expression and growth. We hypothesize that intestinal epithelial MVs biologically differ after HIV infection, which may contribute to biased translocation.
Methods: We isolated fecal MVs from 12 healthy and 12 SIV-infected rhesus macaques (RM, Macaca mulatta) and co-cultured these MVs with isolates of translocated bacterial species. Viable bacteria that had translocated were isolated from mesenteric lymph nodes, livers, and spleens obtained from

end-stage, SIV-infected RM, cultured under aerobic and anaerobic conditions, and identified by MALDI-TOF or 16S rDNA sequencing. Bacterial growth was kinetically assayed by spectrophotometer. MV miRNA profiles were assessed by human miRNA Array cards and qRT-PCR. AMPs alpha defensin 1, beta defensin (bDEF) 1, bDEF2, bDEF4, Lysozyme C, PLA2G2a, and Reg3g were assayed by ELISA.

Results: Utilizing a non-human primate model of AIDS, we observed that MV miRNA profiles differ significantly after SIV infection. Ninety-three of 100 differentially expressed miRNAs displayed upregulated expression, with miR-425 and -484 showing significant upregulation in MVs derived from SIV-infected RM. Among AMPs, bDEF1 showed a significant downregulation among MVs from SIV-infected RMs. Several bacterial species showed dose-dependent growth sensitivity upon MV co-culture. Notably, Lactobacillus salivarius showed significantly accelerated growth when co-cultured with MVs derived from SIV-infected animals while Klebsiella pneumoniae displayed stunted growth.

Conclusion: Fecal MVs can differentially influence the growth of bacterial isolates known to translocate in SIV infection. This effect may be attributable to a shift in MV miRNA content and/or to a shift in AMP content. The identification of the precise mechanisms by which fecal MVs differentially regulate the behavior of translocating bacteria will inform the development of therapeutics aimed at impeding microbial translocation.

209 CHARACTERISATION OF POTENTIAL HIV TARGET MYELOID CELLS IN FORESKIN EPITHELIA

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Background: The human foreskin is an immunologically active tissue containing both lymphoid and myeloid cells. The foreskin has been shown to play an important role in HIV infection as its complete removal during MMC has been shown to reduce the risk of HIV acquisition by up to 60%. CD4+/CCR5+ Langerhan's cells (LCs) and macrophages are known to be resident in both inner and outer foreskin tissue and are potential HIV target cells. To better understand whether foreskin-derived myeloid cells are promiscuous to HIV-1, we exposed them to HIV in ex-vivochallenge assays.

Methods: Foreskin cells were allowed to migrate out of isolated epidermal tissue from adult South African men undergoing vMMC. Briefly, epidermal sheets were obtained after dispase digestion of 1cm$_2$ foreskin tissue. Cells were collected after 48-hour incubation and remnant tissue resident cells were enzymatically isolated using liberase (5 mg/ml). Epidermal LCs and macrophages from the inner and outer foreskins were identified using a multiparameter flow panel: CD207, CD1a, CD80/86, HLA-DR, CD11c, CD209, CD206, CD14, CD4, CCR5, CD169 and zombie (live/dead). Ex-vivoHIV challenge assays were set up using migratory cells and HIV infection was detected using reporter genes, GFP and mCherry as well as p24 antibody.

Results: Tissue resident LCs and macrophages were isolated. LCs (4.8 x 105) were more abundant than macrophages (9.4 x 101), with averages of 5% and 0.009% of the entire cell population respectively. Both migrating CD1a+, CD207+ LCs and CD209+, CD163+ macrophages expressed higher levels of CD80/86 (p=0.006) and HLA-DR (p=0.02) relative to cells that remained in the tissue co-expressing these surface antigens (p=0.015). HIV exposed CD11c+ LCs and macrophages expressed 2% mCherry, 13% p24 and absolute CD4 downregulation.

Conclusion: LCs and macrophages that migrate from foreskin epidermal sheets express high levels of maturation and activation markers CD40, CD80/86 and HLA-DR, they are therefore activated and susceptible to HIV infection as evidenced by reporter gene (mCherry) and p24 expression. CD4 downregulation also indicates HIV infection.

210 IMPACT OF CCL27 ON HIV-1 TARGET-CELL ABUNDANCE IN THE FORESKIN EPITHELIUM

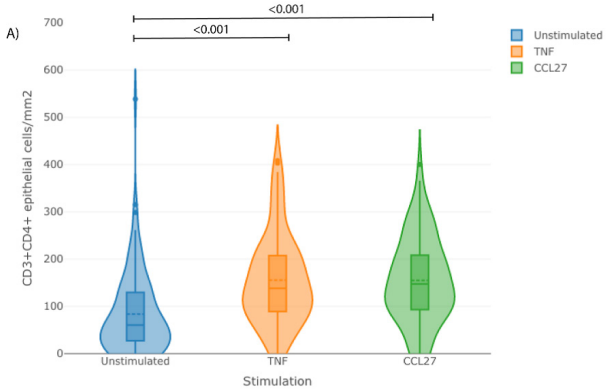
Shorok Sebaa[1], Kyle O'Hagan[1], Nyaradzo T. Chigorimbo-Tsikiwa[1], Sylvie Amu[2], Ramon Lorenzo-Redondo[3], Ann M. Carias3, Francesca Chiodi[2], Gianguido C. Cianci[3], Thomas Hope[3], Clive Gray[1]
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Background: Findings from our laboratory have shown that asymptomatic sexually transmitted infections (STIs) have a significant effect on foreskin immunity, by increasing the density of HIV target cells in the foreskin and altering inflammatory markers in the tissue. Of particular importance, CCL27 transcript and protein were found to be significantly higher in the inner foreskin relative to the outer tissue. We hypothesized that CCL27, a skin-homing chemokine, might have an effect on recruiting HIV target cells to the foreskin epidermis, bringing target cells closer to where they might interact with HIV upon exposure.

Methods: Inner foreskin tissue explants were cultured in either media alone or in the presence of TNFα (100ng/ml) or CCL27 (400ng/ml) for 48 hours. Tissue was embedded and frozen in OCT, sectioned and stained for HIV target cells (CD3+CD4+). A Delta Vision imaging system was used to acquire fluorescent images of the cells. Cell density was then calculated using Integrative Data Language (IDL), accounting for the size of the epidermis.

Results: We observed an increase in the density of CD3+CD4+ T cells in the epithelium of the inner foreskin that was stimulated with CCL27. The data showed a 2- to 3-fold ($q<0.001$) increase in CD3+CD4+ T cell numbers in the epithelium after stimulation with TNFα (from 60 cells/mm$_2$ to 138 cells/mm$_2$) and CCL27 (from 60 cells/mm$_2$ to 147 cells/mm$_2$) compared to the unstimulated samples.

Conclusion: In conclusion, exogenous stimulation of foreskin tissue with CCL27 was shown to significantly increase the population of CD3+CD4+ T cells in the inner foreskin. It is suggested that this increase is due to the migration of CD3+CD+ T cells from deeper layers of the tissue to the epithelium. Interestingly, CCR10 is the cognate receptor for CCL27 that is expressed on T helper 22 (Th22) cells. Th22 cells express CCR5, making them a possible target for HIV infection. Future work can explore how the interaction of CCL27 and Th22 cells in the foreskin affect HIV susceptibility in the male genital tract.



211 IMPACT OF PENILE CIRCUMCISION ON HIV SUSCEPTIBILITY MARKERS IN THE URETHRA

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Background: Penile circumcision (PC) reduces HIV risk by approximately 60%. This may relate to the stochastic reduction in susceptible foreskin tissue and/or alterations in the coronal sulcus (CS) microbiome and associated inflammatory cytokines/chemokines, particularly levels of IL8. However, it is also possible that circumcision mediates protection through effects on the urethral microbiome and immune milieu. Therefore we performed a prospective analysis of the impact of PC on the microbiome and immune milieu of both the urethra and CS.

Methods: HIV-negative, STI symptom-free adult Ugandan men (n=51) undergoing elective PC were enrolled. Swabs were collected from the urethra and either the inner foreskin (pre-PC) or CS (post PC), at baseline and 12 months after PC. Multiplex ELISA quantified chemoattractant chemokines (IL-8, MIP-1b), proinflammatory cytokines (IL-1a, IL-1b) and an epithelial integrity biomarker (E-cadherin). Bacterial abundance was assessed by 16S rRNA qPCR and sequencing. The intra-individual impact of PC was assessed using the paired Wilcoxon test.

Results: At baseline the urethra was enriched for IL-8, MIP-1b and E-cadherin, while the inner foreskin was enriched for IL-1a, IL-1b with a greater total

bacterial abundance (median 27,100 vs. 1,200, gene copies/swab, p=0.001). Anaerobes made up 49% of inner foreskin bacteria, but only 26% of urethral bacteria. PC did not alter urethral IL-8 (median 1058 vs. 818 pg/ml at 12 months and baseline, respectively; p=0.057) or other chemokines/ cytokines, and urethral E-cadherin increased (155,750 vs. 111,928 pg/ml, p=0.012) suggesting reduced epithelial integrity; urethral total bacterial abundance and anaerobe abundance dropped by 5-fold and 7-fold, respectively. In contrast at the CS, where there were dramatic reductions in E-cadherin (900 vs. 15,843 pg/ml, p<0.001) and most proinflammatory chemokines/cytokines (eg: IL-8, 3 vs. 34 pg/ml; p<0.001). IL-1a was increased post-PC at the CS coupled with a 14-fold reduction in total bacterial abundance (p=0.004) and 200-fold reduction in anaerobes (p<0.001).

Conclusion: PC had no impact on urethral immunology and may have reduced epithelial integrity despite some reductions in total bacterial load and anaerobes; in the CS there was enhanced epithelial integrity, near total loss of anaerobes and dramatic immune alterations. This suggests that HIV protection post-PC is mediated through removal of inflamed, HIV-susceptible inner foreskin tissues rather than via the urethra.

212 MEDICAL MALE CIRCUMCISION DISCIPLINES THE PENIS: UNDERSTANDING HIV SUSCEPTIBILITY

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Background: The male foreskin is the main site of HIV entry in heterosexual men as evidenced by the effective protection incurred upon its removal following voluntary medical male circumcision (VMMC). However, the biological mechanism by which circumcision confers this protection remains poorly understood. To understand changes to skin barrier function after VMMC, we measured transepithelial water loss (TEWL) and hydration status in the glans, foreskin and shaft before and after (glans & shaft only) VMMC as in vivo measures for skin barrier integrity. The lower TEWL and higher hydration status equates with more intact skin barrier integrity.

Methods: Hand-held vapometers and moisture meters SC & D, designed to measure water loss and content in the skin (and used extensively in dermatology and the cosmetic industry), were used to quantify TEWL (n=45 adult males), surface hydration in the stratum corneum and water content in the skin (n=31 adults) of the glans, inner foreskin and penile shaft before VMMC. These in vivo proxy measurements for skin integrity were then made two weeks after circumcision. First-pass urine samples were tested for common curable sexually transmitted infections (STIs): Chlamydia trachomatis, Neisseria gonorrhoea, Trichomonas vaginalis & Mycoplasma genitalium.

Results: To date, we show that 20-25% men have an asymptomatic STI. In males who were STI negative prior to circumcision, the inner foreskin and glans had higher TEWL readings compared to the shaft, whereas the surface hydration and water content were the same across all anatomical sites. Two weeks after circumcision, the TEWL readings in the glans significantly decreased (from a median of 27.6 to 17 g/hr/m_2) to match the shaft readings and the hydration content also decreased in all three sites but especially surface hydration in the shaft (from a median of 48 to 28 au, p=0,0061). Comparing men who were STI positive (n=9) versus STI negative at the time of VMMC, there was lower TEWL in the glans in the presence of an STI (median of 26 vs 9 g/hr/m_2, p=0,033), but no differences in the hydration status.

Conclusion: Our data show that prior to VMMC, the inner foreskin and glans had lower skin barrier integrity which increased soon after circumcision in STI negative males, but not in those with an asymptomatic STI. This finding has implications for understanding how MMC disciplines penile tissue and gives insight into how HIV acquisition may be prevented after circumcision.

213 CONDOMLESS RECEPTIVE ANAL INTERCOURSE IS ASSOCIATED WITH MARKERS OF MUCOSAL INJURY

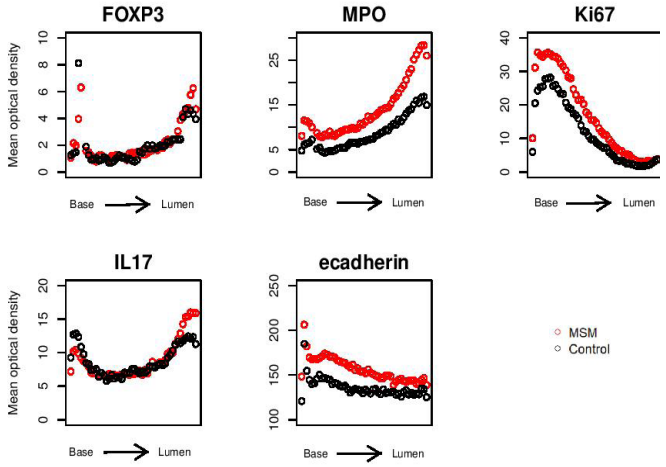
Colleen F. Kelley[1], Rama R. Amara[2], Veronika Fedirko[2], Yijuan Hu[2], Ilana Pollack[2], Rami Yacoub[2], Zhengyi Zhu[2], Roberd Bostick[2]
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Background: We previously found a unique rectal mucosal (RM) immune environment among men who have sex with men (MSM) engaging in condomless receptive anal intercourse (CRAI) typified by a pro-inflammatory response to CRAI and a microbiota enriched for Prevotellaceae over Bacteroidaceae. Further exploration of the RM immune environment among MSM engaging in CRAI will lead to a better understanding of HIV transmission.

Methods: To investigate expression of MPO (neutrophils), IL-17 (inflammatory cells), and FOXP3 (immunosuppressive cells) in the lamina propria and Ki67 (proliferating cells) and e-cadherin (tight junctions) in the crypt epithelium of RM, we used standardized, automated immunohistochemistry and quantitative image analysis in a cohort of 41 MSM engaging in CRAI and 21 men who had never engaged in CRAI (controls) over 2 study visits. The RM microbiota was characterized with 16s rRNA sequencing. Linear mixed effects models were used to examine differences in biomarker expression between study groups over time. A linear decomposition model (LDM) was constructed to examine associations between the biomarkers and microbiota.

Results: Expression of cellular markers MPO, IL-17, and FOXP3 increased from the base of the crypt towards the lumen of the RM; while Ki-67 and e-cadherin decreased (Figure). After adjustment for race and age in mixed effects models, among MSM engaging in CRAI relative to controls, the expression of MPO in the lamina propria and Ki67 in the epithelium were 41% (p<0.05) and 60% (p=0.03) higher, respectively. There were no significant differences in the other 3 biomarkers or in biomarker expression among MSM engaging in CRAI based on timing of sexual intercourse. No significant associations were detected between the 5 biomarkers and global composition of the RM microbiota or individual taxa examined, including Bacteroides and Prevotella genera.

Conclusion: Increased infiltration of neutrophils and proliferation of crypt epithelial cells in the RM of MSM likely represent an injury response to frequent CRAI, which could facilitate HIV transmission through increased inflammation. However, the role of the microbiota in contributing to RM inflammation among MSM remains unclear. Prevention interventions that reduce RM inflammation or that capitalize on the presence of a specific inflammatory mechanism (e.g. neutrophil response) at the time of HIV exposure in the RM could enhance efficacy.



214 IMMUNE CORRELATES OF ANORECTAL HIV SHEDDING IN MEN ON ANTIRETROVIRAL THERAPY

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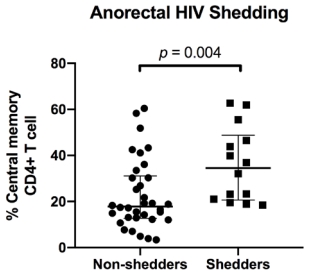
Background: Antiretroviral therapy (ART) effectively suppresses HIV levels in plasma. While HIV levels at mucosal surfaces generally also fall to undetectable levels, several groups have described detectable HIV shedding in the anogenital tissues of ART-treated individuals, and the immune correlates of HIV shedding in the context of effective ART are not well understood. Because mucosal inflammation drives increased HIV shedding in ART-naïve individuals, we hypothesized that anorectal HIV shedding in ART-treated men would be associated with activated mucosal CD4+ T cells.

Methods: Fifty-four HIV-infected, ART-treated men who have sex with men were recruited from Toronto, Canada. Anal swabs were used to test for HIV RNA levels by RT-PCR. High-resolution anoscopy was performed to collect anal biopsies, and lymphocytes isolated from collagenase-treated biopsies were stained for flow cytometric analysis. Markers included: CD38/HLA-DR (immune

activation), CD25/FoxP3 (Tregs), CCR6 (Th17), CCR5 (HIV co-receptor) and CCR7/CD45RA (memory subsets). HIV shedders and non-shedders were compared by Mann-Whitney (SPSS).

Results: Fifteen (27.8%) of 54 ART-treated men had detectable anorectal HIV shedding despite plasma HIV suppression, albeit at low levels (median 206 copies/swab). Surprisingly, HIV shedders did not have increased levels of activated (CD38+HLA-DR+) CD4+ T cells (p= 0.401). However, we observed differences in anorectal CD4+ T cells memory subsets: HIV shedders had a significantly higher proportion of central memory cells (CCR7+CD45RA-; Shedders= 34.5%, Non-shedders= 17.9%; p= 0.004). All other mucosal memory subsets were enriched in HIV non-shedders, including terminally differentiated cells (CCR7-CD45RA+; p= 0.024). No other mucosal T cell differences were observed between HIV shedders and HIV non-shedders.

Conclusion: An increased proportion of central memory cells (TCM), but not of activated mucosal CD4+ T cells, was associated with HIV shedding. This suggests that non-inflammatory mechanisms, such as the homeostatic proliferation of latently infected cells, may be driving mucosal HIV shedding in ART-treated individuals. While the low-level HIV shedding that we observed is unlikely to contribute to sexual transmission of HIV, understanding immune correlates of compartmentalized HIV production in ART-treated individuals may help to optimize strategies for HIV eradication.



215 HIV HIGHLY INFECTS GENITAL CD4+ T CELLS WITH REMODELING FOR SURVIVAL AND MIGRATION

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Background: The female reproductive tract is one of the most common sites of initial HIV transmission yet we lack a detailed understanding of the cells that are most susceptible to infection. One challenge involves the extensive remodeling of host cells by HIV, rendering it difficult to classify infected cells into traditional T cell subsets.

Methods: We exposed specimens of endometrial biopsies and PBMCs from the same donors to a CCR5-tropic transmitted/founder HIV-1 reporter virus, and conducted an extensive phenotypic analysis of uninfected and infected cells using CyTOF. Using bioinformatics analyses of the resultant high-dimensional single-cell datasets, we were able to characterize the subsets of cells that were most susceptible to HIV infection independent of remodeling.

Results: Memory CD4+ T cells were almost exclusively targeted for infection in both the tissue and blood specimens, but those from the endometrium were significantly more susceptible (p<0.01). While a diverse array of endometrial memory CD4+ T cells were targeted for infection, only a small subset of the unstimulated PBMC-derived CD4+ T cells could be infected. In-depth analyses of the features of the endometrial memory CD4+ cells targeted for infection revealed preferential infection of T effector memory (Tem) cells polarized towards the Th1 and Th2 lineages, as well as preferential infection of T resident memory (Trm) and T follicular helper (Tfh) cells. Upon infection, HIV interfered with the TCR signaling apparatus by downregulating CD4, CD45RO, CD28, and ICOS, and upregulated BIRC5 promoting survival of infected cells. Infection also upregulated the chemokine receptors CCR7 and CXCR5 and the tissue retention receptor CD69 while downregulating expression of the CD49d integrin.

Conclusion: These data suggest that unique phenotypic features of memory CD4+ T cells in the genital tract renders these cells highly susceptible to infection by HIV-1, and that upon infection the virus remodels the cell in a manner than undermines TCR signaling while promoting survival and enhancing migration to other lymphoid sites via modulation of homing receptor expression.

216 VAGINAL BACTERIA REGULATE MICRO-RNAs TARGETING THE HIV-HOST INTERACTOME

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Background: Understanding the molecular mechanisms underlying the role of the vaginal microbiome in HIV acquisition risk is an essential step toward safer and more effective HIV prevention. We hypothesized that the resident microbiota regulates micro(mi)-RNAs that can interfere with host pathways exploited by the virus. MiRNAs are endogenous short non-coding RNA molecules that are stably carried in circulation by extracellular vesicles and exert post-transcriptional epigenetic regulation with emerging significance in HIV infection. Their role in the anti-viral mucosal barrier function is unknown.

Methods: The study utilized 112 cervicovaginal specimens from healthy reproductive-age women collected during the luteal phase of the menstrual cycle. All subjects were confirmed negative for sexually transmitted infections at the time of sampling. Vaginal microbiota was classified by Nugent scores and microbiome sequencing. Levels of miRNAs were quantified in extracellular vesicles isolated from the cervicovaginal secretions using the EdgeSeq global transcriptome platform. Differential expression (DE) was determined using Bioconductor DESeq2. miRNA target prediction was performed using miRNAtap Bioconductor package.

Results: Cervicovaginal miRNA profiles varied by both Nugent score categories (0-3 scores – normal, 4-6 – intermediate, and 7-10 – bacterial vaginosis, BV) and by metagenome classification. Higher microbiome diversity was associated with higher number of significantly dysregulated miRNAs (373 in BV versus 119 in Nugent 4-6 compared to Nugent 0-3, FDR<0.1, p<0.01). The miRNAs dysregulated by BV overlapped with 66% of the miRNAs which were up or down regulated in G. vaginalis-dominated compared to L. crispatus-dominated metagenomes. The gene ontology predictions based on BV-dysregulated miRNAs identified enrichment for 88 genes previously validated as part of the HIV-host interactome facilitating infection. Gene clusters identified with highest stringency included proteasome and chaperonin pathways, virus entry receptor clusters, host signaling pathways downstream from NF-KB, TNFα, T-cell receptor and the MAPK cascade. Highest enrichment scores were achieved for the TCP-1 ring complex which interacts with the HIV Vif.

Conclusion: We identified miRNAs regulated by vaginal dysbiosis that may facilitate immune imbalance and cellular pathways associated with HIV risk.

217 LONG-TERM SEX-DIFFERENCES IN OUTCOMES FOLLOWING ACUTE HIV-1 INFECTION

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Background: Women have shown more favorable immunovirological characteristics than men around seroconversion. Here we investigated whether differences persisted under long-term antiretroviral therapy (ART) in individuals treated since acute and early HIV-1 infection (AHI).

Methods: Data was obtained for 262 women and 1783 men enrolled in the French multicenter ANRS PRIMO cohort between 1996 and 2017. We modelled the viral response, long-term immune recovery and total HIV DNA decay in the 143 women and 1126 men who initiated ART within the first three months of infection. Models were adjusted for age, geographical origin, viral load at ART initiation, time from infection to ART initiation and calendar period.

Results: The 1269 participants were mostly white (85%). The median age at AHI diagnosis was 36 years (IQR: 29–44). The median ART duration was 62 months

(IQR: 20–87). Mean pre-ART viral loads were lower in women than men, 5.2 and 5.6 log_{10} copies/mL respectively (P = 0.001). After ART initiation, women more rapidly achieved viral suppression (HIV RNA < 50 copies/mL) than men (age and pre-ART viral load adjusted hazard ratio: 1.33, 95% confidence interval 1.09 - 1.69). They also experienced a faster increase in CD4+ T-cell count and CD4:CD8 ratio during the first two months of treatment. Baseline sex-related differences in CD4+ T-cell counts were more pronounced with increasing age. This led to a sustained mean difference of +99 to +168 CD4+ T-cells/µL depending on age between women and men at 12.5 years of ART. CD4:CD8 ratio of women was persistently higher than that of men by a mean of 0.31. With long-term ART, women and men achieved similar levels of total HIV DNA (mean estimate at the last modelling point: 1.9 log_{10} copies/10^6 PBMCs after 70 months of ART for both sexes).

Conclusion: ART initiated within 3 months of AHI was associated with a larger immunological benefit in women. This benefit was sustained and more pronounced under very long-term ART, which may give women additional protection from adverse clinical outcomes and premature ageing.

218 PERSISTENT IMMUNE ACTIVATION IN HIV-1–TREATED SUBJECTS COMPARED WITH NON-HIV CONTROLS

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[1]INSERM, Le Kremlin-Bicetre, France, [2]CHU de Montpellier, Montpellier, France, [3]Hospital Beaujon AP-HP, Clichy, France, [4]Centre Hospitalier René Dubos, Pontoise, France, [5]Necker Hospital, Paris, France, [6]Cochin Hospital, Paris, France, [7]Hôpital Saint-Louis, Paris, France, [8]Hôpital Bicêtre, Le Kremlin-Bicetre, France

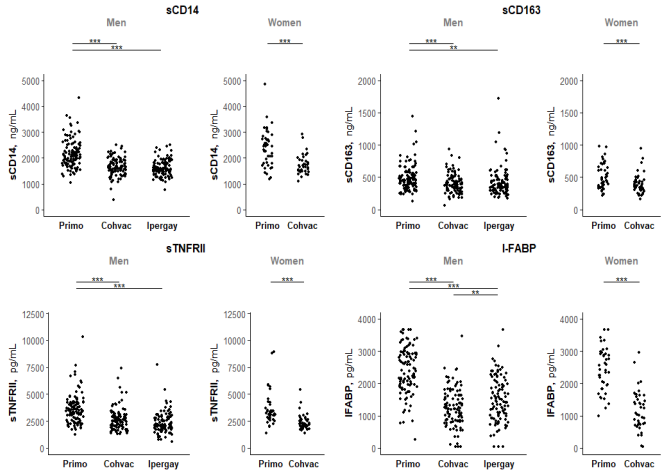
Background: Non-AIDS events under antiretroviral therapy (ART) are attributed to persistent low-grade inflammation. The magnitude of this inflammation is still discussed, partly because there is no standard value for "basal inflammation". Here we compared the inflammation profile of HIV-infected patients under long-term suppressive ART to 2 well-characterised HIV-uninfected groups, at low and high risk of HIV acquisition.

Methods: HIV participants followed since acute/early HIV infection (AHI) in the ANRS PRIMO cohort were selected if treated for ≥36 months with sustained HIV RNA<50 copies/mL and available frozen samples. Sex and age-matched controls were sampled from the ANRS IPERGAY trial of pre-exposure prophylaxis among men who have sex with men at high risk for HIV infection, and the ANRS COHVAC cohort, a long-term safety cohort of volunteers in preventive HIV-1 vaccine trials. Participants with HBV or HCV infection were excluded. We compared the three groups on plasma levels of ten biomarkers: non-specific markers of inflammation (usCRP, IL6, TNFα, sTNFRII), and markers associated with monocyte activation (sCD14, sCD163, CXCL10), gut epithelial dysfunction (I-FABP, IL17) or fibrosis (hyaluronic acid). We also measured plasma ultrasensitive HIV RNA and total HIV DNA in blood. Analyses were performed separately for men and women.

Results: 150 PRIMO subjects (108 men and 42 women) were matched with 141 COHVAC participants (100 men, 41 women) and 102 IPERGAY men. The median age was 47 years. Among PRIMO subjects, 89% had CD4 counts >500 cells/µL and 64% had an undetectable ultrasensitive viral load after a median of 6 years of ART. Smoking and alcohol use were less frequent in COHVAC participants than in the other groups. After adjusting for age, smoking, alcohol use, and body mass index, both HIV-infected men and women had higher levels of sCD14, sCD163, CXCL10, sTNFRII and I-FABP than their non-HIV counterparts. When comparing the two non-HIV groups, IPERGAY men had significantly higher levels of IL17 and TNFα than COHVAC men. Inflammatory levels in HIV subjects were not associated with time since AHI diagnosis, cumulative ART duration, delay of ART initiation, residual viral replication and HIV DNA levels.

Conclusion: After a median of 6 years under ART, HIV-infected participants maintained high levels of monocyte activation and gut epithelial dysfunction.

Figure 1. Inflammatory levels by HIV status and sex



HIV-infected participants are from the ANRS Primo cohort (108 men, 42 women).

HIV-negative controls are from the ANRS Ipergay trial (102 men) and the ANRS Cohvac cohort (100 men, 41 women).

Intergroup comparisons were performed using linear regression, adjusted for age and stratified by sex. **P < .01; ***P < .001.

219 SOCS PROTEINS AND JAK-STAT PATHWAY DYSREGULATION IN SIV-INFECTED SUPPRESSED MACAQUES

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Background: Suppressor of cytokine signaling (SOCS) is a family of proteins upregulated rapidly in response to stimulation by Toll-like receptors, cytokines, grow factors and hormones that provide a negative feedback to the stimulation that triggered them by inhibiting the JAK-STAT signaling pathway. SOCS proteins, in particular SOCS3, have also been described as having a central role in metabolic syndrome, diabetes and atherosclerosis. In vivo data for SOCS levels in HIV-infected patients are very limited.

Methods: Using intracellular staining (ICS) and flow cytometric analyses, we evaluated the expression kinetics of SOCS1 and SOCS3 proteins and their activity by measuring the percentages and the accumulation level, estimated via MFI, of SOCS1, SOCS3, TLRs, IFNs and other JAK-STAT signaling pathway-related proteins in individual subpopulations of blood and lymph node MNC, harvested at day 0, peak of infection, and week 20, and 60 from SIV-infected Rhesus macaques left untreated, treated with ART or ART+p38MAPK inhibitor. Boolean data analysis permitted the evaluation of co-expression of the above proteins.

Results: In the context of untreated or treated chronic HIV or SIV infection, a persistent but aberrant activation of SOCS proteins and their targets is an important feature of the dysfunctional TLR-IFN-SOCS pathway. The percentage of SOCS+ cells remains higher than at peak viremia after 54-59 weeks of ART despite virus suppression and its expression does not correlate with viral loads. SOCS1 and SOCS3 expression is elevated in virtually all mononuclear cell subpopulations yet the inhibition of their targets JAK and STAT is not complete and markers of innate immunity that should be impacted by SOCS activity remain elevated.

Conclusion: Persistent SOCS protein expression during suppressed SIV infection supports the existence of additional stimulation that maintains their expression and/or dysregulation of their negative feedback. Incomplete JAK-STAT pathway suppression by SOCS proteins is consistent with residual activation of innate immunity pathways and dysregulation of antiviral immunity. Given the association of their expression with metabolic conditions, SOCS protein chronic activation could be also relevant to the metabolic complications observed in ART patients.

220 EFFECT OF HIV SUPPRESSION ON CYTOKINES IN BLOOD AND SEMINAL PLASMA

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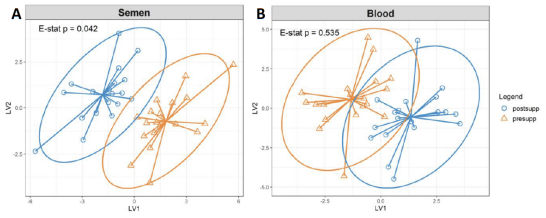
Background: HIV infection disrupts the cytokine network and it remains disrupted after HIV is suppressed by ART. Characterization of this continuing disruption in genital secretions is important for understanding the mechanisms of HIV sexual transmission. Therefore, we undertook to determine the cytokine

network in individuals longitudinally sampled before they began antiretroviral therapy (ART) and after achieving suppression of HIV RNA.

Methods: Concentrations of 34 cytokine/chemokines were measured by multiplex-bead assay in longitudinal blood and seminal plasma from 20 men with HIV from a well-studied cohort with banked blood and seminal samples when viremic and suppressed. We used Partial Least Squares Discriminant Analysis (PLS-DA) to visualize the difference in cytokine pattern between the time points and rank the relative importance of cytokines for determining suppression status. Any cytokines with Variable Importance on PLS Projections (VIP) scores exceeding 1 were deemed important in predicting suppression status and were subsequently tested using Wilcoxon Signed Rank Tests.

Results: Baseline characteristics of our cohort included median age of 33 years (IQR 27-41), median CD4+ T cell count 702/μL (range 324-997), and median pre-ART HIV viral loads in blood $\log_{10}$ 4.7 (range 2.8-6.6). Significant overlap of the PLS-DA projections in blood suggested no significant difference in the overall cytokine network after suppression of viremia, even though individual cytokines changed in line with published findings from other studies. However, the projections are significantly different in seminal plasma, highlighting the importance of immune activation in this compartment. When tested individually, four cytokines were significantly different across time points in semen (MIG, IL-15, and IL-7: all $p < 0.001$; ITAC: $p = 0.019$), while only two were significantly different across time points in blood (MIG and IP-10, both $p = 0.006$).

Conclusion: Our study demonstrates that viral suppression with ART has the most significant decrease in the inflammatory milieu in seminal plasma, while the overall effect on the network of cytokines in the blood is weaker. These results identify specific changes in the cytokine networks in semen and blood—consistent with prior reports—as the immune system acclimates to chronic, suppressed HIV infection and they highlight the utility of novel statistical methods in the analysis of large data sets of cytokine measurements.



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Sample Type	Cytokine	VIP	Adjusted P
Seminal plasma	MIG	1.76	<0.001*
	IL-15	1.86	<0.001*
	IL-7	1.79	<0.001*
	ITAC	1.50	0.019*
	IP-10	1.04	0.112
	M-CSF	1.33	0.169
	Eotaxin	1.24	0.084
	cmvIL-10	1.49	0.158
	IL-12	1.56	0.081
Blood	IP-10	2.14	0.006*
	MIG	2.15	0.006*
	IL-18	1.40	0.14
	IL-16	1.22	0.182
	ITAC	1.77	0.164
	MIP-1β	1.00	0.182
	MCP-1	1.29	0.464

Figure: PLS-DA projections of cytokine networks in semen **(A)** and blood **(B)** before (orange ellipse) and after (blue) HIV suppression. To view the data differently, individual cytokines are plotted on the same latent variables for semen **(C)** and blood **(D)** with the Variable Importance on PLS Projections (VIP) value for each cytokine indicated by color of the dot, with red being higher VIPs. **(E)** shows results of Wilcoxon Signed Rank Test for cytokines with VIP > 1 in each respective sample type. Shaded values have adjusted P value > 0.05.

221 MARKERS OF IMMUNE ACTIVATION AND FUNCTION IN OBESE AND NONOBESE SUBJECTS WITH HIV

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Background: Obesity is an emerging health issue in people with HIV (PWH). Both obesity and HIV are associated with systemic inflammation contributing to metabolic and cardiovascular complications. How obesity impacts on immune-mediated inflammation in PWH is unclear. We analysed differences in markers of inflammation and immune activation in obese and non-obese PWH.

Methods: We recruited PWH with and without obesity (BMI>30 kg/m_2) from the UCD ID Cohort, a multicentre prospective cohort, in a ratio of 1:2, obese versus non-obese, matched for age, gender and ethnicity. In a bead-based, multiplex, quantitative ELISA we measured 25 plasma biomarkers covering pathways related to systemic inflammation (hsCRP, IL-2, IL-6, TNFR1, TNFR2, TNF-α, IL-1β), coagulation (vWF, D-dimer, sCD40L), endothelial function (E-selectin, P-selectin, sICAM-1, VCAM), atherosclerosis (MPO, Lp-PLA2), immune regulation (IL-4, IL-1RA), innate immune activation (MIP-1, MCP-1, sCD163, sCD14) and microbial translocation (IL-18, LBP). We explored associations between biomarkers and obesity using logistic regression adjusted for age, gender, ethnicity, smoking status, NRTI backbone and use of INSTI. Data are median [IQR] or odds ratio (OR) [95% CI]

Results: We included 99 PWH on ART, 33 obese (BMI 33.6;[30.7, 45.5] Kg/m_2), age 41 [36, 48] years; 45% African with 54% and 56% men in the obese and non-obese groups. Overall 63% were heterosexual, 18% MSM and 8% IDU; 94% had HIV-RNA <40 cps/mL. Use of INSTI was 57% vs 38%, and TAF 36% vs 33% in obese and non-obese. 9 markers were significantly associated with obesity in adjusted analyses: hsCRP (OR 2.1, [1.4,3.1]), IL-6 (2.18, [1.2,4.1]), TNF-α (3.9, [1.3,11.6]), TNFR2 (2.19, [1.0,4.7]), vWF (4.64, [4.6,14.5]), E-selectin (5.52, [1.3,23.6]), MPO (3.95, [1.3,12.0]), IL-4 (1.04, [1.0,1.1]), IL-1RA (6.31, [2.4,16.5]). Obese phenotype was characterised by increases in markers of systemic inflammation, coagulation and endothelial function rather than innate immune activation or microbial translocation (Fig 1)

Conclusion: In the first study of biological patterns of inflammation in obese PWH, obese phenotype was associated with increases in systemic inflammatory, vascular and coagulation pathways, rather than in innate immune activation or microbial translocation, previously associated with HIV infection. Whether these distinct patterns of inflammation contribute to greater risk of comorbidities in obese PWH remains to be determined

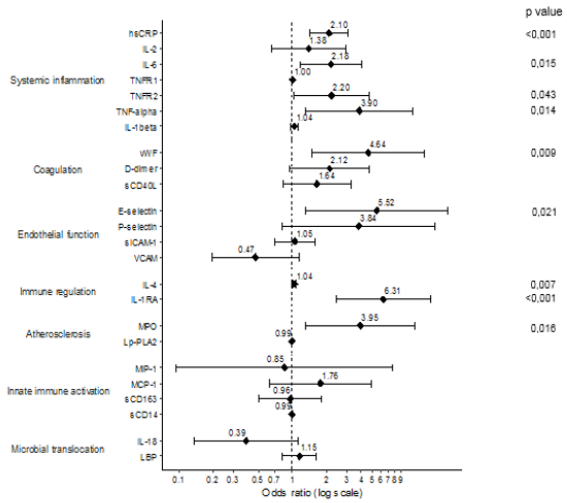


Figure 1. Forest Plot: association between biomarkers and obese phenotype, adjusted for age, gender, ethnicity, smoking status, INSTI and NRTI backbone. Odds ratios and p values for the statistically significant associations are shown. hsCRP: high-sensitivity C-reactive protein; TNF-α: tumor necrosis factor alpha; TNFR: TNF receptor; vWF: von Willebrand factor; sCD40L: soluble CD40 ligand; sICAM-1: soluble intercellular adhesion molecule 1; VCAM: vascular cell adhesion molecule; MPO: myeloperoxidase; Lp-PLA2: lipoprotein-associated phospholipase A2; IL-1RA: interlukin-1 receptor antagonist; MIP-1: macrophage inflammatory protein 1; MCP-1:monocyte chemoattractant protein 1; LBP: lipopolysaccharide binding protein.

222 RESIDUAL IMMUNE ACTIVATION IN AFRICANS ON ART PREDICTS CD4 RECOVERY AND VIRAL REBOUND

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Background: There are limited data on the clinical implications of persistent chronic immune dysregulation in HIV-1-infected African populations on suppressive antiretroviral therapy (ART). We investigated the prognostic value of elevated plasma immune biomarkers, during suppressive ART, in predicting impaired CD4 T-cell recovery and virological rebound during 6 years of follow-up.
Methods: In a multi-country African adult cohort, we measured 8 selected systemic biomarkers (IL-6, IP-10/CXCL10, MCP-1/CCL2, MIG/CXCL9, LBP, CRP, sCD163, and sCD14) in 398 participants with suppressed plasma HIV-RNA (<50 cps/mL) after 12 months of non-nucleoside reverse-transcriptase inhibitor-based ART. We estimated associations between each of the month-12 biomarkers and 2 long-term outcomes: 1) CD4 T-cell recovery, using a multivariable linear mixed model; and 2) virological rebound (defined as single HIV-RNA>1000 cps/mL), using multivariable interval-censored survival analysis.
Results: 229 participants (58%) were female, median age was 37 years (IQR 33-43), and country of origin was Kenya (n=92), Nigeria (n=57), South Africa (n=65), Uganda (n=121) and Zambia (n=63). Median CD4 T-cell count rose from 291 cells/µL (IQR 216-395) at month 12 to 458 cells/µL (IQR 340-602) at month 72. Participants with elevated levels of sCD14 (coefficient -83.38, 95%CI -163.49 to -3.27; p=0.041), IP-10 (-46.79, 95%CI -95.05 to 1.47; p=0.057), MIG (-34.78, 95%CI -67.27 to -2.29; p=0.036), and CRP (-28.49, 95%CI -45.95 to -11.04; p=0.001) were more likely to experience impaired CD4 T-cell recovery. From month 12 after ART initiation onwards, we recorded 1148 person-years of follow-up, with 47 events of virological rebound (incidence rate of 40.9, 95%CI 30.8-54.5, per 1000 person-years). Risk of virological rebound was increased for participants with an elevated IP-10 level (hazard ratio [HR] 1.81 per $\log_{10}$ pg/mL unit increase, 95%CI 1.03-3.18; p=0.038), and reduced for those with an elevated MCP-1 level (HR 0.25 per $\log_{10}$ pg/mL unit increase, 95%CI 0.07-0.87; p=0.030). None of the other biomarkers were significantly associated (figure).
Conclusion: Persistent systemic inflammation and immune activation during suppressive ART was associated with impaired long-term CD4 T-cell recovery and virological rebound; the counterintuitive MCP-1 association requires further investigation. Further research needs to explore the potential for adjunct therapies targeting relevant inflammatory pathways.

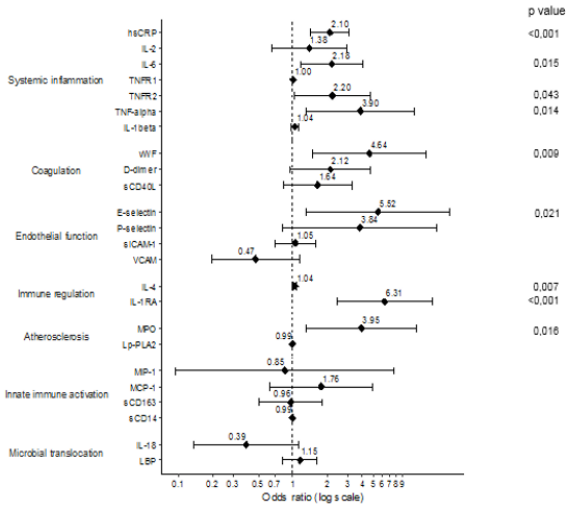


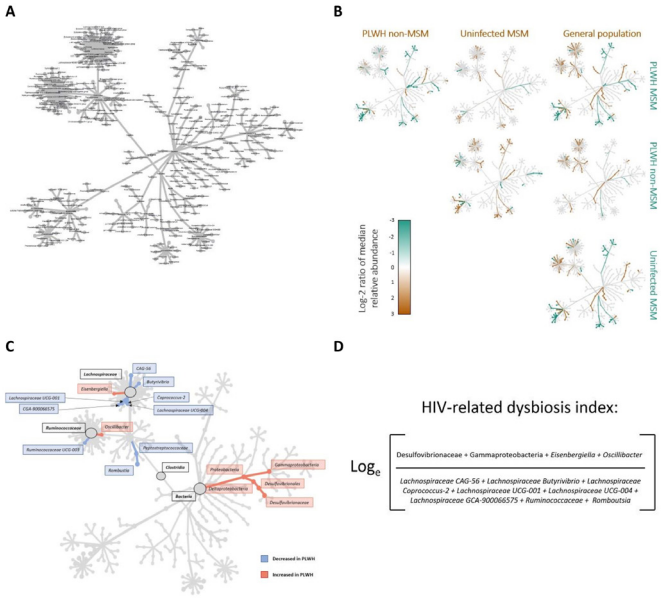
Figure 1. Forest Plot: association between biomarkers and obese phenotype, adjusted for age, gender, ethnicity, smoking status, INSTI and NRTI backbone. Odds ratios and p values for the statistically significant associations are shown. hsCRP: high-sensitivity C-reactive protein; TNF-α: tumor necrosis factor alpha; TNFR: TNF receptor; vWF: von Willebrand factor; sCD40L: soluble CD40 ligand; sICAM-1: soluble intercellular adhesion molecule 1; VCAM: vascular cell adhesion molecule; MPO: myeloperoxidase; Lp-PLA2: lipoprotein-associated phospholipase A2; IL-1RA: interlukin-1 receptor antagonist; MIP-1: macrophage inflammatory protein 1; MCP-1:monocyte chemoattractant protein 1; LBP: lipopolysaccharide binding protein.

223 HIV-RELATED MICROBIOME, PREVIOUS IMMUNODEFICIENCY, AND EXCESS METABOLIC RISK

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Background: We aimed to identify an HIV-related microbiota signature, independent of sexual preferences and demographic confounders, to assess a possible impact of the microbiome on metabolic comorbidities.
Methods: 405 HIV-infected and 111 uninfected individuals, stratified to sexual behaviour (men who have sex with men, MSM and non-MSM), were included from the COCOMO study. Stool samples were analyzed using 16S rRNA sequencing. Hypotheses were tested using regression models adjusting for known confounders.
Results: Microbiota alterations in HIV-positive MSM and uninfected MSM were largely overlapping. After filtering out MSM-associated microbiota traits and adjusting for relevant confounders, we identified an HIV-related dysbiosis, consisting of lower biodiversity, increased relative abundance of Gammaproteobacteria and Desulfovibrionaceae and decrease in several Clostridia (Figure 1). HIV-related dysbiosis was associated with previous immunodeficiency (low nadir CD4), elevated microbial translocation markers (soluble CD14 and LPS-binding protein, p<0.05), and a 2-fold (adjusted Odds Ratio (aOR) 1.97 [1.12; 3.46]) increased excess risk of metabolic syndrome, the latter driven by increase in Desulfovibrionaceae and decrease in several Clostridia of the Lachnospiraceae and Ruminococcaceae families (Butyrivibrio, Coprococcus-2, Lachnospiraceae UCG-001 and CAG-56). In individuals with a history of AIDS, this microbiota profile was associated with 8-fold (aOR 8.14 [1.74; 38.07]) excess risk of metabolic syndrome and 6-fold (aOR 6.71 [1.35; 33.50]) excess risk of abdominal obesity.
Conclusion: HIV infection was associated with altered bacterial composition, independently of sexual behaviour and demographic factors. HIV-related dysbiosis was associated with increased risk of metabolic syndrome, particularly in individuals with previous severe immunodeficiency. The excess metabolic risk was driven by increased Desulfovibrionaceae, H2S-producing bacteria with toxic effects on the gut epithelium, and decrease of potentially butyrate-producing Clostridia. As outgrowth of Desulfovibrio and reduction in Clostridia have been shown to trigger metabolic alterations in immunodeficient mice, our findings suggest a potential interplay between HIV-related dysbiosis, previous immunodeficiency and future risk of metabolic comorbidities.

Figure 1. Identification of HIV-related microbiome changes



224 ALTERED GUT MICROBIOTA AND HOST LIPID METABOLITE PROFILES IN HIV INFECTION

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Alterations in gut microbiota (GMB) and host blood metabolite profiles have been noted in people living with HIV (PWV). However, it remains unclear

whether alterations in GMB and related functional groups may contribute to disrupted host metabolite profiles in PWV.

Methods: This study included 185 women (128 with long-standing HIV infection, 88% under antiretroviral therapy; and 57 HIV-uninfected women from the same geographic location with comparable characteristics) from the Women's Interagency HIV Study. Stool samples were analyzed by 16S rRNA V4 region sequencing. GMB function was inferred by PICRUSt. Plasma metabolomic profiling (133 metabolites including amino acids, biogenic amines, acylcarnitines and lipids) was performed using liquid chromatography tandem mass spectrometry. Linear discriminant analysis effect size (LefSe) and partial least squares discriminant analysis (PLSDA) were used to identify GMB and plasma metabolite signatures of HIV infection, respectively.

Results: LefSe identified four predominant bacterial genera associated with HIV infection, with higher abundances of Ruminococcus and Oscillospira and lower abundances of Bifidobacterium and Collinsella in HIV-infected women compared to HIV-uninfected women. PLSDA revealed a distinct plasma metabolite profile (Figure 1A) for HIV-infected women, featured with elevated glycerophospholipid levels, compared to HIV-uninfected women. The two HIV-increased bacterial genera, notably Ruminococcus, showed positive correlations with plasma glycerophospholipids but not with amino acids or biogenic amines (Figure 1B). The two HIV-decreased microbial genera, Bifidobacterium and Collinsella, showed little correlation with plasma metabolites. Functional analyses also indicated that GMB lipid metabolism was enriched in HIV-infected women. Ruminococcus and Oscillospira were among the top bacterial genera that contribute to the GMB glycerophospholipid metabolism pathway and showed positive correlations with host plasma glycerophospholipid levels. One bacterial functional capacity in the acetate/propionate biosynthesis pathway was identified to be mainly contributed by Bifidobacterium.

Conclusion: Our integrative analyses suggested that altered gut microbiota with related functional capacities are associated with disrupted plasma metabolite profiles in HIV-infected women.

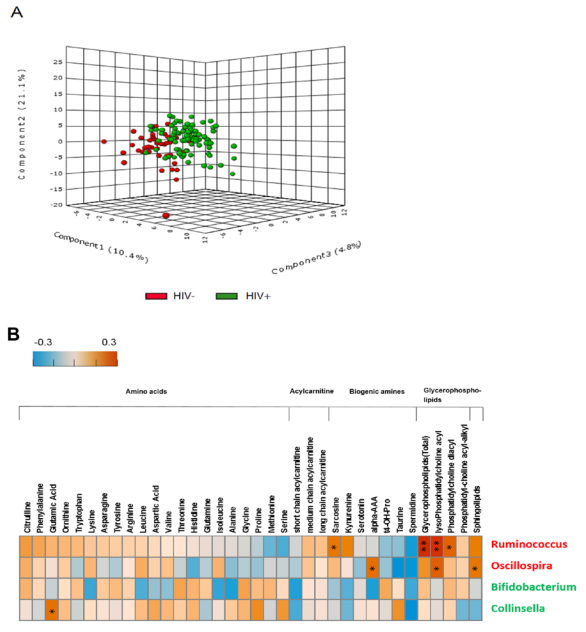


Figure 1 HIV infection, gut bacterial genera and host plasma metabolites.

(A). Plasma metabolomic profiles and HIV infection. Three dimensional Partial Least Square-Discriminant Analysis (PLSDA) score plot by HIV status, based on 133 plasma metabolites.

(B). Correlations between four HIV-associated bacterial genera and plasma metabolites. Red and green labels depict bacterial genera which showed increased and decreased relative abundance in HIV-infected individuals. The glycerophospholipid column represents total plasma glycerophospholipid concentration (sum of all glycerophospholipid species); the lysoPhosphatidyl-choline acyl, phosphatidyl-choline diacyl, and phosphatidyl-choline acyl-alkyl columns represent the total concentration for each glycerophospholipid sub-category, respectively. **P<0.01; *P<0.05.

225 ART REVERSES LOSS OF DIVERSITY & RICHNESS OF INTESTINAL MICROBIOME IN HIV+ NAIVE

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Background: Changes in the intestinal microbiome, known as dysbiosis, and its metabolites promote inflammation and systemic immune activation in persons living with HIV, which may contribute to the persistence of HIV during ART.

Methods: To define the major factors that drive dysbiosis we contrasted the diversity and composition of the fecal microbiome of persons living with HIV before beginning ART (HIV+ naïve; 13 patients) with those on ART (57 patients) for 133 months (HIV+ ART+) by16S rRNA sequencing. Results were compared to the microbiome in 55 healthy HIV-uninfected controls.

Results: Overall, 76 % were males of median age of 44. Groups were similar in demographics. HIV+ ART+ had a median CD4 count of 685 and 88% had HIV-1 RNA of < 20. Principal component analysis (PCA) of the intestinal microbiome at the phylum level reveals that b-diversity of the microbial composition in HIV+ naïve and HIV+ ART+ individuals is similar and quite distinct from the uninfected controls. Individual a-diversity, as measured by the Shannon index, and richness, reported by the Chao-1 index, are decreased in HIV+ naive patients (p=0.009) and are partially reversed after ART treatment. However, the balance in the abundance of the core microbiota, Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, and Verrucomicrobia, distinguishes HIV+ naïve from HIV+ ART+ individuals. The HIV+ naïve population exhibits decreased Actinobacteria (p = 0.04) and Proteobacteria (p=0.009) compared to the uninfected group. The decrease in abundance of these communities in the HIV+ naïve group is exchanged for a significant increase in Actinobacteria (p=0.008) and Firmicutes (p=0.008), and a decrease in Bacteroidetes (p=0.001), thereby seemingly normalizing bacterial diversity, but not composition in HIV+ ART+ individuals.

Conclusion: These results indicate that HIV reduces the diversity and breadth of microbes in the intestine and that after ART, the diversity of the microbiota increases due to an undergrowth of Bacteroidetes and excess colonization by Actinobacteria and Firmicutes.

226 MICROBIOTA MODULATES HIV TARGET-CELL LEVELS AT SITES OF MUCOSAL HIV ACQUISITION

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Background: Most HIV infections are acquired at the mucosa of the gut or female genital tract (FGT). Given that resident microbiota regulate mucosal immune homeostasis, we hypothesized that microbiota modulates HIV target cell levels at these sites of HIV transmission which could affect HIV acquisition, pathogenesis, persistence, and PrEP efficacy.

Methods: We used bone marrow/liver/thymus (BLT) humanized mice to examine the effect of microbiota on HIV target cell levels in the gut and FGT. The systemic presence of human immune cells in BLT mice including the gut and FGT is well documented. Specifically, we bioengineered germ-free (GF) BLT humanized mice using rederived GF immunodeficient NSG mice. GF NSG mice were implanted with human thymus/liver tissue and transplanted with autologous stem cells in a GF surgical isolator. The GF status of mice was monitored by the National Gnotobiotic Rodent Resource Center. BLT mice colonized with microbiome were also constructed. To directly evaluate the effect of microbiota on HIV target cell levels in the gut and FGT, we quantitated the number of human CD4+ T cells and myeloid cells in both models with flow cytometry. We also quantitated the number of CCR5+ CD4+ T cells and activated (HLA-DR+CD38+) CD4+ T cells in the gut. We analyzed the small intestine (S), cecum (C), and large intestine (L) intraepithelial (IEL) and lamina propria (LPL) layers separately.

Results: Numbers of human CD4+ T cells were higher in the SIEL (p=0.0001), SLPL (p=0.0009), CIEL (p=0.0232), LIEL (p=0.0005), and LLPL (p=0.0015) of colonized BLT mice compared to GF BLT mice. Numbers of CCR5+ CD4+ T cells were consistently higher in the gut of colonized BLT mice (SIEL p=0.0002, SLPL p=0.0401, CIEL p=0.0004, CLPL p=0.014, LIEL p=0.0005, LLPL p=0.0022). The presence of microbiome also resulted in higher numbers of activated CD4+ T cells in the SIEL (p=0.0011), SLPL (p=0.0279), and CIEL (p=0.0364). Higher numbers of human myeloid cells were observed in the SIEL (p=0.0015) and SLPL (p=0.0005) of colonized BLT mice. In the FGT, the presence of microbiome resulted in higher numbers of human CD4+ T cells (p=0.0079) but had no effect on human myeloid cell levels.

Conclusion: Our results provide direct evidence that microbiota modulate HIV target cell levels and in particular, CD4+ T cell levels at key mucosal sites of HIV acquisition.

227 KEY FEATURES OF GUT-MICROBIAL DYSBIOSIS IDENTIFIED IN ALCOHOLIC HIV-1 PATIENTS

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Background: Heavy alcohol drinking and HIV-1 infection are independently associated with the development of gut-microbial dysbiosis and increase in intestinal permeability and microbial translocation. These gut-associated events are major pathogenic factors driving local and systemic inflammation and development of comorbidities. Significantly, the combinatorial effects of HIV-1 infection with a history of heavy alcohol consumption have not been determined. We will evaluate the qualitative and quantitative changes occurring in the gut microbiome (dysbiosis) associated with heavy alcohol consumption in people living with HIV (PLWH)

Methods: Fecal samples were obtained, from 102 participants in the St PETER (Russia) HIV and alcohol use cohort (RCHIV-Alc). Metagenomics analysis of the 16S rRNA gene was done by amplification of V3-V5 regions, on the Illumina MiSeq platform. Operational taxonomic units (OTUs) tables profiling microbiome were generated using QIIME. Important statistical analyses included LEfSe (Linear discriminant analysis Effect Size), Pearson's correlation, multivariate analysis, Mann- Whitney U test and ANOVA with Tukeys correction. Cytokine levels were determined using the MSD platform

Results: Metagenomics analysis revealed that as compared to control, RCHIV-Alc patients showed a major loss of butyrate producing bacteria. This loss correlated with a decrease in microbial diversity and F/B ratio along with an increase in immune activation and inflammation markers sCD14, IL6 and MIP-1b (Table 1A,B). Further, LEfSe analysis determined that there was a significant enrichment of pathogenic Enterobacteriaceae (LDA score > 1.5, $p < 0.05$), only in very heavy alcohol drinking RCHIV-Alc patients with an AUDIT score≥20 (Table 1A). Significantly, this increase in Enterobacteriaceae also correlated with a decrease in microbial diversity and CD4+ counts along with a concomitant increase in viral load and TNFa, IFNg, IL-6, IL-8, MCP-1, MIP-3a and sCD14(Table1B)

Conclusion: The study identifies a significant loss of butyrate producing bacteria in RCHIV-Alc patients. Notably, in a subset of HIV patients with very heavy alcohol use (AUDIT score≥20) the gut microbial dysbiosis is further characterized by a significant enrichment of "pro-inflammatory" Gram negative bacteria represented by Enterobacteriaceae. These findings identify the characteristics of gut microbial dysbiosis occurring in response to the combinatorial effects of alcohol and HIV-1 infection that can adversely affect HIV-1 pathogenesis

TABLE 1: Significant features of gut-microbial dysbiosis in RCHIV-Alc patients

Table 1A

Comparsion	Results	pvalue
RCHIV-Alc versus Normal (non-HIV, non-Alc)	↓ in alpha diversity	p<0.00001
RCHIV-Alc versus Normal (non-HIV, non-Alc)	↑ in *Bacteroidetes* (B)	p<0.0001
RCHIV-Alc versus Normal (non-HIV, non-Alc)	↑ in *Proteobacteria*	p<0.0001
RCHIV-Alc versus Normal (non-HIV, non-Alc)	↓ in Firmicutes (F)	p<0.0001
RCHIV-Alc versus Normal (non-HIV, non-Alc)	↓ in F/B	p<0.05
RCHIV-Alc versus Normal (non-HIV, non-Alc)	↑ in Intestinal fatty acid binding protein	p<0.001
RCHIV-Alc versus Normal (non-HIV, non-Alc)	↓ in butyrate producing families	p<0.05
RCHIV-Alc versus Normal (non-HIV, non-Alc)	↓ in butyrate synthesizing genes	p<0.05
Within RCHIV-Alc: Audit >=20 versus Audit <20	Expansion of *Enterobacteriaceae*	p<0.05
Within RCHIV-Alc: FIB4>1.5 versus FIB4<1.5	Expansion of *Enterobacteriaceae*	p<0.05
Within RCHIV-Alc: HVL(log10)>3 versus HVL(log10)<3	Expansion of *Enterobacteriaceae*	p<0.05
Within RCHIV-Alc: CD4<500 versus CD4>500	Expansion of *Enterobacteriaceae*	p<0.05
Statistical Analysis- Multivariate analysis, Mann-Whitney U Test, ANOVA with Tukeys Correction and LEfSe		

Table 1B

Pearsons Correlation Analysis x-axis	y-axis	Type of correlation	r^2	p-value
Relative abundance of *Enterobacteriacea* (only in Audit >=20)	sCD14 (ng/ml)	Direct	0.50	p<0.0001
Relative abundance of *Enterobacteriacea* (only in Audit >=20)	TNFα (pg/ml)	Direct	0.25	p<0.01
Relative abundance of *Enterobacteriacea* (only in Audit >=20)	IFN-γ (pg/ml)	Direct	0.30	p<0.01
Relative abundance of *Enterobacteriacea* (only in Audit >=20)	IL6 (pg/ml)	Direct	0.33	p<0.001
Relative abundance of *Enterobacteriacea* (only in Audit >=20)	IL8 (pg/ml)	Direct	0.23	p<0.01
Relative abundance of *Enterobacteriacea* (only in Audit >=20)	MCP-1 (pg/ml)	Direct	0.20	p<0.05
Relative abundance of *Enterobacteriacea* (only in Audit >=20)	MIP-3α (pg/ml)	Direct	0.20	p<0.05
Relative abundance of butyrate producing families (all RCHIV-Alc)	F/B	Direct	0.53	p<0.0001
Relative abundance of butyrate producing families (all RCHIV-Alc)	Chao1 Index	Direct	0.34	p<0.0001
Relative abundance of butyrate producing families (all RCHIV-Alc)	OTUs	Direct	0.40	p<0.0001
Relative abundance of butyrate producing families (all RCHIV-Alc)	Shannon Index	Direct	0.50	p<0.0001
Relative abundance of butyrate producing families (all RCHIV-Alc)	sCD14 (ng/ml)	Inverse	0.06	p<0.05
Relative abundance of butyrate producing families (all RCHIV-Alc)	IL6 (pg/ml)	Inverse	0.10	p<0.05
Relative abundance of butyrate producing families (all RCHIV-Alc)	MIP-1β (pg/ml)	Inverse	0.10	p<0.05

228 PREVOTELLA IS RELATED TO A DYSREGULATION OF IFN AND T-CELL RESPONSE IN HIV INFECTION

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Background: Altered interplay between gut mucosa and dysbiotic microbes during HIV infection has been linked to chronic immune dysfunction, commonly characterized by high levels of IFN and immune activation markers as well as by a severe depletion of Th17 T cells in the gastrointestinal tract. We hypothesized that a specific gut microbial communities imbalance in HIV-infected individuals could affect the antiviral defense and T cell immunity.

Methods: Ten HIV-infected subjects on long-term suppressive combined antiretroviral therapy (cART) underwent endoscopic procedures and blood collection. Lamina propria lymphocytes were isolated from five different intestinal sites (e.g. terminal ileum, cecum, ascending, transverse, and descending colon). Phylum, Family, Class, Order and Genus identification was performed on bacterial 16S ribosomal DNA sequences obtained from fecal samples collected for all patients. Measurements of CD4 and CD8 T cell activation (CD38+, HLA-DR+, CD38+HLADR+) and IFNγ and IL-17 expression on both CD4+ (Th1, Th17) were performed by flow cytometry. Gene expression level of IFNβ, IFN receptor 1(IFNAR1) and the well-known Interferon Stimulated Gene(ISG), Myxovirus resistance gene A(MxA), was also evaluated in both anatomical sites by RT/real-time PCR. Nonparametric t-tests were used for statistical analysis.

Results: Fecal microbiota analyses confirmed that all HIV-1 individuals showed a distinct pattern of gut microbiota composition characterized by elevated levels of the genus Prevotella(relative abundance of 6.10%). Abundance of Prevotella was directly correlated with CD4+38+, CD4+DR+ and CD4+38+DR+ in both peripheral blood and gut ($p<0.05$ for all these measures). Additionally, the same trend was observed for the activated CD8+ T cell subsets in both compartments. By contrast,Prevotella levels were inversely associated with the frequencies of Th17 T cells in blood (R=-0,454, p=0,00005)and in gut compartment (R=-0,284, p=0.01). Notably, higher levels of IFNβ(R=-0.662, p=0.042), MxA(R=-0.774, p=0.012), and IFNAR1(R=-0.662, p=0.042), were associated to lower abundance of the genus Prevotella in the gut mucosa.

Conclusion: Our findings suggest that abundance of the genus Prevotella could affect gut mucosal type I IFN pathways and modify T cell response in HIV-infected subjects.

229 ANTIINFLAMMATORY EFFECT OF METFORMIN ON MICROBIOTA IN NONDIABETIC PEOPLE WITH HIV

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Background: People living with HIV (PLWH) on antiretroviral therapy (ART) remain at increased risks of inflammatory comorbidities. Metformin, an anti-diabetic drug with anti-aging effect, was shown to decrease inflammation by improving glucose metabolism and changing gut microbiota composition in diabetic people. Herein, we report results from the LILAC (CIHR/CTN PT027) clinical trial evaluating the effect of 12 weeks of metformin on blood/gut inflammation and gut microbial composition in PLWH on ART.

Methods: A total of 22 non-diabetic (HbA1c <6%) PLWH, on ART with viral load <50 copies/ml for more than 3 years and CD4/CD8 ratio ≤0.7, received 12 weeks of metformin 850 mg bid. Blood and stools were collected at baseline (V1), after 12 weeks of metformin (V2), and 12 weeks after metformin discontinuation (V3). Soluble CD14 was measured in plasma. DNA was extracted from stools and 16S rRNA sequenced. Bacterial microbiota composition variations were analyzed using LefSe. Serum short chain fatty acids (SCFA) were measured by LC-MS. The beneficial Akkermansia muciniphila, enriched in stools of diabetic people initiating metformin, was quantified by qPCR.

Results: CD4 T-cell count, CD4/CD8 and HbA1c levels did not vary between visits, however plasma sCD14 levels decreased at V2 and V3 compared to V1.

Bacterial alpha diversity tended to increase at V2 and V3. However, we observed a significant increase of Escherichia/Shigella and Lachnoclostridium and a decrease of Collinsella abundance at V2 compared to V1. The abundance of Lachnospiraceae, which are specialized in butyrate production, was increased at V3 compared to V1. Accordingly, we found increased serum butyrate/isobutyrate levels at V2 and V3 compared to V1. No differences were observed for other SCFA propionate, succinate and methylmalonate. A. muciniphila abundance remained stable between visits.
Conclusion: A 12-week metformin therapy in non-diabetic PLWH on ART decreased plasma levels of the inflammation marker sCD14 in association with an enrichment of butyrate-producing bacteria in stools and increased serum butyrate levels. To confirm our study findings, a longer metformin treatment should be conducted in non-diabetic PLWH.

230 FUNCTIONAL RESTORING OF GUT BARRIER AFTER MODULATION OF INTESTINAL MICROBIOTA

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Background: A complex series of events starting from enterocytes modifications, mucosal immune dysfunction, damage to the intestinal epithelial barrier, microbial translocation, and chronic systemic immune activation, contribute to HIV disease progression. This study aimed to verify whether the modulation of microbiota plays a role in restoring the intestinal barrier integrity focusing on cellular morphology, cellular apoptosis machinery and mitochondrial restoring.
Methods: 10 Caucasian cART-treated HIV-1+ patients and 10 healthy age and gender matched controls were recruited at the Department of Public Health and Infectious Diseases, Sapienza University of Rome (Italy). HIV+ participants received for six months two sachets, each containing 450 × 109 billion bacteria, twice a day of Vivomixx®. All patients underwent to pancolonoscopy and blood sampling before (T0) and after 6 months of probiotic supplementation (T6). Cellular morphology, cellular apoptosis machinery and mitochondrial restoring were analyzed in mucosal biopsies taken from different colonic tracts of intestine at T0 and T6.
Results: After the probiotic administration, sections of intestinal mucosa showed an improvement of epithelial integrity and a reduction of diffuse interstitial inflammatory infiltrate. The rate of enterocytes, undergoing apoptosis both in epithelium and intestinal crypts, was significantly reduced at T6 ($p=0.04$). Mitochondria number and size differed from the 2 groups of patients ($p>0.05$): samples taken at T6 showed significant increased number of larger mitochondria and the levels of these organelles were similar to healthy samples ($p>0.05$).Ultrastructural morphological data regarding mitochondria were confirmed by mt-DNA evaluation at T6 that indicated an increase concentration of mitochondria in all tested patients ($p<0.005$) and a similar trend for CYCC concentration ($p<0.005$), with substantial reduction of HSP60 and 70 m-RNA expression in mucosal biopsies ($p<0.005$). LPS and cCK18 plasma levels significantly decreased at T6 ($p<0.05$).
Conclusion: The modulation of intestinal microbiota ameliorates histopathologic alterations characterizing HIV enteropathy, reducing inflammatory cells infiltration,villous blunting and widening, vacuolated enterocytes, crypt hyperplasia. All these data are in accord with a decrease in LPS and cCK18 plasma levels after probiotic supplementation, respect to levels that were observed at baseline.

231 CELLULAR STRESS BIOMARKERS ARE ASSOCIATED WITH MARKERS OF MICROBIAL TRANSLOCATION

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Background: Microbes and microbe components that translocate from the lumen of the GI tract can directly stimulate the immune system and contribute to inflammation. Given that microbial translocation occurs in many chronic diseases, defining reliable biomarkers that reflect microbial translocation is essential for proper inflammatory diagnoses. Host proteins produced in response to microbial antigenic stimulation are often used as surrogates of microbial translocation; however, many of these can be produced in response to self-proteins produced by dead and dying cells. We measured levels of biomarkers associated with GI damage, innate immune responses, and cell death associated proteins in cohorts of HIV-infected individuals and SIV-uninfected and infected pigtail and rhesus macaques to identify potentially confounding contributors to microbial translocation biomarkers.
Methods: We measured plasma levels of sCD14, HMGB1, RAGE, IFABP, and zonulin by ELISA in human and non-human primates (NHPs). Our cohorts consisted of 38 ARV-naïve and treated HIV-infected human patients; 9 pigtail macaques (PTs) and 12 rhesus macaques (RMs) longitudinally pre-SIV and during acute and chronic infection; and an unmatched cohort of 6 chronically SIV-infected RMs and 6 SIV-uninfected RMs
Results: We observed significant reductions in systemic levels of sCD14 and RAGE post-ARV in HIV-infected individuals. sCD14, HMGB1, and IFABP levels increased in chronically SIV-infected NHPs relative to their pre-infection plasma levels. Surprisingly, both sCD14 and zonulin levels decreased longitudinally, pre- to acute-SIV infection. No markers strongly associated with sCD14 consistently in all three groups. In humans, sCD14 associated most strongly with HMGB1 plasma levels. However, in NHPs, sCD14 only correlated with RAGE levels in the RM cohort. The strongest association between markers within the NHP cohort was between RAGE and IFABP ($P<0.0001$).
Conclusion: Our data suggest that cellular proteins which are secreted during generalized cellular stress, and which specifically induce sCD14 production may contribute to elevated levels of sCD14 observed in HIV/SIV-infected individuals. These cellular stress biomarkers, specifically RAGE and IFABP may be released into circulation due to epithelial barrier damage.

232 CMV SEROPOSITIVITY AND MICROBIAL TRANSLOCATION IN HIV ELITE CONTROLLERS

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Background: Elite controllers (EC) are people living with HIV (PLWH) who maintain plasma HIV viral load below 50 copies/mL without antiretroviral therapy. However, EC present with chronic inflammation and remain at increased risk of developing non-AIDS comorbidities. Microbial translocation is a contributor to chronic inflammation and CMV co-infection has been recently linked to increased gut damage. We previously reported that CMV seropositivity was associated with elevated epithelial gut damage and microbial translocation in ART-treated PLWH and HIV-uninfected controls. As Canada has one of the lowest CMV co-infection prevalence in the world, we evaluated the link between CMV seropositivity, microbial translocation, and inflammation among EC.
Methods: Study samples were collected from 37 EC (25 CMV+, 12 CMV-). By HLA typing, we categorized participants with/without protective HLA alleles (B*27, B*57, B*58, n=16). We measured CD4 and CD8 T-cell counts, anti-CMV IgG and anti-EBV IgG titers, markers of epithelial gut damage REG3a and I-FABP, markers of microbial translocation LPS, sCD14 and B-D-Glucan (BDG), as well as total IgG, IgM, IgA, IL-1B, IL-6 and kynurenine/tryptophan.
Results: As expected, participants with protective HLA alleles had higher CD4 T-cell count compared those without protective alleles ($p=0.03$). Plasma levels of markers of epithelial gut damage and microbial translocation were similar among EC with and without protective HLA alleles. CMV seropositive and seronegative EC presented with similar age, male/female ratio, and CD4 T-cell counts. Conversely, CMV seropositive EC had elevated CD8 T-cell counts ($p=0.002$), I-FABP ($p=0.01$), sCD14 ($p=0.04$), LPS ($p=0.02$), BDG ($p=0.02$), IL-1B ($p=0.001$), IL-6 ($p<0.001$), and kynurenine/tryptophan ratio ($p=0.002$) compared to CMV seronegative EC. Moreover, anti-CMV IgG titers were also associated with plasma levels of I-FABP ($r=0.48$; $p=0.02$), sCD14 ($r=0.3$; $p=0.05$), LPS ($r=0.42$; $p=0.04$), BDG ($r=0.69$; $p<0.001$), IL-1B ($r=0.52$; $p=0.01$), and IL-6 ($r=0.37$; $p=0.05$). Conversely, anti-EBV IgG titers and total IgG, IgM, IgA were not associated with these markers.
Conclusion: Markers of epithelial gut damage, microbial translocation, and inflammation were higher in CMV seropositive EC, irrespective of protective HLA

alleles. CMV co-infection emerges as an important contributor to gut damage and microbial translocation and may contribute to non-AIDS comorbidities in EC.

233 FROM GUT TO BLOOD: REDISTRIBUTION OF ZONULIN IN HIV+ PATIENTS

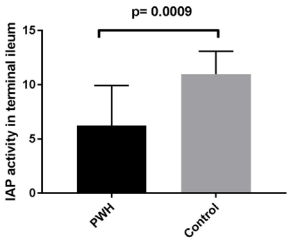
Max Augustin[1], Carola Horn[1], Meryem S. Ercanoglu[1], Vincent Bondet[2], Isabelle Suarez[1], Seung-Hun Chon[1], Dirk Nierhoff[1], Elena Knops[1], Eva Heger[1], Gerd Fätkenheuer[1], Jan Rybniker[1], Darragh Duffy[2], Michaela Müller-Trutwin[2], Clara Lehmann[1]
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Background: Gastro-intestinal mucosal damage in HIV infection causes microbial translocation and immune activation, which in turn results in non-infectious comorbidities. Combined antiretroviral therapy (cART) restores this intestinal damage only partially. Various biomarkers of the epithelial barrier have been reported but some are not considered specific while others are impacted by cART. Zonulin is a modulator for epithelial tight junctions. Previous studies found an elevated level of circulating Zonulin in the blood during HIV infection, while others reported a decrease. We measured Zonulin in serum and intestinal tissue sections and compared it with inflammatory markers and the virus reservoir in the blood (PB), ileum (TI) and rectum (R) of HIV+ and controls.
Methods: Biopsies and gut tissue sectionsfrom TI, R and PB were collected from 5 treatment naïve (HIV+NAÏVE) and 10 cART-treated (HIV+cART) HIV+ individuals and 11 controls (CTRL). Lamina propria mononuclear cells were isolated. Following flow cytometry and cell sorting of CD4+ T cells, total HIV-DNA was quantified in PB, TI and R. In serum circulating Zonulin was measured by ELISA (Immundiagnostik) and in gut sections by semi quantitative immunohistochemistry. Ultrasensitive digital ELISA (Simoa; Quanterix) was used to measure IFN-α in serum and tissue supernatants.
Results: Median CD4+T cell count [cells/µl] in HIV+NAÏVEwas 70(30-255) versus 426(293-787) in HIV+cART. Median time on ART[years]was 6(9-10). Circulating Zonulin levels [ng/ml]were highest in treatment-naïve HIV+when compared to cART-treated HIV+(p=0.04) or CTRL (p=0.0087; HIV+NAÏVE>HIV+cART>CTRL). Similarly, HIV+NAÏVE showed higher IFN-α and HIV-DNA levels in PB when compared to HIV+cART(IFN-α: p=0.04; HIV-DNA: p=0.04). In gut tissue sections however, Zonulin was higher in CTRL when compared to HIV patients. Circulating Zonulin in serum was negatively correlated to plasma CD4 cell count (r= -0.54, p=0.04), CD4+T cell frequencies in TI (r= -0.58 p=0.04) and positively to IFN-α in TI (r=0.65, p=0.05).
Conclusion: The data indicate that upon HIV infection, Zonulin levels decrease in gut, but increase in plasma. The latter were associated with loss of intestinal CD4+T cells and increased inflammation in the gut, suggesting that increased levels of systemic Zonulin correlate with intestinal damage. An increased understanding of the regulation of gut tight junctions during HIV infection may be crucial for the design of future therapies.

234 GUT BARRIER PROTECTANT INTESTINAL ALKALINE PHOSPHATASE IS REDUCED IN PEOPLE WITH HIV

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Background: Gastrointestinal (GI) microbial translocation in people with HIV (PWH) is associated with systemic immune activation and inflammation. The intestinal brush border enzyme intestinal alkaline phosphatase (IAP) is important for maintaining healthy GI barrier function. IAP promotes intestinal homeostasis by regulating the pH of the gut luminal surface via bicarbonate secretion and by detoxifying lipopolysaccharides (LPS). After IAP dephosphorylates the lipid moiety of LPS, the modified LPS is no longer active to induce proinflammatory responses through TLR4 and subsequent MyD88-dependent signaling pathways in the gut. IAP is reduced in human diseases in which intestinal dysbiosis has been implicated, such as inflammatory bowel disease and diabetes mellitus. Furthermore, exogenously administered IAP reversed intestinal inflammation and metabolic syndrome in animal models. We hypothesized that IAP would be lower in PWH given the known intestinal damage and dysbiosis in PWH.
Methods: IAP activity was measured in fluid from the terminal ileum collected by colonoscopy in 30 participants with chronic HIV and 6 controls without HIV. For IAP activity, luminal fluid is mixed with phosphatase assay reagent containing p-nitrophenyl phosphate followed by determining optical density at 405nm. All participants did not have known GI disease, and participants with HIV were treated with stable ART > 6 months and had suppressed HIV RNA. IL-1β was measured in the terminal ileum fluid by ELISA. IAP and IL-1β were both normalized to total protein measured in the intestinal fluid.
Results: In PWH, IAP activity was significantly lower compared to controls (6.25±3.69 [mean±SD] vs 10.98±2.10, p=0.0009). Proinflammatory IL-1β trended to be higher in the intestinal fluid of PWH compared to controls (33.16±73.55 vs. 5.97±8.96 pg/mg protein, p=0.099). BMI (27.3±4.3 vs 26.9±4.2 kg/m_2, p=0.83), and HbA1c (5.5±0.3 vs 5.5±0.4 %, p=0.86) were similar between the groups. Peripheral CD4+ cell count was 729±234 cells/µL in PWH.
Conclusion: We demonstrated significantly lower IAP in the terminal ileum of PWH compared to uninfected controls, which has not been reported previously. This novel finding of reduced IAP in PWH may provide additional insight into the pathogenesis of intestinal barrier dysfunction and its associated comorbidities in PWH. Future studies are needed to further elucidate the role of IAP in HIV-associated GI dysfunction and the potential use of exogenous IAP to reduce LPS-mediated inflammation in PWH.



Terminal ileum IAP activity is lower in PWH compared to people without HIV. Height of the bar represents the mean and error bar represents the standard deviation.

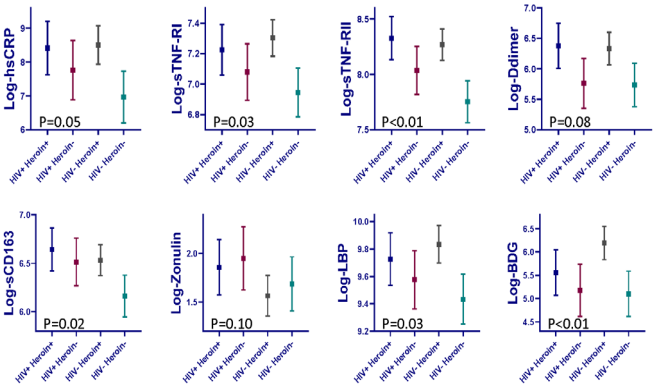
235 IMPACT OF INTRAVENOUS HEROIN AND HIV ON GUT INTEGRITY AND IMMUNE ACTIVATION

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Background: Altered gut integrity and translocation of microbial products appear to be central in HIV-related immune activation. Opioid use may promote similar changes in gut permeability potentially augmenting immune activation in HIV-infected opioid users. Injection as a route administration may also heighten inflammation. Excess immune activation may increase risk of co-morbid metabolic conditions and contribute to the increased risk of mortality in people with HIV who inject opioids.
Methods: HIV+ and HIV- heroin users and HIV+ and HIV- never heroin users were prospectively enrolled. Never users were matched to HIV+ heroin users by sex, age and CD4+ count (HIV+ only). Soluble markers of systemic inflammation, monocyte activation, gut integrity and microbial translocation were quantified by ELISA. ANOVA and multivariable linear regression were used to compare markers between groups and to test for effect modification by HIV status.
Results: 100 enrolled (19 HIV+ Heroin+; 38 HIV- Heroin+; 19 HIV+ Heroin-; 24 HIV- Heroin-). Groups were similar except HIV+ Heroin+ had lower trunk fat (p<0.01) and lower current (p=0.02), but similar nadir CD4+ counts. Heroin+ groups were more likely to be Hispanic (p<0.01), have active hepatitis c (p<0.01) and be current smokers (p<0.01). Overall, median age was 42 years and 75% were men. For HIV+ groups, median known duration of HIV was 13 years and all but 3 had HIV-1 RNA <200 copies/ml. For Heroin+ groups, 98% were current smokers; 49% also used cocaine and 11% used methamphetamine. Active heroin use was associated with higher soluble tumor necrosis factor alpha receptors-I and –II (sTNF-RI and –II), high sensitivity C-reactive protein (hsCRP), D-dimer, soluble CD14 (trend only), soluble CD163, LPS binding protein (LBP) and beta-D-glucan independent of HIV status, age, sex, race, trunk fat, hepatitis c and smoking. HIV was only associated with sTNF-RII (trend), sCD163 and zonulin in adjusted models. HIV status tended to modify the effect between heroin use and hsCRP and LBP (p<0.10 for interactions); however, in stratified models, HIV-Heroin+ had larger difference in both markers compared to Heroin-. While some

markers were qualitatively higher in HIV+ Heroin+ compared to HIV- Heroin+, only zonulin was statistically higher.

Conclusion: IV heroin use is associated with immune activation and altered gut integrity. Although not statistically significant, some markers were higher in HIV+ than HIV- heroin users which may portend higher risk of poor outcomes.



Symbols represent adjusted means for each marker by group. Error bars show 95% confidence intervals around the means. P-values <0.05 indicate there are differences in means among the groups. Means adjusted for age, sex, race, trunk fat, hepatitis C and smoking. hsCRP, high sensitivity C-reactive protein; sTNF-RI, soluble tumor necrosis factor alpha receptor-I; sTNF-RII, soluble tumor necrosis factor alpha receptor-II; sCD163, soluble CD163; LBP, lipopolysaccharide binding protein; BDG, beta-D-glucan

236 VALGANCICLOVIR EFFECTS ON GUT AND PULMONARY EPITHELIAL BARRIER MARKERS IN TREATED HIV

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Background: The CMV drug valganciclovir broadly suppressed markers of innate and adaptive immune activation in a trial of people living with HIV (PLWH) with incomplete CD4 recovery during antiretroviral therapy (ART). As CMV replicates in and is shed from gut and pulmonary mucosa, we hypothesized that valganciclovir might affect soluble markers of gut and pulmonary epithelial barrier function.

Methods: Plasma was assessed from a placebo-controlled trial of valganciclovir (900mg daily for 8 weeks) among 30 HIV/CMV co-infected individuals with incomplete ART-mediated CD4 recovery and high CD8+ T cell activation (>10% CD38+HLA-DR+ CD8+ T cells). Markers of gut barrier dysfunction (sCD14, LPS binding protein [LBP], intestinal fatty acid binding protein [I-FABP], B-D-glucan, and regenerating islet-derived protein-3a [Reg3a]) and pulmonary barrier dysfunction (clara cell secretory protein [CC16], surfactant D), were assessed every 4 weeks. Changes from baseline at each timepoint were compared between arms with linear mixed models, log-transforming variables and normalizing to the baseline interquartile range (IQR) to facilitate comparisons between biomarkers.

Results: Among 14 valganciclovir-treated and 16 placebo-treated PLWH, most (93%) were men, 9 (30%) had detectable plasma HIV RNA levels, and median CD4 count was 190 cells/mm$_3$. At baseline, there were significant correlations between sCD14 and both I-FABP and B-D-glucan (rho: 0.19-0.21, P<=0.05), but not with other putative measures of gut barrier integrity. Surfactant D appeared to be associated with sTNFR1 (rho: 0.39, P=0.03) and IL-6 (rho: 0.58, P=0.002). In the valganciclovir arm, sCD14 declined by over a quartile from baseline, an effect that persisted for 4 weeks after treatment cessation and was significantly greater than placebo at weeks 4 and 12 (see Table). LBP also appeared to decline by over a quartile in the valganciclovir arm through week 12. Less consistent changes were observed in other markers of gut and pulmonary barrier dysfunction.

Conclusion: Treating asymptomatic CMV for 8 weeks in PLWH with incomplete ART-mediated CD4 recovery significantly reduces sCD14 and LBP, without clear effects on more specific markers of microbial translocation and epithelial barrier function. Given high within-subject variability for some of these analytes and the potential for greater effects with longer treatment duration, a longer and larger trial of treating asymptomatic CMV infection is required to definitively test these hypotheses in vivo.

	Relative Change from Baseline Per Interquartile Range in Baseline Level (95% CI)					
	Valganciclovir			Placebo		
Plasma Biomarker	Week 4	Week 8	Week 12 (off drug)	Week 4	Week 8	Week 12 (off drug)
Gut						
sCD14	**0.45 (0.26-0.77)***	**0.48 (0.28-0.82)**	**0.40 (0.23-0.68)***	0.99 (0.68-1.5)	0.69 (0.47-1.02)	1.4 (0.97-2.0)
LBP	0.54 (0.26-1.1)	**0.33 (0.16-0.67)**	**0.25 (0.12-0.51)***	1.14 (0.55 to 2.3)	0.76 (0.37-1.6)	0.91 (0.45-1.8)
I-FABP	0.6 (0.26-1.4)	1.4 (0.62-3.3)	0.9 (0.38-2.0)	0.73 (0.30-1.8)	1.2 (0.48-2.9)	1.1 (0.4-2.0)
B-D-Glucan	0.42 (0.10-1.7)	0.59 (0.14-2.4)	**0.24 (0.06-0.97)**	0.55 (0.11-2.7)	0.57 (0.12-2.9)	**0.16 (0.03-0.77)**
Reg3a	0.92 (0.64-1.3)	0.84 (0.59-1.2)	0.92 (0.64-1.3)	1.1 (0.89-1.4)	1.0 (0.80-1.3)	0.90 (0.72-1.1)
Pulmonary						
CC16	**0.71 (0.53-0.96)**	0.83 (0.63-1.1)	1.1 (0.80-1.4)	0.94 (0.72-1.2)	0.94 (0.72-1.2)	1.2 (0.91-1.5)
Surfactant D	1.0 (0.82-1.3)	1.0 (0.83-1.3)	1.1 (0.88-1.4)	0.94 (0.73-1.2)	0.90 (0.69-1.2)	1.0 (0.78-1.3)

*Significant between arms, P<0.05

237 LIPID ABNORMALITIES MAY CONTRIBUTE TO ALTERED MACROPHAGE PHENOTYPE IN PEOPLE WITH HIV

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Background: HIV infection and antiretroviral therapy (ART) are associated with dyslipidemia and increased cardiovascular disease (CVD) risk. Macrophages accumulate in arterial walls and produce factors that contribute to vascular inflammation. The relationships among lipids and macrophage phenotype in people with HIV (PWH) are unclear.

Methods: Coronary artery calcification (CAC) in people with (n=40) and without (n=15) HIV was quantified by computed tomography scanning. PBMCs from HIV+ART+ (n=20) and HIV- donors (n=20) were cultured for 5 days in medium containing 20% autologous serum to generate monocyte derived macrophages (MDMs). Concentration and composition of serum lipids was measured by mass spectrometry. MDM transcriptomes and differential gene expression (DGE) were analyzed using our R Bioconductor pipeline. Foam cell formation was assessed by Bodipy staining. Immune activation was assessed by flow cytometry.

Results: PWH (ages 27-67) had significantly increased CAC scores compared to people without HIV (ages 25-70) (CAC=367 v 25, p=0.01). Traditional risk assessments categorize individuals with CAC scores <100 at low risk, and >400 at high risk for CVD events. Older (over 55) PWH (n=17) had an average CAC score of 423, compared to a score of 71 in older people without HIV (n=7). PWH had increased serum levels of free fatty acids (FFAs), with enrichment of saturated fatty acids (SaFAs) and a reduction in polyunsaturated fatty acids (PUFAs). DGE analysis of MDMs from participants with and without HIV identified alterations in immune signaling, DNA damage repair, mitochondrial dysfunction, and lipid processing pathways. Levels of SaFA and PUFA lipid species correlated with unique DGE signatures and altered metabolic pathway activation in MDMs. Bodipy staining indicated greater lipid accumulation. MDMs from PWH also produced more TNFa, IL-6, and ROS, and had increased HLA-DR surface expression. SaFA levels were directly related, whereas PUFAs were inversely related to HLA-DR expression on MDMs from PWH. HIV- MDMs exposed to HIV+ pooled serum displayed greater intracellular lipid accumulation and DGE than cells exposed to HIV- pooled serum.

Conclusion: Lipid abnormalities in HIV infection may contribute to a pro-atherogenic MDM phenotype. MDMs from PWH readily form foam cells, have altered transcriptional profiles, and produce mediators of vascular inflammation, which may enhance CVD risk, particularly in the aging HIV population.

238 LIPIDOME ALTERATIONS WITH EXERCISE AMONG PEOPLE WITH AND WITHOUT HIV

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Background: An increasing burden of age-related comorbidities and impairment of physical function in aging people with HIV (PWH) can be improved, in part, through exercise interventions. The effect of exercise and HIV serostatus on the mechanisms underlying these improvements, such as changes in lipidome composition, is not known.

Methods: Sedentary adults (50-75 years old) with (N=24) or without (N=25) HIV participated in supervised endurance/resistance exercise for 24 weeks. In this exploratory secondary analysis of The Exercise for Healthy Aging Study, concentrations of plasma lipids (~1200 lipid species from 13 lipid classes) at

baseline and week 24 were measured by mass spectrometry. Changes in log_{10} lipid concentrations were compared by HIV serostatus using t-tests. P-values unadjusted for multiple comparisons (unadj-p) and Benjamini-Hochberg corrected (adj-p) are reported.

Results: Among PWH and controls, at baseline, there were no statistically significant differences in concentrations of total lipids. With the exercise intervention, changes in total triacylglycerol (TAG) levels significantly differed among people with and without HIV (unadj-p=0.006, adj-p=0.078): TAGs tended to decrease in PWH (% Change: -4.5 [-14.1, 6.2]), but significantly increased in controls after 24 weeks of exercise (% Change: 14.7 [6, 24.1]). Concentrations of TAG species (Table) composed of long chain fatty acids increased among uninfected controls but not PWH (unadj-p=0.001-0.036, adj-p =0.10-0.12) from baseline to week 24. Total diacylglycerols (DAGs) increased in PWH from baseline to week 24 (% Change: 6.1 [0, 12.5]), but decreased in controls (% Change: -5.1 [-12.7, 3.2]) (unadj-p=0.03, adj-p=0.2). Baseline to week 24 changes in specific DAGs composed of palmitic acid (16:0), palmitoleic acid (16:1), and stearic acid (18:0) varied by serostatus, with increases in PWH (unadj-p=0.009-0.03; adj-p 0.10-0.12) and non-significant decreases in controls (Table). The change in concentrations of lysophosphatidylcholine (LPC) species composed of saturated fatty acids (LPC FA(15:0;16:0;17:0)) also differed by serostatus, with increases in PWH and decreases among controls (unadj-p=0.02-0.05; adj-p=0.12-0.21); Table.

Conclusion: Although exploratory, the effects of exercise on the plasma lipidome may differ among people with and without HIV, potentially due to underlying alterations in lipid processing and fatty acid oxidation in PWH.

	People with HIV	Controls	P-value	Adjusted P-value#
TAG				
FA 18:0	-3.6 [-14.7, 8.9]	16.5 [6.9, 26.9] *	0.01	0.12
FA 18:1	-6.1 [-17.2, 6.5]	17.3 [7.4, 28.1] *	0.01	0.10
FA 18:2	-7.1 [-18.6, 6.1]	17.3 [7, 28.6] *	0.01	0.10
FA 20:4	-8.8 [-20.2, 4.2]	9.3 [0.5, 19] *	0.02	0.14
FA 20:5	-7.7 [-19.4, 5.6]	9.2 [0, 19.3] *	0.04	0.17
FA 22:1	-6.7 [-17.3, 5.2]	19.2 [9.1, 30.1] *	0.001	0.08
DAG				
FA 14:1	18.4 [-2.1, 43.2]	-9.6 [-23.6, 6.9]	0.03	0.17
FA 16:0	11.1 [0.9, 22.3] *	-10.3 [-20, 0.7]	0.01	0.10
FA 16:1	10.5 [2, 19.8] *	-6.8 [-15.8, 3.2]	0.01	0.11
FA 18:0	14.1 [3.2, 26.1] *	-6.6 [-16.9, 5]	0.01	0.11
LPC				
FA 15:0	9.2 [-0.6, 20.0]	-5.9 [12.7, 1.5]	0.01	0.12
FA 16:0	4.7 [-1.6, 11.3]	-4.5 [-11.3, 2.8]	0.05	0.21
FA 17:0	7.1 [-3.3, 18.6	-9.0 [-18.2, 1.2]	0.03	0.15

Other TAGs with p<0.05: FA 18:3, 20:0, 20:1, 20:2, 20:3; *p<0.05 within group change; #Benjamini-Hochberg correction for multiple comparison; Fatty Acid (FA)

239 FECAL CALPROTECTIN IS ELEVATED IN HIV AND RELATED TO SYSTEMIC INFLAMMATION

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Background: Fecal calprotectin (FCP), a biomarker of gastrointestinal inflammation, is used in the diagnosis and management of inflammatory bowel disease. HIV infection severely damages gut-associated lymphoid and epithelial tissues leading to gut inflammation, microbial translocation and systemic inflammation/immune activation. We sought to investigate FCP in people with HIV (PWH) for the first time and determine its relationship to HIV-specific factors and systemic inflammation/immune activation.

Methods: PWH naïve to ART, ART-treated and uninfected controls were prospectively enrolled. Stool samples were collected and FCP was measured by ELISA. Plasma biomarkers of inflammation/immune activation were also measured. FCP was evaluated as a continuous variable and by thresholds. Spearman correlations were used to investigate associations with FCP.

Results: 101 PWH (83 ART-treated, 18 naïve) and 89 uninfected controls were enrolled. ART-treated were older than naïve (51 vs 31 yrs; P=0.006), but sex and race were similar (overall 78% males, 66% blacks). All but one ART-treated had HIV RNA <200 copies/mL. CD4 counts for treated and naïve were 683 and 410 cells/µL, resp. Controls had a median age of 37 yrs (78% males, 22% blacks). There was a difference (P=0.001) in FCP among the 3 groups with the highest median (25th, 75th %ile) FCP in ART-naïve [144 (33, 262) µg/g] followed by ART-treated [78 (36, 141) µg/g] and then controls [41 (21, 89) µg/g] (Fig). 56% of ART-naïve had FCP >100 µg/g vs 37% in treated and 19% in controls (P=0.0003). In PWH, high-sensitivity C-reactive protein (R=0.30; P=0.008), soluble tumor necrosis factor-II (R=0.28; P=0.006), and soluble vascular cellular adhesion molecule (R=0.21; P=0.04) were positively associated with FCP. Interleukin-6 (R=0.29; P=0.01) and soluble CD163 (R=0.54; P=0.04) were also positively associated with FCP in treated and naïve, resp. FCP was inversely associated with CD4 (R=-0.24; P=0.02), but not with other HIV variables, nor age, sex, or race.

Conclusion: Stool concentrations of FCP are elevated in PWH. ART appears to reduce FCP but not to concentrations seen in uninfected controls. FCP concentrations are positively correlated with several markers of systemic inflammation/immune activation, and negatively with CD4. FCP may serve as a useful biomarker to monitor gastrointestinal inflammation and associated systemic inflammation/immune activation in HIV.

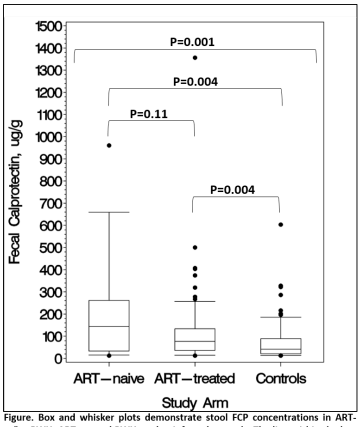


Figure. Box and whisker plots demonstrate stool FCP concentrations in ART-naive PWH, ART-treated PWH, and uninfected controls. The line within the box marks the median, upper and lower boundaries of the box represent 25th and 75th percentiles, error bars denote 10th and 90th percentiles, and small circles outside of the box represent outlier data points. One extreme outlier has been removed from the ART-treated group to aid in visualization of the plots.

240 LONG-TERM ELEVATED IL-6 AND D-DIMER AFTER DELAYED ART INITIATION IN THE START TRIAL

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Background: Inflammation and coagulation are associated with disease risk among persons with HIV. ART reduces inflammation, but whether time of initiation during infection affects this reduction has not been studied experimentally. We report on the interleukin-6 (IL-6) and D-dimer trajectories in the immediate versus deferred arms of the START trial

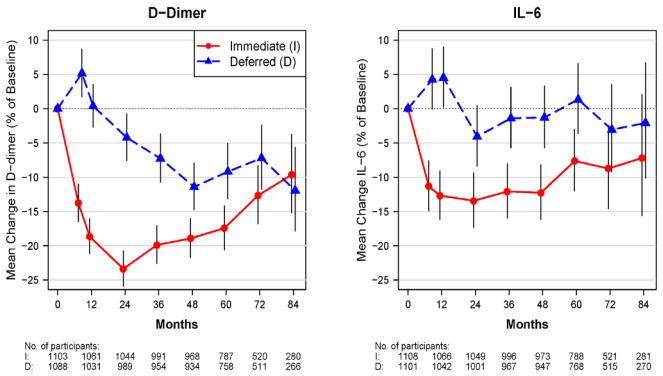
Methods: In participants randomized to immediate (CD4>500 cells/µL) vs. deferred (CD4 <350 cells/µL) ART initiation, IL-6 and D-dimer levels were measured from stored plasma specimens at baseline, month 8, and annually up to 7 years. Mean change from entry and from start of ART in log2-transformed levels were compared between the deferred versus immediate groups using longitudinal mixed models adjusted for age, sex, geographic region, baseline biomarker levels and visit. Results were presented as percent change

Results: Among 2209 participants (median age 36 years, 20% female, 67% enrolled in high-income countries), the median levels at entry of IL-6 were 1.47 pg/mL, D-dimer 0.31 µg/mL, and CD4 counts 649 cells/µL. In the immediate group, 94-97% had viral load <200 cp/mL at all annual visits, whereas the deferred group suppression rates increased over time: 18%, 61%, 89%, and 95% at years 1, 3, 5, 7, respectively. In the deferred group, IL-6 and D-dimer levels remained significantly higher than the immediate group through 5 years (Fig). Over the follow-up period, treatment difference in IL-6 was 10.3% (95%CI: 7.6 to 12.9, p<0.001), and D-dimer 14.0% (95%CI: 11.5 to 16.5, p<0.001). When comparing treatment groups based on the time from ART start, biomarker levels were higher in the deferred compared to the immediate group over at least the first 2 years of ART. At 2 years on ART est. diff. 9.9% (95% CI: 4.0 to 15.8; p<0.001) for IL-6 and 10.0% (95% CI: 6.4 to 13.6, p<0.001) for D-dimer, and >96% in each group had HIV RNA <200 cp/mL

Conclusion: Compared to immediate ART, deferral of ART was associated with higher levels of IL-6 and D-dimer over at least 5 years. During the first 2 years of ART treatment, despite viral suppression in both groups, biomarker levels

were higher in the deferred compared to immediate group. Follow-up continues in START to determine the clinical consequences of excess inflammation from delayed diagnosis and treatment

Figure. Mean change in IL-6 and D-dimer levels (percent of baseline) for the immediate and deferred ART groups in START. Bars denote 95% CIs for the means.



241 NON-AIDS—DEFINING EVENTS IN HIV CONTROLLERS VS ART-CONTROLLED PATIENTS

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Background: HIV controllers (HICs) are rare persons living with HIV who spontaneously maintain low or undetectable viremia. Low-grade chronic inflammation persisting in this population could lead to higher rates of non-AIDS defining events (nADEs) than in patients who achieve low or undetectable viremia on antiretroviral therapy (ART).
Methods: From the ongoing multicenter ANRS CODEX cohort, we enrolled 315 HICs with a known HIV-1 infection ≥5 years, with at least 5 consecutive viral loads (VL) below 400 HIV RNA copies/mL in the absence of ART. The ongoing multicenter ANRS PRIMO Cohort enrolls HIV-1 infected patients diagnosed during primary infection (≤3 months). From this latter cohort, we included 328 patients who initiated ART ≤1 month after the diagnosis, with undetectable VL ≤12 months following ART initiation and for at least 5 years ("ART-subjects"). Incidence rates (IR) of first nADEs, i.e. malignancies, cardiovascular, pulmonary, hepatic, psychiatric or bone events were compared between HICs and ART-subjects; potential determinants were assessed by using Cox regression models.
Results: The most common events observed in the 2 cohorts were non-AIDS related infections (36.9%), psychiatric (17.2%), cardiovascular (6.8%), and malignancies (6.1%), with no statistically significant differences in distribution between the 2 cohorts. Two and 4 non-AIDS related deaths were observed among HICs and ART subjects, respectively. All-cause nADEs incidence rates were 2.8 per 100 person-years (py) and 5.3 per 100 py among HICs and ART subjects, respectively (Hazards Ratio HR=0.53 [95%Confidence Interval (95%CI), 0.40-0.71]. After adjustment for the cohort, demographic and immunological characteristics, the only other factor associated with all cause nADEs occurrence was age 36-43 (vs. 18-29) years at beginning of control (HR=1.56 [95%CI, 1.06-2.30]). Baseline CD4 T-cell count or nadir, CD4/CD8 ratio, history of viral blips, HBV/HCV co-infection and tobacco use, were not associated with an increased risk of nADEs.
Conclusion: HICs, defined on the basis of ≥5-year period of spontaneous viral control, experienced two times less nADEs than virologically suppressed patients on ART. Age was the only other factor independently associated with nADEs occurrence, irrespective of immune or virologic parameters. These results do not argue in favor of expanding the indication for ART for HICs subjects but rather a case-by-case approach considering clinical outcomes such as nADEs besides immune activation.

242 TOTAL HIV DNA LEVELS DO NOT PREDICT NON-AIDS-DEFINING EVENTS

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Background: Despite antiretroviral therapy (ART), individuals with HIV maintain an HIV reservoir with high levels of systemic inflammation and are more likely to have non-AIDs-defining events compared to those without HIV. We performed a case-control study of AIDS Clinical Trials Group (ACTG) participants to assess the relationship of HIV reservoir size with levels of systemic inflammation, viral co-infections, and risk of non-AIDS-defining events.
Methods: Participants were ART-naïve at the time of enrollment, maintained plasma HIV-1 RNA levels <400 copies/mL after ART initiation, and were part of a long-term ACTG follow-up cohort. Cases were defined as participants who had a non-AIDS-related event (MI, stroke, non-AIDS-defining malignancy, serious bacterial infection, or death from a non-AIDS-defining event). Controls were identified and matched based on age, sex, baseline CD4+ T-cell count, and ART regimen. PBMCs and plasma specimens were collected at both 1 year after ART initiation and at the pre-event time point, and analyzed for levels of IL-6, sCD14, interferon γ (IFN-γ), inducible protein 10 (IP10), sTNFR-I, sTNFR-II, D-dimer, CMV and EBV DNA and antibody levels. T-cell phenotyping was performed by flow cytometry. Total HIV DNA levels in PBMCs were measured by qPCR. Adjusted and unadjusted conditional logistic regression analyses were performed to determine if HIV DNA levels predicted the occurrence of non-AIDS-defining events.
Results: Samples from 102 cases and 201 controls at year 1 and from 65 cases and 110 controls pre-event were included. Total HIV DNA levels at either 1 year after ART initiation or pre-event were not predictive of non-AIDS-defining events in either unadjusted models or models adjusted for baseline viral load, immune status, or other co-morbidities. One year after ART initiation, there were modest associations between levels of HIV DNA and CMV IgG (Spearman r=0.20, p=0.01), EBV DNA (r=0.14, p=0.05), IL-6 (r=0.18, p=0.01), D-dimer (r=0.22, p<0.01), sCD14 (r=0.18, p=0.01), and sTNFR-I (r=0.15, p=0.03).
Conclusion: The size of the HIV reservoir, as reflected by the levels of total HIV DNA, was not predictive of non-AIDs-defining events. The associations of HIV reservoir size with EBV/CMV co-infections and inflammatory markers suggest potential interactions between host immune responses and HIV persistence.

243 PRINCIPAL COMPONENTS ANALYSIS TO IDENTIFY BIOMARKERS PREDICTIVE OF NON-AIDS EVENTS

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Background: Improvements in technology (new assays, multiplex panels) and large repositories of clinical samples accelerate investigations of numerous individual biomarkers with potential for increased risk of type 1 error. Approaches to combine biomarkers can gain biological understanding and improve statistical efficiency to assess risk of clinical events; however, the best high-dimensional analytic methods are not clear.
Methods: Seventeen biomarkers measured at year 1 of suppressive ART were analyzed, from an ACTG case-control study of predictors of subsequent non-AIDS clinical events (141 cases and 310 matched controls). A targeted subset of 10 biomarkers of monocyte and macrophage activation was pre-specified, which we hypothesized to be most predictive of cardiovascular events. Three statistical approaches were considered for data reduction: 1) simple, equally weighted average of all cytokines, 2) optimally weighted combination of targeted cytokines from confirmatory factor analysis, 3) optimally weighted combination of all cytokines from principal components analysis (PCA). Cytokines were log-transformed and normalized (mean 0, SD 1) prior to analysis. Scores from each method were analyzed in conditional logistic regression models to evaluate risk of subsequent non-AIDS events.
Results: The best analytical approach was PCA, as principle component (PC) scores had reduced variability when included in regression models compared to other approaches. Based on scree plots and other diagnostics, selecting 2 PCs described the data best, compared to 1 or 3 PCs. The 2 PCs were primarily

composed of distinct subsets of the cytokines (Table). IL6, IP10, KT Ratio, sCD14, sCD163, sTNFrI, sTNFrII, and suPAR primarily contributed to PC1 (consistent with the a priori list); CMV IgG, EBV IgG, and EBV DNA primarily contributed to PC2. Higher levels of PC1 were associated with increased risk of non-AIDS events and the subset of MI/Strokes; effect sizes were similar to those reported individually for sTNFrI and II and suPAR (Tenorio 2014, Hoenigl 2018).

Conclusion: PCA is a useful high-dimensional analytic approach to reduce the number of statistical comparisons, to characterize unique, meaningful cytokine profiles, and to identify specific biomarkers to consider for endpoints in future interventional trials. In our analysis we confirmed that sTNFrI and II and suPAR were the strongest predictors of non-AIDS events, supporting sTNFrII as the primary endpoint of ACTG studies of letermovir and anti-CMV vaccine.

	Two Principle Components	
	PC1	PC2
BDG*	0.08	0.21
CMV IgG*	0.11	0.63
CMV DNA	-0.14	0.19
D-Dimer	0.36	0.02
EBV IgG	-0.001	0.80
EBV DNA	0.06	0.59
I-FABP*	0.08	0.18
IL-6*	0.52	0.18
IP-10	0.48	0.35
KT Ratio	0.64	0.19
LBP*	0.27	0.11
oxLDL	0.24	-0.09
sCD14*	0.49	0.07
sCD163*	0.50	0.31
sTNFr-I*	0.82	0.06
sTNFr-II*	0.88	0.08
suPAR*	0.71	0.01

244 AGING, TRENDS IN CD4/CD8 RATIO, AND CLINICAL OUTCOMES WITH HIV SUPPRESSION

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Background: Data addressing aging's effects on T cell phenotype suggest that age blunts CD4 cell count (CD4) improvements observed with ART-induced viral suppression. Prolonged viral suppression reduces immune activation, reflected by a rising CD4/CD8 ratio (T4/T8). We studied T4/T8 over time to determine whether it could predict risk for select comorbidities or mortality among aging persons with HIV (PWH) and ≥1year (y) virologic control.

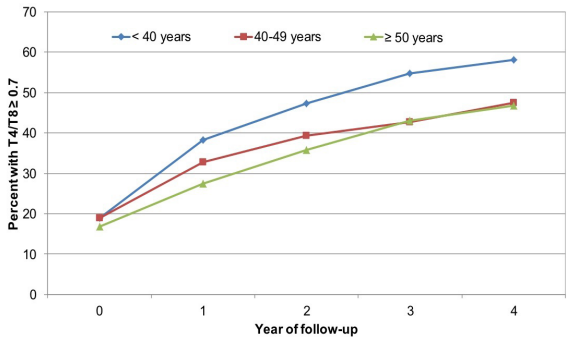
Methods

We analyzed data from HIV Outpatient Study (HOPS) participants (ppts) seen at 12 U.S. HIV clinics who were followed from 2000-2018 with known baseline CD4, ART initiation date, all viral loads (VL) <200 copies/mL during 1st observation y, ≥1y of follow up with ≥2 T4/T8 measures. We analyzed T4/T8 <0.7 by age group. Cochran-Armitage trend tests were used to compare proportions across time, and by baseline age. Clinical outcomes included any cancer, dyslipidemia and all-cause mortality. Case-control analyses were performed using conditional logistic regression (CLR) to assess for associations of T4/T8 with outcomes matching 1:1 for smoking, hepatitis C, nadir CD4, race/ethnicity, sex and insurance, with age as an independent variable.

Results: 1,910 ppts were included. Median follow up was 7.2y. At date of first VL <200 copies/mL, 908 (46%) were <40y, 626 (33%) 40-49y, and 376 (20%) ≥50y; 82% male; 50% Non-Hispanic (NH) white, 34% NH black, and 12% Hispanic; 62% were on their 1stART regimen, 20% on their ≥4thregimen; 38% had a nadir CD4 <200 cells/mm$_3$. Baseline T4/T8 was 0.3 (interquartile range: 0.2-0.6), not statistically different for the 3 age groups. T4/T8 increases by baseline age differed through 4y of follow up (P<0.001 for each year). Over time, the percentage of ppts with T4/T8 ≥0.7 increased for all ages, but less among 40-49y and ≥50y than <40y group (Figure). In clinical outcomes analyses (n=77 deaths, n=167 cancer, and n=461 dyslipidemia) using CLR, accounting for age, T4/T8 <0.7 at last measurement was associated with mortality (Odds Ratio [OR] 2.96, 95% Confidence Interval [CI] 1.30-6.74), cancer (OR 1.83, CI 1.11-3.02), and dyslipidemia (OR 4.02, CI 2.90-5.58).

Conclusion: Pre-treatment immune injury may persist as assessed by T4/T8 which may not resolve even with prolonged viral suppression and may have clinical consequences in aging PWH

Figure: Percent of participants with T4/T8 ≥ 0.7 by baseline age group and year of follow-up, the HIV Outpatient Study, n = 1,910.



Baseline age, years	Year 0	Year 1	Year 2	Year 3	Year 4	P-value* across time
< 40	908	851	810	728	649	< 0.001
40-49	626	590	564	518	482	< 0.001
≥ 50	376	343	338	313	291	< 0.001
P-value* between age groups	0.43	< 0.001	< 0.001	< 0.001	< 0.001	

*Cochran-Armitage test of trend

245 SYSTEMIC AND VASCULAR INFLAMMATION PREDICT COMORBIDITIES IN TREATED HIV INFECTION

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Background: Although inflammation and immune dysfunction are implicated in pathogenesis of comorbidities in treated people with HIV (PWH), whether an immune risk profile can predict PWH at higher risk of comorbidities is unclear.

Methods: In the UCD Infectious Diseases cohort study of PWH on anti-retroviral therapy, we measured 24 biomarkers using bead based quantitative ELISA, covering pathways of systemic inflammation (hsCRP, IL6, TNFR1,2, TNFa), innate immune activation (sCD14, sCD163, MCP1, MIP1, sCD40), endothelial function (Pselectin, Eselectin, sVCAM, sICAM), coagulation (Ddimer, vWF) and intestinal permeability (IL18, LBP). Principal component analysis was performed followed by unsupervised hierarchical clustering to partition subjects into biomarker derived clusters. Logistic regression assessed association between clusters and prevalent comorbidities (CVD, kidney, liver, hypertension, dyslipidemia). Data are median[IQR] or odds ratio (OR) [95%CI].

Results: We included 99 PWH, age 41 (36,48) years; 44% male; 54% African; 93% with HIVVL<40cps/ml, duration of ART 7.1 (2.3,10.8) years. We observed 3 distinct clusters, two characterized by higher inflammation; cluster 2 (19% subjects) reflecting platelet/macrophage pathways and cluster 3 (34% subjects), systemic, vascular and endothelial pathways (see Table 1). PWH in cluster 3 were older, more likely male and Caucasian. Although prevalence of comorbidities was higher in cluster 2 (42%) and 3 (48.9%) versus cluster 1 (20%), only cluster 3 was associated with prevalent comorbidites in regression analysis (OR 3.1 [1.1, 8.3] p= 0.03). This association remained significant after adjustment for CMV seropositivity, smoking and CD4:CD8 ratio, (OR 3.3 [1.1, 9.8] p=0.03). Further adjustment for age, gender and ethnicity attenuated the relationship (OR 2.4 [0.7, 7.9] p=0.16). Conversely Cluster 1, characterized by lower levels of inflammation, was associated with reduced risk of comorbidities (OR 0.28 [0.10, 0.74] p=0.01), an association which persisted after adjustment for baseline demographics, smoking and T cell ratio (OR 0.29 [0.10, 0.85] p=0.02).

Conclusion: We have identified distinct inflammatory patterns in treated PWH that predict prevalent co-morbidities. That these patterns, characterized by pathways including systemic and vascular inflammation remain associated with clinical outcomes even after correction for CMV and CD4:CD8 ratio suggest a number of distinct pathways contributing to co-morbidities in PWH.

	Cluster 1	Cluster 2	Cluster 3	P value
N	35	19	45	
Age (IQR)	40.7 (37.6, 47.9)	40.4 (34.9, 44.5)	44.3 (39.1, 49.3)	**0.047**
Male	10 (22.7%)	8 (18.2)	26 (59.1%)	**0.032**
African	26 (74.0%)	14 (73.7%)	14 (31.1%)	**0.001**
Transmission risk				0.343
Heterosexual	23 (65.7%)	13 (68.4%)	37 (60.0%)	
MSM	6 (17.1%)	2 (10.5%)	10 (22.2%)	
Smoking	6 (17.1%)	4 (21.1%)	12 (26.7%)	0.591
Drug Use	3 (8.6%)	2 (10.5%)	4 (8.9%)	0.970
BMI (IQR)	27.3 (24.6, 29.7)	26.7 (22.7, 33.6)	28.3 (23.7, 30.7)	0.124
Nadir CD4+ count	364 (230, 526)	332 (269, 427)	363 (181, 506)	0.798
CD4/CD8 ratio	0.8 (0.5, 1.1)	0.9 (0.7. 1.3)	0.9 (0.7, 1.2)	0.353
ART duration	4.8 (1.5, 10.8)	8.2 (2.5, 10.7)	7.49 (3.7, 11.6)	0.218
CMV IgG pos	31 (88.6%)	17 (89.4%)	37 (82.3%)	0.57
HCV Ab pos.	4 (11.4%)	1 (11.1%)	8 (17.8%)	0.373
Statin Use	1 (2.9%)	2 (10.5%)	5 (11.1%)	0.369
HIV RNA <40 copies/ml	34 (97.0%)	18 (94.5%)	41 (91.0%)	0.526
Comorbidity	7 (20%)	8 (42%)	22 (48.9%)	**0.027**
Multimorbidity	1 (2.8%)	3 (15.8%)	6 (13.3%)	0.200

Cluster Characterization by Quantitative variable analysis (v-test)

Contribution Rank *	Cluster 1	Cluster 2	Cluster 3
1	Low MIP-1	High vWF	High E-Selectin
2	Low CD40-L	High IFN Gamma	High TNF R1
3	Low P-Selectin	High CD40 L	High IL 18
4	Low TNFR1	High MIP-1	High IL1-RA
5	Low E-Selectin		High LpPLA2
6	Low IL1-RA		High s-ICAM1

*Contribution to Cluster characterization as determined by quantitative variables V-test;
IQR, Inter-quartile range; BMI, Body Mass Index; ART, Anti-retroviral therapy; CMV IgG pos, CMV seropositivity, HCV Ab pos, Hepatitis C seropositivity; MIP-1, Macrophage inflammatory Protein-1;TNFR1, Tumour Necrosis Factor receptor 1; IL1- RA, Interleukin 1 Receptor Antagonist; vWF, von Willebrand Factor; IFN gamma, Interferon gamma; IL 18, Interleukin 18; LpPLA2, Lipoprotein Phospholipase A2; s- ICAM, soluble Intracellular Adhesion Molecule

Table 1: Cluster characterization by demographic and biomarker contribution

246 GUT MUCOSAL IL22+ T CELLS ARE RELATED WITH INCOMPLETE CD4 RESTORATION DESPITE cART

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Background: Gut mucosal immunity plays a central role in the HIV pathogenesis but large gaps of knowledge remain, particularly in the scenario of the incomplete CD4-recovery. Impaired gut junctional complexes and increased markers of intestinal permeability and damage have been described in such scenario. Our aim was to explore gut mucosal T-cell function and its potential relationship with the mucosal damage and immune reconstitution.
Methods: Biopsies of both, caecum (CA) and terminal ileum (TI), in parallel of peripheral samples, of non-HIV subjects and treated, virally-suppressed HIV-infected subjects were obtained: subjects with CD4 T-cell counts bellow 250 cell/ul after two years of suppressive-treatment (INR) and control subjects overcoming such threshold (IR). Histological assessment of mucosal damage was performed using a semi-quantitative scale of five physical parameters. MMCs were digested, isolated and stimulated (PMA/Iono) to quantify the T-cell production of different homeostatic cytokines by flow-cytometry. Th22, Th17, Th1 and Treg, as well as their production of combined cytokines, were analyzed. The expression of mucosal caspase-3, gal-3, Zo-1 and mucin was analyzed by immunofluorescence. LBP levels, as a marker of intestinal permeability, was measured by ELISA in peripheral samples. Potential correlations were explored using Spearman rank test.
Results: The highest mucosal damage was observed in both types of biopsies from INR subjects. The production of IL22 by T-cells correlated with peripheral CD4 T-cell counts and CD4/CD8 T-cell ratio (stronger with mucosal than peripheral T-cells; P<0.005 for both locations). INR showed the lowest frequencies of IL22+CD4+ mucosal T-cells, whereas the highest IL17+/IL22+CD4 T-cells ratios, independent of the location. INR showed increased frequencies of FoxP3+CD4+ mucosal T-cells, particularly at TI, and reduced Th17/Treg and Th22/Treg ratios at both locations. IL22+CD4+/Treg ratios negatively correlated with mucosal damage (p<0.001 at both locations). At TI, the % IL22+CD4+ T-cells correlated with the mucosal expression of caspase-3 and Zo-1 (negatively), as well as with the expression of gal-3 (positively), and showed a negative correlation with LBP levels (p<0.05).
Conclusion: Subjects with incomplete CD4-recovery show reduced capacity of gut mucosal T-cells to produce IL22. This cytokine, with a dual "inflammatory-protective" role during tissue responses to inflammation, could have a protective-regenerative potential on the gut potentially necessary for the normal CD4-recovery.

247 INCREASED GUT AND BLOOD CD4+ T-CELL EXHAUSTION IN IMMUNOLOGICAL NONRESPONDERS

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Background: Immunological non-responders (INR) have increased inflammation and non-AIDS related morbidity. We hypothesized that their insufficient immune recovery is associated with a gut-induced exhausted T cell phenotype.
Methods: Blood samples and mucosal biopsies from terminal ileum and sigmoid colon were collected from Caucasian men; 19 INR (ART>4 years with HIV RNA <50 copies/ml and CD4 count <400 cells/µL for >3.5 years); 20 immunological responders (IR) (ART>4 years with HIV RNA <50 copies/mL and CD4 count >600 cells/µL for >3.5 years) matched on nadir CD4 count and age; and 20 age-matched healthy HIV-negative controls (HC). Peripheral blood and lamina propria mononuclear cells were analyzed with a multi-color flow cytometry panel to investigate the expression of the exhaustion markers PD1 and TIGIT in addition to T cell surface markers (CD3, CD4, CD8, CD25,, CD38, CD45RA, CD127, HLA DR) and the gut homing marker integrin β7. Immunohistochemistry was applied to detect PD1 ligand 1 (PD-L1).
Results: INR had increased fractions of PD1+ and TIGIT+ CD4+ T cells compared with IR and HC both in blood (p<0.01) and gut (p<0.05). PD1 and TIGIT expression in blood and gut both correlated negatively with systemic CD4:CD8 ratio. In the blood, but not in the gut, INR had more activated (def.: CD45RAneg) gut-homing β7high CD4+ T cells than both IR and HC (p<0.05), but these cells did not display more exhaustion markers than activated non-gut homing CD4+ T cells. Immunohistochemistry staining of gut biopsies showed that neither INR nor IR expressed PD-L1.
Conclusion: INR have a more exhausted CD4+ T cell pool than IR, both in blood and gut, supporting the hypothesis that T cell exhaustion may be a contributor to insufficient immunological response to ART. The higher prevalence of blood activated gut-homing CD4+ T cells in INR implies an enhanced stimulation and activation CD4+ T cells in the gut of in INR compared with IR, but this feature is not associated with differential expression of PD-L1.

248 NOVEL MECHANISM OF HIV-1 ELITE CONTROL BY ENRICHING GUT DIPEPTIDES AS CCR5-ANTAGONIST

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Background: A small subset (<0.5%) of HIV-1 positive individuals, the "Elite Controllers" (EC), controls viral replication for a long duration of time without receiving antiretroviral therapy. Due to the lack of data from well-controlled clinical EC cohorts, the mechanisms by which EC can control the virus remain mostly unknown. Transcriptomics analysis of blood cells has shown that CCR5 was downregulated in EC compared to viremic progressors (VP). Here we used untargeted plasma and fecal metabolomics to identify the metabolomic signature in EC followed by in vitro and ex vivo mechanistic studies.
Methods: Blood and fecal material were collected from EC (n=14), matched HIV-negative control (HC, n=12) and VP (n=16). Untargeted metabolomics was performed by Ultra-High-Performance Liquid Chromatography/Mass Spectrometry/Mass Spectrometry (UHPLC/MS/MS). Microscale thermophoresis (MST) was performed to describe the peptide-protein interactions. Viral infection and release assays were performed in TZMBI-cell lines and primary CD4+ T-cells, respectively. The significance was considered p<0.05 and false discovery rate <0.1.
Results: In total 825 biochemicals were identified in feces and 950 biochemicals in plasma of which 485 and 294 biochemicals had group effects identified by ANOVA in fecal and plasma samples respectively. The top 30 metabolites important for group separation identified by random forest analysis were part of lipid metabolism, nucleotide metabolism, and amino acid metabolism. However, among the 19 identified peptides 79% (15/19) were significantly enriched in EC compared to HC and VP in feces. Of these, 47% (7/15) were significantly enriched in the plasma of EC compared to VP. We synthesized these seven dipeptides in amide forms (DP-am) and performed MST with protease and gp120 proteins. The DP-am binds to gp120 but not to the protease. This was further supported by infection assays in TZMbl cells lines which gave an

EC_{50} ranging from 5.3uM to 49.1uM in HIV-1 subtype B and C: CCR5-tropic viruses but not CXCR4-viruses. The viral release assay showed significantly low released measured by p24 in presence of DP-am.

Conclusion: We posit that the enriched dipeptides act as CCR5-antagonist that efficiently controls viral replication in EC, and this mechanism contributes to the efficient HIV elite control status.

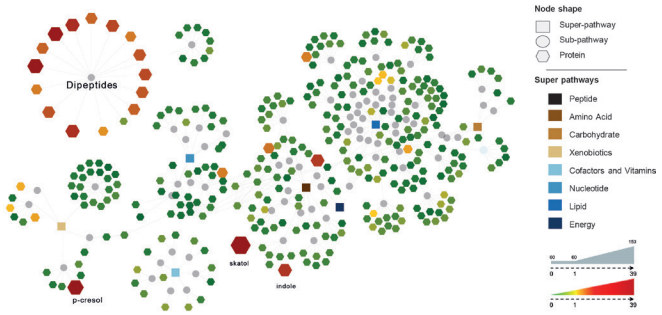


Figure 1. Enrichment of metabolites in Elite Controllers compared to Viremic Progressor.

249 OVERT GUT IL-32 ISOFORM EXPRESSION DURING TREATED HIV INFECTION: REGULATION BY IL-17A

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Background: The interplay between intestinal epithelial cells (IEC) and Th17 cells is key for mucosal immunity homeostasis. HIV infection provokes intestinal barrier function impairment and chronic immune activation, which are not normalized by antiretroviral therapy (ART). Such alterations coincide with the overexpression of IL-32, a newly described cytokine, with multiple isoforms. IL-32 overexpression was predictive of the loss of viral control in HIV slow progressors and associated with non-AIDS co-morbidities such as cardiovascular disease (CVD). The role of specific IL-32 isoforms in HIV pathogenesis remains poorly investigated. Here, we quantified the expression of IL-32 isoforms in the colon and blood of ART-treated people living with HIV (ART+PLWH), and explored the regulation of IL-32 expression by the Th17 hallmark cytokine IL-17A.

Methods: Matched PBMC and sigmoid colon biopsies were available from n=17 ART+PLWH (median age: 55 years; CD4 counts: 679 cells/ul; time on ART: 72 months) and n=5 age-matched HIV-uninfected controls. The HT-29 IEC line was used to study the modulation of IL-32 expression upon exposure to recombinant TNF-α and/or IL-17A, the TLR-3 agonist Poly:IC, or the HIV NL4.3BaL or THRO strains. IL-32α, β, γ, d, ε, t mRNA expression was measured by real-time RT-PCR. IL-32 protein production was measured in cell-culture supernatant and cell lysates by ELISA.

Results: Our results reveal a significant increase in IL-32 mRNA expression, specifically IL-32β and ε, in colon biopsies and PBMC of ART+PLWH compared to uninfected controls. IL-32 mRNA expression, especially IL-32β, γ and ε, was induced by exposure of HT-29 cells to recombinant TNF-α, Poly:IC and HIV THRO strain. IL-32 mRNA levels positively correlated with intracellular IL-32 protein expression, but no soluble IL-32 was detected in cell culture supernatants, indicative that IL-32 protein expression in IEC is mainly intracellular. Of note, recombinant IL-17A significantly decreased IL-32 mRNA/protein expression induced by TNF-α and Poly:IC, supporting an immune-regulatory role played by IL-17A.

Conclusion: Our results document the overexpression of specific IL-32 isoforms in colon biopsies and PBMC of ART-treated PLWH and point to the negative consequences of mucosal Th17 paucity, in line with our discovery that IL-17A acts as a negative regulator of IL-32 isoforms with pro-inflammatory and/or antiviral features.

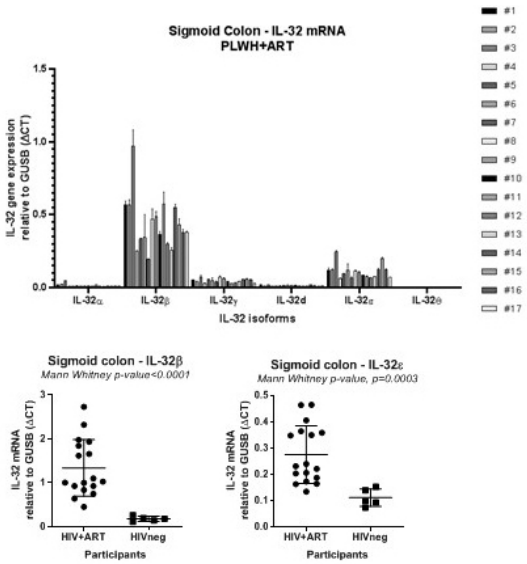


Figure 1: Overexpression of IL-32β and ε isoforms in the sigmoid colon biopsies of ART-treated PLWH compared to uninfected participants.

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250 DISTINCT INTERFEROMES ASSOCIATE WITH CHRONIC HIV PATHOGENESIS IN THE GUT

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Background: Type I Interferons (IFN-Is) protect against early HIV infection, but were linked to pathogenesis during the chronic stages. Previously, we showed that IFNβ, but not IFNα, was upregulated in the colon of chronically infected people with HIV (PWH) relative to uninfected persons (PMID29762170). To gain understanding on how IFNβ may influence chronic gut HIV pathogenesis, we profiled the transcriptome of uninfected gut CD4 T cells exposed to dominant IFNα subtypes or IFNβ in vitro. This analysis revealed a set of IFN-stimulated genes (ISGs) upregulated by all IFN-Is tested (core ISGs) and genes specifically induced by IFNβ (βISGs). Here, we evaluated these 2 gene sets in chronic, untreated HIV-1 infection.

Methods: Colon biopsies (previously collected with informed consent) from 19 untreated, chronically infected PWH (median VL 26000 HIV-1 RNA/ml; median CD4 count 429 cells/µl) and 13 uninfected controls were transcriptomically profiled using RNAseq. Differential gene analysis was conducted using edgeR and correlations between ISGs and clinical/immunological parameters tested using linear regression models adjusted for age and gender and corrected for multiple comparisons. Significance was established at FDR <5% for all analyses.

Results: Of 246 core ISGs, 51% were significantly altered in PWH vs. controls. Of these 126 altered core ISGs, 89% were upregulated in PWH. Upregulated core ISGs included genes linked to innate sensing (e.g. IRF9 3.9x; NLRC5 3.5x), immune activation (e.g. CD38 2.4x) and exhaustion (e.g. LAG3 6.2x). Majority (78%) of altered core ISGs positively correlated with gut IFNβ transcripts and plasma LPS levels and inversely with gut CD4 T cell frequencies. Of 406 βISGs, 28% were significantly altered in PWH. Of these 112 altered βISGs, >90% were downregulated in PWH and included genes linked to anti-inflammatory responses (e.g. SMAD4 -1.5x) and maintaining genomic DNA integrity (e.g. NUP54 -1.6x, MUS81 -1.6x). In contrast to the core ISGs, majority (85%) of altered βISGs inversely correlated with IFNβ and LPS levels, and 50% positively correlated with gut CD4 T cell frequencies.

Conclusion: Our data reveals a complex picture of how IFNβ may promote HIV pathogenesis in the gut. While IFNβ is associated with increased core ISG expression linked to inflammation, immune activation and exhaustion, it is also linked to decreased expression of genes with potential anti-inflammatory properties. These data could guide IFN-I blockade strategies to reduce chronic inflammation in PWH.

251 OPPOSING ASSOCIATIONS OF NK AND MZ B CELLS IN RECTAL EXPLANT MODEL OF HIV INFECTION

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Background: Our understanding of innate immune cells in human rectal mucosal tissues (RM) and their contributions to promoting or restricting HIV transmission is limited. Studies focused on systemic responses or utilizing PBMC are not suitable proxies for mucosal responses. Here, we utilized the rectal explant model to elucidate associations between RM innate cell subsets and HIV-1 BaL replication ex vivo.

Methods: **Plasmacytoid dendritic cells (pDCs); CD1c+ myeloid DCs; neutrophils;** macrophages; natural killer cells (NK); Marginal Zone-like B cells (MZBs); gd T cells; and mucosal-associated invariant T cells were quantified in RM from 69 HIV-negative men aged 18-65 years by flow cytometry. Associations between these cell subsets and HIV replication (p24 production over days 3-18) in ex vivo RM explant challenge experiments from the same study participants were examined. Hierarchical Stochastic Neighbor Embedding (HSNE) analysis was used to compare MZB and NK from blood and RM. From the explant supernatants, longitudinal production of 22 cytokines were quantified via LegendPlex analysis.

Results: In RM, pDCs were the least abundant innate cell subset ($p<0.001$), while MZB and NK cells were most abundant ($p<0.01$). There was an inverse correlation between the percentage of NK cells in RM and p24 production in parallel RM explants ($r=-0.36$, $p=0.005$); but there was a positive correlation between MZB cells and HIV replication ($r=0.49$, $p<0.0001$). No other innate subset was associated with p24 production. Comparison of RM and blood MZB and NK subsets illustrated quantifiable differences (Figure). Of the 22 cytokines quantified, IL17A, IFNg, IL10, IP10, GMCSF, Granzyme A (GzA), Granulysin, and Perforin, were positively correlated with HIV replication ($p<0.01$ for all). Detection of IL17A, IFNg, IL10, and GMCSF on day 3 positively correlated with later p24 production ($p<0.01$ for all).

Conclusion: Our data demonstrate novel associations between MZB and NK cells and p24 production in RM, highlighting their potential importance in HIV replication, and that RM NK activity is likely mediated by GzA, Granulysin, and Perforin. Our data also underscore the critical importance of pro-inflammatory cytokines IL17 and IFNg early in mucosal HIV infection. Defining the innate cells subsets and their effector mechanisms that facilitate or hinder HIV infection in RM could identify new targets for biomedical interventions.

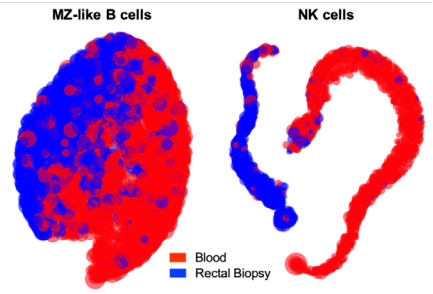


Figure 1: Hierarchical Stochastic Neighbor Embedding (HSNE) analysis of blood (red) and rectal mucosal-resident (blue) Marginal Zone-like B cells (left, CD20+, HLA-DR+, CD1c+) and Natural Killer cells (right, CD16+/-, CD56+/-).

252 IgA PRESERVATION IN GUT IN SIVagm INFECTION IS ASSOCIATED WITH INFLAMMATION CONTROL

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Background: Lymph nodes (LN) and intestine are the major HIV reservoirs. During SIVagm infection in African Green Monkeys (AGM), NK cells express CXCR5 and migrate into B cell follicles (BCF) of peripheral LN (pLN) where they efficiently control SIVagm replication. In the intestine, SIVagm replicates at high levels but this does not lead to bacterial translocation and chronic inflammation. IgA are important for the control of bacterial translocation and inflammation in the gut. In this study, we aimed at investigating whether there is a link between NK cell-mediated viral control in BCF and intestinal inflammation control via maintenance of IgA production.

Methods: AGM and cynomolgus macaques (MAC) were infected with SIVagm. sab92018 and SIVmac251, respectively. We collected blood, mesenteric LN (mLN), jejunum, ileum and colon from each animal before infection, at day 9p.i. and during chronic infection. B, T and NK cell analyses were performed by fluorescence microscopy and/or flow cytometry. Immunoglobulins were isolated by affinity chromatography and quantified by ELISA. To determine IgA/IgG ratios and gp140 antibody specificity, trimeric SIVagm and SIVmac gp140-foldon Env proteins and an IgA-specific probe were produced. Soluble markers of microbial translation and inflammation (i.e. sCD14) were quantified in plasma by ELISA.

Results: NK cells migrated into BCF of mLN during acute SIVagm infection. CXCR5+NK cells showed a negative correlation ($p=0.0004$; $r2=0.66$) in LN with follicular Th1 cells, a population responsible of hypergammaglobulinemia. In AGM, intestinal IgA levels (jejunum, ileum and colon) were comparable between acutely infected (mean=0.51-0.45AU), chronically infected (mean=0.53-0.39AU) and non-infected animals (mean=0.49-0.4AU). In acute SIVmac infection, intestinal IgA levels (mean=0.5-0.47AU) were similar to those of uninfected MAC (mean=0.54-0.42AU), but strongly decreased in chronically infected animals (mean=0.12-0.05AU). Similarly, IgA were decreased in BCF of chronically infected MAC. There was a negative correlation between sCD14 and IgA levels in MAC ($p= 0.0037$; $r2=0.32$) and not in AGM ($p= 0.72$; $r2=0.012$).

Conclusion: Our data unraveled a negative correlation between gut IgA titres and inflammation in SIVmac infection, with a dramatic loss of intestinal IgA in SIV-infected MAC while IgA levels in chronic SIVagm infection remain stable. Hence, we propose that the viral control in BCF could help maintaining normal IgA responses and a better control of gut inflammation.

253 ALTERED DNA METHYLATION OF CCR5 IN SIGMOID MUCOSAL TISSUES OF TRANSGENDER THAI WOMEN

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Background: Transgender women (TGW) have a high global prevalence of HIV. Lifestyle factors including hormone use have been shown to alter epigenetic patterns and transcriptional regulation in tissues. Thus, host epigenetic modifications in TGW may link exogenous factors and altered HIV-related cell gene regulation leading to increased risk of HIV transmission.

Methods: In a pilot study of HIV uninfected Thai volunteers, cross-sectional sigmoid mucosa biopsies were obtained from men who have sex with men (MSM, n=10), cisgender women not on hormonal contraception (CW, n=9), and TGW who had undergone gender affirmation surgery and remained on hormonal therapy (n=3). DNA methylation was measured genome-wide using the HumanMethylationEPIC array on the biopsies. Immunophenotyping of peripheral and mucosal mononuclear cells was performed to assess T cell subsets for CCR5 expression by flow cytometry. Statistical analysis included t-tests, non-parametric tests, and false discovery rate.

Results: Among TGW, mean age of hormone initiation was 14 yrs, and sex reassignment surgery 19 yrs. Median duration of hormone use in TGW was 8.5 yrs, with 1/3 using estrogen/ progesterone, and 2/3 estrogen only. All TGW reported anal and neovaginal sex and median lifetime sexual partners was significantly higher in TGW compared to CW ($P = 0.005$). We observed the greatest differences in DNA methylation at 219,788 CpG sites showing absolute mean differences in methylation greater than 5% between TGW and MSM ($\Delta\beta$-value $> |0.05|$ and significant at FDR adjusted $P < 0.05$) in sigmoid biopsies. There were fewer differences between TGW and CW (188,833 methylation sites) and even fewer between CW and MSM (5,162 methylation sites). Of known HIV acquisition risk genes, methylation at CpGs at the promoter region of the CCR5 gene were significantly decreased in TGW compared to both CW ($P < 0.05$) and MSM ($P < 0.05$). Furthermore, mucosal CCR5+ CD4 T cell frequencies were higher in TGW compared to MSM ($P = 0.002$), but not different compared to CW ($P = 0.419$). Notably, methylation levels of CCR5 associated with the frequency of mucosal CCR5+ CD4 T cells ($P = 0.016$).

Conclusion: The gut mucosal epigenome appears to be altered in TGW compared to CW and MSM Thai volunteers. This occurred at several gene loci including CCR5 that are known to affect HIV susceptibility. Further investigations of biological HIV risk factors specific to TGW are needed to inform additional HIV prevention strategies

254 DECREASED EXPRESSION OF MUCOSAL TYPE I IFN RESPONSE IN HPV-INFECTED MSM PATIENTS

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Background: Innate immunity pathways, especially those related to type I interferon (IFN-I) are involved in Human Papillomavirus (HPV) recognition and clearance. Among HIV-1 positive men who have sex with men (MSM), the extremely high incidence of HPV infection is strongly associated with an increased risk of squamous cell carcinoma of the anal canal. We hypothesized that HPV, through evasion strategies adopted to overcome the host immune defense and establish persistent infection, might target different IFN-I genes in HIV-1 MSM patients.
Methods: Anal brushings were collected from 86 Caucasian MSM HIV-1 infected patients, with a median age of 46 ±11 years, on long-term antiretroviral therapy (ART), attending Policlinic Umberto I Hospital in Rome. Detection of HPV DNA and genotyping were performed by PCR and sequencing. The mRNA levels of IFN alfa, IFN beta, IFN epsilon, an emerging component of innate immune defence at mucosal sites, IFN alpha receptor (subunits R1 and R2) in anal brushings, were measured by TaqMan RT–PCR.
Results: Anal HPV DNA was detected in 71 MSM patients (83%), with 43% of the cases having a high-risk (HR) HPV genotype, mainly HPV16. Out of 86 patients, 54% showed HSIL/LSIL. A decreased mucosal expression of IFN beta, IFN epsilon, IFNAR1 and IFNAR2 was recorded in HR compared to low-risk (LR) HPV positive and HPV negative patients (Mann-Whitney U test $p < 0.05$ for all genes). No differences were found on levels of IFN-I components according to the presence or absence of SIL. By contrast, the expression of IFN beta, IFN epsilon, IFNAR1 and IFNAR2 was reduced in patients with a persistent HPV infection (18%) compared to those who spontaneously cleared the infection (11%) (Mann-Whitney U test $p < 0.01$ for all genes).
Conclusion: HPV persistent infection may dysregulate IFN-I response and contribute to the establishment of an immunosuppressive microenvironment in mucosal epithelia, which is essential for precancerous anal lesions progression.

255 HIGH-RISK HUMAN PAPILLOMAVIRUS ONCOPROTEINS DYSREGULATE INTERLEUKIN-1 SIGNALING

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Background: High-risk human papillomavirus (HPV) infection causes cervical, anogenital, and oropharyngeal cancers that account for ~5% of cancer cases worldwide. The incidence of these AIDS-defining (cervical) or non-AIDS-defining (anal, oropharyngeal) malignancies is increasing among HIV-infected individuals. A mutation in any one of several components of the interleukin-1 (IL-1) signaling pathway predisposes individuals to develop HPV-associated malignancies, suggesting that IL-1 signals restrict either HPV infection or development/progression of HPV-positive neoplasia. IL-1ß is a pro-inflammatory cytokine and the IL-1 pathway is subject to complex regulation. The purpose of the study was to define the effects of high-risk HPV E6 and E7 oncoproteins on IL-1-related gene expression and signaling.
Methods: We used several models to assess HPV oncoprotein-dependent changes in the IL-1 pathway. First, we compared human keratinocytes engineered to express high-risk HPV E6/E7 to negative controls. Complementary experiments used HPV-positive and HPV-negative head and neck squamous cell carcinoma (HNSCC) cell lines. Finally, we employed a panel of HPV-positive and HPV-negative patient-derived xenografts (PDX). In each model we measured the levels of IL-1 signaling-related transcripts, the response of cells to IL-1 treatment, and the production of IL-1 upon exposure to the inflammasome-activating agent nigericin.
Results: In both cell lines and PDXs, the presence of HPV oncogenes was associated with decreased expression of IL1B and increased expression of SIGIRR, a negative regulator of IL-1 signaling. HPV16 E6/E7-expressing cells were less able to produce IL-1ß upon treatment with nigericin. The HPV16 E6/E7-positive cells were less responsive to stimulation with IL-1ß as assessed by the transcription of IL8 and TNFA.
Conclusion: High-risk HPV E6/E7 oncoproteins induced several changes in the IL-1 pathway consistent with reduced pathway activity. These changes were recapitulated in a PDX panel consisting of 8 HPV-negative and 8 HPV-positive models. HPV oncoprotein-expressing cells upregulated fewer genes related to inflammation upon treatment with IL-1ß and were impaired in the production of IL-1ß following nigericin treatment. Future studies will aim to assess the role of IL-1 dysregulation in HPV-mediated carcinogenesis.

256 25-HYDROXYCHOLESTEROL INHIBITS HERPESVIRUSES BY ACTIVATING INFLAMMATORY PATHWAYS

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Background: Kaposi's Sarcoma Herpesvirus (KSHV/HHV-8) expresses several viral products during latency and lytic replication cycle that block innate immune responses. It is therefore of interest to study antiviral approaches that can tip the balance and help the host mount an effective immune response. Recently, we have described how 25-hydroxycholesterol (25HC), a derivative of cholesterol, can block KSHV de novo infection of primary endothelial cells (HUVEC) at a post-entry step and decreases expression of viral genes. We wanted to determine whether 25HC inhibits other gammaherpesviruses. More importantly, we aimed to study how 25HC exerts its antiviral effect.
Methods: To test the antiviral effect of 25HC against Epstein-Barr Virus (EBV), another oncogenic gammaherpesvirus (often co-infecting certain cancers with KSHV, e.g. PEL), we performed de novo infection of primary B cells with 25HC treatment and measured apoptosis using flow cytometry. We also quantitated EBV viral transcript levels using RT-qPCR. To characterize the gene regulatory pathways triggered by 25HC, we performed RNA sequencing (RNA-Seq) of HUVEC treated with 25HC and de novo infected with KSHV. Validation was performed by RT-qPCR. Single and combinatorial siRNA knockdown of candidate target genes screened from RNA-Seq analysis were performed to identify which genes were required for the antiviral activity of 25HC.
Results: We found that 25HC increased apoptosis in EBV-infected cells, decreasing the number of EBV-transformed lymphoblastoid cell lines (LCLs). 25HC downregulated an RNA Pol III-transcribed EBV transcript, but not an RNA Pol II EBV transcript. RNA-Seq showed global suppression of KSHV viral gene expression with treatment of 25HC. On the other hand, 25HC increased Type I interferon-stimulated genes (ISGs), including inflammatory cytokines and chemokines. Using single and combinatorial siRNA-mediated knockdown, we found that depletion of certain candidate genes resulted in recovery of viral gene expression, validating their contribution towards the antiviral effect of 25HC in KSHV.
Conclusion: 25HC rendered EBV-infected B cells unable to form LCLs. RNA-Seq data showed induction of inflammatory cytokines due to 25HC treatment. Loss-of-function experiments confirmed their role in the antiviral activity of 25HC. Our studies aim to elucidate how we can augment these intrinsic antiviral responses to pave the way for developing therapeutic strategies for multiple viral infections.

257 ANAL HPV INFECTIONS DO NOT ASSOCIATE WITH RECTAL HIV-RNA SHEDDING IN HIV+ PATIENTS

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Background: Rectal HIV-RNA shedding occurs in a not negligible proportion of HIV+ pts with undetectable plasma HIV-RNA. Since multiple HPV infections are often detected in anal swabs from HIV+ pts, a causal effect of HPV in triggering rectal HIV replication could be hypothesized.
Methods: A cross-sectional, monocentric study was conducted, in which consecutively-enrolled, HIV+, virologically-suppressed pts undergoing

routine anal pap and HPV-testing (DNA and E6/E7 mRNA) were also tested for rectal HIV-RNA. A backward stepwise multivariate logistic regression analysis was performed to verify the association of multiple HPV infections with the detection of rectal HIV-RNA by including confounders and other variables significantly related with the outcome at univariate regression (at a p-value <0.100).

Results: One hundred and one pts were eligible for the analysis. They were mostly men (92.1%), mainly with homosexual intercourses as risk factor for HIV infection (80.2%) and with 50 years of median age. The median duration of HIV disease and of exposure to antiretrovirals was 12 and 10 years, respectively; 32 pts (31.7%) had a history of AIDS-defining events. Median time since last HIV-RNA ≥50 copies/mL was 72 months, but 26 pts (25.7%) had a residual viremia (defined as target detected <50 copies/mL) and 11 (10.9%) a detectable rectal HIV-RNA. Median number of HPV infections was 4, with the most frequent among high-risk genotypes being HPV 16 (26.7%), and among low-risk genotypes HPV 42 (33.7%). No other symptomatic sexually-transmitted infections were reported.

Pts were divided into two groups, based on having 4 or less HPV infections (62 pts) versus more than 4 (39 pts). Differences between study groups are summarized in table 1. At multivariate analysis, the presence of more than 4 HPV infections did not confirm any statistically-significant association with detectable rectal HIV-RNA (aOR 2.79, 95% CI 0.49-15.77; p=0.247). Conversely, residual plasma viremia (versus undetectable HIV-RNA, aOR 16.45, 95% CI 2.43-111.40; p=0.004) and older age (per 10 years more, aOR 4.64, 95% CI 1.12-19.24; p=0.034) had an independent association with rectal HIV shedding, after adjusting for ethnicity, previous AIDS-events and months since last plasma HIV-RNA>50 copies/mL.

Conclusion: Rectal HIV shedding was independently associated with residual viremia and older age, but not to a higher number of HPV genotypes. Larger studies are needed to confirm these results.

Table 1. Characteristics of study population according to number of HPV infections (≤4 versus >4 infections).

Variables	Four or less HPV infections N= 62 (%)	More than four HPV infections N= 39 (%)	*p*-value
Age*	52 (44-57)	45 (38-54)	0.018
Caucasians ethnicity	56 (90.3)	33 (84.6)	0.388
Risk factor for HIV:			0.040
- Heterosexual	11 (17.7)	1 (2.6)	
- MSM	45 (72.6)	36 (92.3)	
- IDU	6 (9.7)	2 (5.1)	
CDC stage C	21 (33.9)	11 (28.2)	0.551
Nadir CD4 count (cells/µL)*	286 (136-460)	285 (127-466)	0.802
Time since HIV diagnosis (years)*	13 (7-21)	11 (4-24)	0.529
Residual plasma HIV-RNA (target detected<50 copies/mL)	13 (21.0)	13 (33.3)	0.166
Months since last HIV-RNA≥50 copies/mL	88 (30-137)	40 (7-136)	0.099
Detectable rectal HIV-RNA	5 (8.1)	6 (15.4)	0.250
Antiretroviral therapy:			0.268
- 2NRTIs plus anchor drug	40 (64.5)	31 (79.5)	
- Lamivudine plus dolutegravir or protease inhibitor	20 (32.3)	7 (17.9)	
- Other	2 (3.2)	1 (2.6)	
Number of high-risk HPV-DNA*	1 (1-2)	3 (3-4)	<0.001
HPV-mRNA (at least one)	21 (33.9)	30 (76.9)	<0.001

Values within brackets are expressed as percentages except for * continuous variable (interquartile range).

258 INTEGRATED ANALYSIS OF MULTICELLULAR IMMUNE DYNAMICS DURING HYPERACUTE HIV INFECTION

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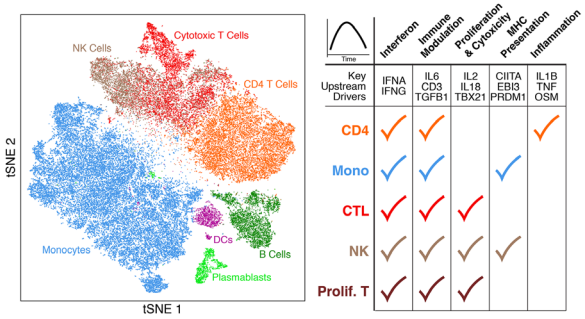
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Background: Development of effective vaccines and therapeutics is facilitated by understanding the earliest moments of infection. Studies in S(H)IV models have characterized the quality and duration of the interferon-stimulated gene (ISG) response in acute infection. However, longitudinal immune responses to acute HIV infection are underexplored. Moreover, contributions and interactions of different cell subsets are unknown. Here, we longitudinally profile multicellular immune responses in hyper-acute HIV infection detected in Fiebig Stage I.

Methods: High-throughput single-cell RNA-sequencing was performed on peripheral immune cells throughout acute HIV-1 infection (pre-infection, HIV detection – 1 year) on 4 FRESH participants (Dong, The Lancet, 2018). Cell subsets were identified by unsupervised clustering analyses. Shared and cell subset specific immune responses were elucidated using a gene-module discovery approach. Modules were tested for significant changes in expression over time and qualitatively compared across individuals. Cellular features of 2 participants who later develop spontaneous control of HIV were also described.

Results: Across all individuals we profiled >59,000 single cells. Onset of viremia induced conserved ISG responses integrated across multiple lymphocyte and myeloid lineages, wherein monocytes and natural killer (NK) cells significantly contributed to the cytokine milieu. Otherwise obscured in bulk analyses, we describe a second layer of responses following ISG upregulation: pro-inflammatory T cell differentiation, prolonged monocyte MHC-II upregulation, and persistent NK cytolytic killing. Predicting upstream drivers, we propose both shared and cell subset specific intra- and inter-cellular regulation by several key cytokines. Two participants who later develop viremic control associated with elevated frequencies of proliferating cytotoxic cells following HIV detection, inclusive of a previously unappreciated proliferating NK cell subset.

Conclusion: We present an experimental and computational framework to longitudinally characterize multicellular responses in viral infection at high-resolution in humans. Applied to hyper-acute HIV infection, our approach reveals both cooperative and cell subset specific immune responses with temporal resolution. We nominate cell subsets and signaling pathways to perturb in future vaccines and therapeutics and highlight the importance of monocytes and NK cells in driving coordination and potentially influencing clinical trajectory.



259 UNCOUPLED CELLULAR AND PLASMA MARKERS OF MONOCYTE ACTIVATION IN EARLY HIV INFECTION

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Background: Monocytes are chronically activated in HIV infection, showing increased expression of CD16 and downregulation of CD14. This observation is concomitant to increased plasma levels of sCD14 and sCD163, which are considered surrogate markers of monocyte activation. Nevertheless, phenotypic abnormalities of monocytes during primary HIV infection (PHI) are not fully characterized.

Methods: We longitudinally studied monocytes in individuals at PHI (n=40) followed for 1 year. HIV-uninfected individuals (n=58) and treated or untreated chronic HIV infected individuals (CHI;n=56) were also cross-sectionally analyzed. Participants were recruited at the Manhiça District Hospital in Mozambique. Monocyte activation was assessed by multicolor flow-cytometry, while plasma levels of sCD14, sCD163 and IFN-a were assessed by ELISA or Luminex.

Results: Plasma HIV viremia peaked at one month after infection and immunological (CD4 and CD8 counts) and virological (VL) plateau was reached after month 4 of infection. The percentage of circulating monocytes was stable during PHI. Activated (CD14+CD16+) and highly activated (CD14−CD16+) monocytes were significantly increased in untreated CHI patients compared to HIV-uninfected individuals (p<0.005). During PHI, the frequency of these subsets remained similar to that of uninfected individuals for the first five months, rising after. In contrast, plasma sCD163 levels peaked at month 2-3 after infection, while the levels of sCD14 showed the highest value at one month after infection and then decreased to reach the levels observed in chronic patients. The expression of the Type-I IFN regulated protein Siglec-1 on monocytes showed a kinetics similar to VL and plasma IFN-a, showing the highest percentage at month 2 after infection and remaining at high levels during the

first year of infection. Furthermore, CD16– monocytes showed significantly higher levels of Siglec-1, suggesting that CD16+ and Siglec-1+ monocytes were activated by different pathways.
Conclusion: Early monocyte activation and plasma IFN-a levels showed similar dynamics during PHI. In contrast, CD16 expression significantly increased after 6 months of infection and was uncoupled from plasma sCD14 and sCD163 levels. Considering the role of activated monocytes in cardiovascular disorders and aging of the innate immune system, an early treatment may potentially reduce monocyte activation, resulting in long-term clinical benefit.

260 IMMUNOLOGICAL AND CYTOKINE CHANGES IN BLOOD AND GUT MUCOSA FROM PHI BY AN EARLY ART

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Background: The initiation of ART during primary HIV-1 infection (PHI) decreases transmission, contains viral reservoir establishment, prevents damage to immune system and reduces immune activation. The aim of this study was to analyse immunological changes in cell subsets in blood and rectal tissue as well as mucosal cytokine profile after initiating an intensified-5-drug ART regimen during very early PHI.
Methods: Patients started an intensified ART consisting on abacavir/lamivudine/dolutegravir regimen during 48 weeks plus darunavir-r and maraviroc the first 12 weeks. Rectoscopies were done at w0 and w48. Immunological subsets in blood (PBMC) and rectal tissue (MMC) were compared between w0 and w48 and between cases (Fiebig I-II, n=6) and controls (Fiebig II-IV, n=11) by multi-parametric flow cytometry. The analysis of 25-cytokines on rectal fluid was performed using Luminex assay. Clinical Trials NCT02588820.
Results: At w48, all except one patient in the controls have undetectable plasma VL. At w48, a higher increase of blood CD4+ T cells was observed in cases (from 39.05% to 47.47% p=0.031) than in controls (from 36.50% to 36.10%, p>0.05). CD4/CD8 ratio was also higher in cases both in PBMCs and in MMCs. ART highly decreased activated CD8+ T cells in both cases (from 24.3% to 12.6%, p=0.0313) and controls (from 30.1% to 7.5%, p=0.004) from PBMCs and MMCs (from 39.55% to 22.80% in cases, p=0.0087 and from 52.8% to 36.9% in controls, p=0.004). Concerning naïve CD4+ and CD8+ T cells, higher percentages were seen in cases with respect to controls even before initiation of ART and were maintained at week 48. Moreover, CD8+ TSCM cells were higher in cases before and after ART (p=0.014 and p=0.005, respectively). At mucosal tissue, percentage of macrophages (CD11c+ CD163+) was higher in controls than in cases (p=0.009) at w0 and decreased in controls (p=0.006) at w48. In general, a decrease of pro-inflammatory cytokines, such as IL-8, occurred mainly in samples from cases at w48 (721.4 vs 485.5, p=0.008). In addition, levels of Th1 (IFN-γ, IL-12, MIP-1β), Th2 (IL-4, IL-10) and Th17 cytokines and chemokines decreased similarly in both cases and controls at w48.
Conclusion: An extremely early and intensified ART in PHI patients allowed good immunological reconstitution, decreased immune activation and reduced inflammatory profile in different body compartments.

261 IDENTIFICATION OF BROADLY NEUTRALIZING ANTIBODIES FROM SHIV-INFECTED CHINESE MACAQUES

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Background: Broadly neutralizing antibodies (bnAbs) have been obtained from HIV-1-infected individuals after 2-4 years of infection. However, bnAbs with similar breadth and potency have not been isolated from SHIV-infected rhesus macaques. Understanding how bnAbs develop in SHIV-infected non-human primates (NHPs) will have important implications in use of rhesus macaques to study efficacy of HIV-1 vaccines.
Methods: Single memory B cells were sorted with a pair of HIV-1 Env V2 differentiating baits from an SHIV1157ipd3N4-infected rhesus macaque which showed broad neutralization activity in plasma after 6 years of infection. Paired variable heavy and light chains were amplified from the same B cells. The recombinant IgG proteins were expressed in Expi293 cells. Neutralization activity was determined using 17 hard-to-neutralize tier-2 viruses on TZM-bl cells.
Results: 48Abs were expressed and 12 of them were found to bind HIV-11157gp120. Six (J029, J031, J033, J038, J040 and J044) from the same lineage (VH4-2*01 F and VK1-20*01 F) neutralized 2-12 viruses. Among them, J038 and J033 had the broadest neutralizing activities, neutralizing ~70% of 17 tier-2 viruses. Both Abs also had the highest somatic mutation rate (~20%) and 18 amino acids in the HCDR3 region. Inferred UCA of the J033 lineage Abs had no neutralization activity, indicating the broad neutralization activity was obtained during the lineage maturation. No Abs from other lineages neutralized any of 17 tier-2 viruses. Epitope mapping with CAP45 mutants showed that N160A/T162A (deletion of a glycosylation site) and K169E mutants rendered the virus fully resistant to both mAbs, similar as human V2-target bnAbs. Both J038 and J033 bound deglycosylated gp120 at much reduced levels, confirming that neutralization mediated by both Abs depends on glycosylation in V2. Analysis of the viral sequences showed that the three mutations (I165L, K171R and V172A) together in V2 rendered the virus more resistant to both Abs, suggesting viruses with these mutations had escaped from this lineage of Abs.
Conclusion: Similar bnAbs as those identified in humans can be elicited in rhesus macaques during natural SHIV infection. Further characterization the maturation pathway of these bnAbs by comparing to bnAbs with the similar specificities in humans will provide unprecedented insight into mechanisms of bnAb development in NHPs.

262 VH GENE POLYMORPHISM ASSOCIATED WITH POTENT ANTI-SIV NEUTRALIZING ANTIBODY INDUCTION

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Background: Induction of potent broadly-neutralizing antibodies (bNAbs) is a key for anti-HIV vaccine development. The boosting method for B-cell maturation toward bNAb induction has not been established, although recent studies have developed germline-targeting immunogens for priming. Here, we present a unique macaque model to analyze B-cell responses leading to anti-simian immunodeficiency virus (SIV) bNAb induction.
Methods: In our previous study, we obtained four rhesus macaques inducing potent anti-SIV bNAbs, VH3.33-restricted B404-class Abs, after SIVsmH635FC infection. In the present study, we examined B404-class Ab induction in six SIVsmH635FC-infected rhesus macaques. Monoclonal anti-SIV Fab clones were isolated from lymph nodes (LNs) by Bio-panning using phage display. B cell receptor (BCR) VH sequences derived from peripheral lymphocytes and LNs were analyzed by next generation sequencing (NGS).
Results: B404-class Ab induction was observed in one of the six SIVsmH635FC-infected macaques but undetectable in the remaining five.Investigation of germline VH3.33 genes in five B404-class Ab inducers (one in the present study and four in the previous study) and five non-inducers revealed association of B404-class Ab induction with VH3.33 polymorphisms. Analysis of germline-reverted B404 mutants revealed that the VH3.33 residue 38 is the determinant for B404-class Ab induction. A B404-associated VH3.33 allele-positive macaque dominantly induced B404-class Abs even under undetectable viremia.
Conclusion: Our results first demonstrate restriction of bNAb induction by germline VH-gene polymorphism in a macaque AIDS model. Analysis using B404-associated VH3.33 allele-positive macaques could facilitate understanding of B-cell maturation leading to potent Ab induction.

Table 1. Germline VH3.33 alleles in B404-class Ab inducers and non-inducers

Macaques	VH3.33 allele*		B404-class Ab induction
#1964	VI	VI	none
#1967	VI	VI	none
#1978	VI	VI	none
#1994	VI	VI	none
#1980	ET	VI	positive
#2008	VI	VI	none
H704	ET	ET	positive
H709	ET	ET	positive
H714	ET	VT	positive
H723	ET	ET	positive

*ET, VH3.33 having 38E and 65T; VI, VH3.33 having 38V and 65I; VT, VH3.33 having 38V and 65T. Animals having VH3.33_ET showed B404-class Ab induction, but others not.

263 POLY/AUTOREACTIVITY AND BROAD NEUTRALIZATION ARE DETERMINED BY DIFFERENT MUTATIONS

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Background: Nearly half of broadly neutralizing antibodies (bnAbs) are polyreactive and/or autoreactive (poly/autoreactive). Some of them, like CH103, gain poly/autoreactivity during bnAb maturation. However, whether poly/autoreactivity and broad neutralization are governed by the same mutations during bnAb maturation is not well understood.

Methods: Mutations in Ab pairs differing in poly/autoreactivity within the CH103 lineage were individually introduced back into the Ab from each pair with less (or no) poly/autoreactivity. Recombinant Abs were expressed and purified from transfected Expi293 cells. Neutralization activity against HIV-1 was determined using the TZM-bl assay. Poly/autoreactivity was analyzed by their ability to bind HEp-2 cells, host proteins and UBE3A. Positions and properties of mutations were analyzed using Swiss-Model.

Results: Poly/autoreactivity became detectable for intermediate antibody 1 (IA1) and mature bnAbs during evolution of the CH103 lineage. There were 2, 17 and 11 amino acid (aa) differences between IA2/IA1, IA3/IA1, and CH103/CH106 Abs, respectively. Each of these aa differences was introduced into the Abs without (IA2 or IA3) or weak (CH103) poly/autoreactivity, and they had little effects on neutralization. The IA2 variable heavy (VH) N60S mutant Ab and the CH103 VH E56H mutant Ab reacted to HEp-2 and many host proteins and dsDNA, while the IA2 VH E64K mutant Ab was only reactive to histone. The protein array analysis using ~9000 human proteins showed that the IA2 N60S mutant Ab is poly/autoreactive, while the E64K mutation did not render IA2 poly/autoreactive. The UBE3A binding analysis of all mutants showed that only the VH E64K mutation in IA2 and IA3 as well as the VH E56H and VL E45D mutations in CH103 rendered their parental Abs reactive to UBE3A. Structure modeling showed all those mutations were in VH CDR2 or upstream of VL CDR2 but the aa substitutions were not thought to affect binding to HIV-1 Env. However, aa charge changes in the VH and VL CDR2 regions may play an important role in increased poly/autoreactivity.

Conclusion: Development of poly/autoreactivity during maturation of the bnAb CH103 lineage is determined by several somatic mutations not required for developing broad neutralization. The charge changes in the CDR2 regions of VH and VL mini-genes may play an especially important role in specifying poly/autoreactivity in this bnAb lineage.

264 POLYFUNCTIONAL ANTIBODY RESPONSE TO SHORT-SCHEDULE EBOLA VACCINE IN HIV+/– SUBJECTS

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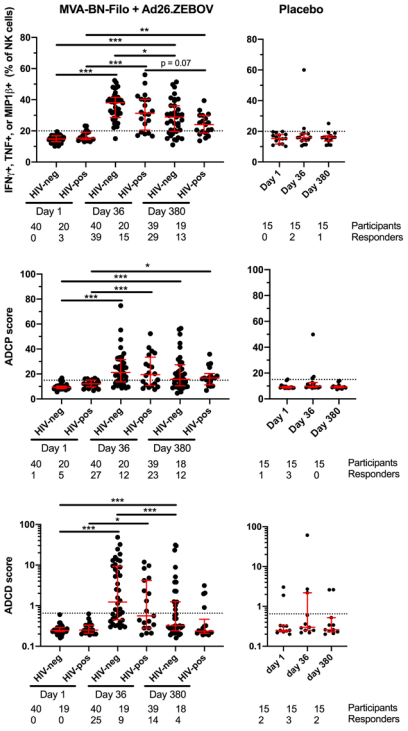
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Background: Ebola outbreaks occur in areas with a higher prevalence of HIV infection that may impact vaccine efficacy as ART-treated HIV+ subjects have been shown to generate lower responses to other vaccines. Non-neutralizing functions of antibodies may contribute to protection from Ebola virus infection, but it is unclear if HIV modulates these responses after vaccination. Antibody functionality was explored in HIV+ and HIV- subjects following an accelerated Ebola vaccination schedule that is not intended for licensure.

Methods: Polyfunctional antibody effector functions were examined following IM administration of 1x108 Inf U MVA-BN-Filo (dose 1) followed by 5x1010 vp Ad26.ZEBOV IM 14 days later in ART-treated HIV + and HIV- adults in the US. Plasma samples from days 1, 36, and 380 were used to evaluate antibody dependent cellular phagocytosis (ADCP), complement deposition (ADCD), and induction of NK cell cytokine production by flow cytometry.

Results: 40 HIV- and 20 HIV+ subjects received the heterologous vaccine schedule and 15 individuals received placebo (10 HIV- and 5 HIV+). The vaccine was well tolerated and binding antibodies were detected to the Ebola glycoprotein in all vaccinees after completion of the 2 dose regimen. Significant increases from baseline in effector antibody responses were observed at day 36 (peak) in HIV+ and HIV- subjects. Placebo subjects had no response. At day 36, there was no significant difference between HIV+ and HIV- subjects in effector antibody functions but responses in HIV+ subjects tended to be lower. Responses declined in both populations by day 380, see figure 1. The majority of subjects in both populations (HIV-infected 50%, HIV- uninfected 59%) show polyfunctional capability, defined as 2 or more effectors, at day 380. Lower antibody polyfunctionality in HIV-infected subjects was not associated with the CD4 to CD8 ratio. Given the small sample size, definitive conclusions about any observed differences can not be made.

Conclusion: Polyfunctional antibody effector functions were significantly increased from baseline in response to an accelerated Ebola vaccination schedule in HIV+ and HIV- subjects. Although responses declined in both populations, at least 2 antibody effector functions persisted in the majority of subjects until day 380.



265 PULMONARY TUBERCULOSIS DISEASE ENHANCES HIV-1 ANTIBODY RESPONSES

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Background: Mycobacterium tuberculosis (TB) is an integral component of complete Freund's adjuvant which is known to augment antibody production. We hypothesized that active TB disease enhances the development of HIV-1 broadly neutralizing antibodies (bnAbs) in people living with HIV-1.

Methods: We compared anti-HIV-1 antibody response among treatment-naive plasma samples from 15 HIV-1 patients with active pulmonary TB (HIV-1/TB) and 16 HIV-1 only infected individuals. Ability to inhibit 12 different tier 1 and 2 HIV-1 variants of diverse subtypes in the TZM-bl neutralization assay was used to estimate a neutralization breadth and potency (BP) score. Total IgG and cytokine levels were estimated using multiplex Luminex based assays. Neutralization heatmaps were used to identify potential targeted HIV-1 envelope epitopes. Comparisons were done using the Wilcoxon rank-sum and Fischer's exact tests.

Results: HIV-1/TB and HIV-1 only infected individuals had similar baseline plasma virus levels (p= 0.33) and CD4 counts (p= 0.40). HIV-1/TB individuals had a significantly higher BP score (0.59 ± 0.05, range 0.34-0.98) than the HIV-1 only group (0.43 ± 0.02, range 0.25-0.59, p= 0.006). Four of the HIV-1/TB but

none of the HIV-1 only infected individuals had a similar or higher BP score as that observed among 2nd generation bnAbs (BP score range 0.71-0.98, p= 0.04). Neutralization BP score correlated with the total plasma IgG (r = 0.51, p= 0.003), but not with baseline viral load, absolute CD4 count, IL-6, soluble CD163 or MCP-1 concentrations. After completing TB treatment and starting HIV-1 therapy, HIV-1/TB (0.68 ± 0.07, n= 6, range 0.28-0.88) as compared to HIV-1 only infected subjects (0.57 ± 0.07, n= 8, range 0.34-0.82) still had higher neutralizing capacity, but the difference was not statistically significant (p= 0.56). The plasma activity of the 4 HIV-1/TB individuals with high baseline BP score clustered with CD4 binding site and membrane-proximal external region targeting bnAbs.

Conclusion: Our results suggest that active TB enhances anti-HIV-1 antibody response, possibly leading to the emergence of bnAbs that target conserved envelope domains. Dissecting mechanisms that account for the enhanced HIV-1 neutralization in HIV-1 cases with TB could be leveraged in the generation of a more effective humoral response in HIV-1 vaccination and treatment.

266 IMPACT OF IMMUNE CHECKPOINT INHIBITORS IN VACCINE-INDUCED ANTI-HIV RESPONSES

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Background: To attain the control or elimination of HIV-1 infection it is critical to delineate immune interventions capable of boosting or reinvigorating HIV-1-specific CD8+ T-cell responses. Immune interventions, including therapeutic vaccines or immune checkpoint inhibitors (ICIs), have been postulated to achieve this goal. However, the potency of combining both immune interventions has not yet been tested. Here, we assessed ex vivo the impact of ICIs on vaccine-induced HIV-1 CD8+ T cell responses in samples from a vaccine trial conducted in early-treated HIV-1 infected individuals.

Methods: We selected PBMCs of individuals from the BCN01 (NCT01712425) trial receiving early treatment and a ChAdV63.HIVconsv/MVA.HIVconsv prime-boost regimen (Etvac; n=12). For comparison, we selected PBMCs from early treated not vaccinated individuals (Et; n=13) and chronically treated individuals (Chro; n=11). PBMCs were CFSE-stained and stimulated with an HIV-1 peptide pool in the presence of anti-PD-1, anti-TIM-3, anti-PD-1+TIM-3 or isotype antibodies. After seven days, we quantified the frequency of CFSE-, IFNg+ and HLA-DR+/CD38+ HIV-1-specific CD8+ T cells by polychromatic flow cytometry. Also, we measured a panel of 17 human cytokines in the culture supernatants by multiplex assay.

Results: The blockade of PD-1 in Etvac boosted the frequency of vaccine-induced HIV-1-specific CD8+ T-cell responses in terms of proliferation (p=0.004), IFNγ production (p=0.04), and HLADR+/CD38+ expression (p=0.004). These results were consistent for anti-PD-1+TIM-3 in the absence of response to anti-TIM-3. In Et, ICI did not have any effect while Chro individuals showed an increase in the frequency of HIV-1-specific CD8+ responses upon PD-1 or PD-1+TIM-3 inhibition. The cytokine profiling in Etvac individuals revealed a specific signature of IFNg, sFasL, GM-CSF, sCD137, IL-5, IL-13, Granzyme A, Granzyme B, MIP-1b and Perforin secretion in response to anti-PD-1 that differed in Chro by the lack of IL-5 and IL-13 and the presence of IL-4 and IL-10.

Conclusion: Our data demonstrate a significant increase in the magnitude of vaccine-induced HIV-1-specific CD8+ T-cell responses by ICIs linked to a particular cytokine signature profile in Etvac. Thus, we propose the combined use of ICI and therapeutic vaccines to boost vaccine-induced anti-HIV CD8+ responses in vivo. In addition, the use of combined ICI as an anti-HIV immunotherapeutic strategy in Chro warrants further investigation.

267 CHARACTERIZING "EXCEPTIONAL" CONTROL AMONG HIV ELITE CONTROLLERS

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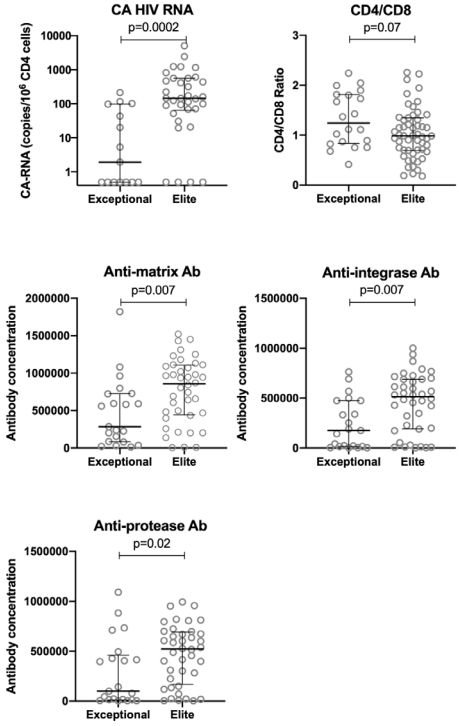
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Background: Studies of "elite controllers" (ECs) might lead to novel approaches for HIV cure. We characterized the clinical, immunologic and virologic characteristics of ECs with very low reservoirs ("exceptional controllers"). Such individuals may prove to be models for a functional cure.

Methods: We systematically applied a clinical case definition to identify ECs within the SCOPE cohort. A related ART-treated cohort (n=80) was used for comparison. We measured CD4 T cell-associated (CA) HIV DNA and RNA using PCR from median 9M PBMCs, HIV-specific antibody responses using luciferase immunoprecipitation systems (LIPS), and T cell responses using flow cytometry. We stratified the sample by reservoir size and compared clinical outcomes, antibody response, and T cell immunophenotypes. Exceptional controllers were defined as ECs with no detectable HIV DNA. Clinical progression was defined as loss of virus control or CD4 decline requiring ART.

Results: 96 individuals met our case definition. Median CA DNA and CA RNA was 1.5 (0-7.6) and 99 (4.8-317) copies/10^6 cells, respectively. These levels were significantly lower than those on ART (CA DNA 10.8 and CA RNA 2138 copies/10^6 cells, p<0.001 for both). CA DNA levels highly correlated with CA RNA levels (0.74, p<0.001). CA DNA levels were associated with antibody levels targeting matrix (r=0.30, p=0.008), integrase (r=0.26, p=0.03), and protease (r=0.27, p=0.02), but not envelope, or measures of T cell activation. 22 (23%) met our virologic definition of exceptional control. Exceptional controllers were more likely to have a protective HLA allele (B27 or 57; p=0.002) and less likely to progress clinically (18% vs 49%, p=0.02). Compared with the rest of the EC cohort, exceptional controllers had lower antibody levels to matrix (p=0.007), integrase (p=0.007), and protease (p=0.02), but comparable levels of T cell activation. In a logistic regression model, exceptional control was associated with presence of protective HLA alleles (6.8 fold effect, p=0.002).

Conclusion: We identified a subset of controllers with very low HIV DNA and RNA levels, low HIV antibody levels, and lower risk of clinical progression. These individuals are enriched for certain HLA alleles, arguing that CD8+ T responses mediate control. Such individuals may not need ART and might prove to be a model for a "functional cure" or remission.



268 HIV-SPECIFIC CD8+ T CELLS EXHIBIT POOR CYTOLYTIC POTENTIAL IN THE HUMAN AIRWAY

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Background: HIV mRNA and proteins are detectable in airway samples from individuals on long-term ART with undetectable plasma viral load. Effector CD8+T cells play a direct role in the control of HIV replication through direct

killing of infected cells or the production of β-chemokines that block HIV-co-receptor usage. However, it remains unclear whether effector HIV-specific CD8+T cells expressing cytolytic molecules are present within the airway, a site of HIV persistence.
Methods: We recruited 80 HIV-uninfected healthy controls and 80 asymptomatic ART-naïve HIV-infected adults who were followed up for a year on ART. We collected paired bronchoalveolar lavage (BAL) fluid and peripheral blood samples on all participants. We performed flow cytometry-based characterization of CD8+T cell phenotypes and also quantified HIV (Gag, Nef and Pol)-specific IFN-g-producing CD8+T cells in BAL and blood cells.
Results: CD8+ T cells expressing Perforin and Granzyme B were found predominantly in the blood compared to the airway, regardless of HIV infection status. The frequency of Eomes+CD8+ T cells was higher in blood-derived cells compared to those from the airway lumen. PD1 or 2B4-expressing CD8+ T cells were higher in airway-derived cells compared to blood. Untreated HIV-infected adults had more Eomes+PD1+CD8+T cells compared to healthy controls; predominately in the airway compared to the systemic circulation. HIV-specific (Gag, Nef and Pol) CD8+T cells exhibited a higher breadth in the airway than in blood. There was no correlation between HIV-specific CD8+T cell responses in the airway and peripheral blood. HIV-specific CD8+ T cells did not express Perforin and Granzyme B but expressed high levels of PD1 and Eomes, markers associated with immune regulation and exhaustion in HIV infection.
Conclusion: We demonstrate that airway-derived HIV-specific CD8+T cells poorly express cytolytic molecules (Granzyme B and Perforin) and possess markers consistent with high immune regulation (PD1 and Eomes). The poor cytolytic potential and highly regulated phenotype of airway HIV-specific CD8+T cells could promote the persistence of HIV-infected cells in the airway in individuals on long term ART.

269 HIGH FREQUENCY OF CD8 ESCAPE MUTANTS IN ELITE CONTROLLER AS NEW OBSTACLE TO HIV CURE

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Background: The shock and kill strategy to purge the reservoir has failed likely as a consequence of several obstacles. The existence of escape mutations in regions of the HIV proviral sequence coding for epitopes of CD8 immune response has been postulated as one of the reasons for this failure. Herein, we have analyzed the frequency of these mutations in two different groups of HIV patients with complete viral suppression: patients on successful cART and elite controller patients.
Methods: Twenty HIV patients were included: 7 elite controllers (EC) and 10 non-controller patients on successful cART (TX). CD4 resting memory cells were immunomagnetically purified and total genomic DNA was extracted. The entire Gag gene was amplified by nested PCR and a pair-end sequencing run on a MiSeq system was performed. Sequences were mapped and aligned to the consensus HXB2 sequence. Optimal Gag epitopes of CD8 immune response were predicted for each patient based on their HLA class I haplotype (A, B, C). The prevalence of mutated epitopes as well as its impact on HLA recognition were calculated for each patient.
Results: EC and TX groups were matched for age, years of HIV diagnosis and CD4 T-cell counts. TX patients had been on cART for a median of 12[9-16] years. The whole HIV-Gag sequence was successfully amplified and sequenced in all patients. The median number of CD8 Gag epitopes predicted for EC and TX patients were 7[4-7] and 7[6-12], respectively. Of note, the prevalence (%) of mutated CD8 epitopes was 75[46-100] and 54[48-74] in EC and TX respectively (p=0,432). Moreover the frequency (%) of mutated peptides with a significant impact reducing HLA recognition was similar in both groups (50[33-50] in EC and 41[19-52] in TX, p=0,552).
Conclusion: Our results show a high prevalence of mutations in HIV-Gag epitopes of CD8 T-cell response not only in the HIV reservoir of patients with successful cART-mediated control, but also in patients with spontaneous HIV control in whom control is reached at an early stage of infection. Indeed, many of these mutations have a potential negative impact on antigen recognition. These findings support the role of existence of escape mutations as another obstacle to purge the HIV reservoir. This could provide a proof of concept challenging the current HIV cure strategies based on reservoir reactivation.

270 ASSOCIATION OF POLYFUNCTIONAL CMV-SPECIFIC T CELLS WITH FRAILTY IN HIV-INFECTED MEN

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Background: Cytomegalovirus (CMV) infection is associated with both HIV infection and frailty. CMV-specific T cell responses correlated differently with immune activation and inflammatory markers, depending on donor HIV and frailty status; and the proportion of CD4 T-cells producing IL-2 in response to CMV predicted onset of frailty. Here, we studied T-cell production of IFN-γ and TNF-α as well as IL-2 as predictors of a) onset of frailty in nonfrail men, and b) stability of frailty in frail men, in HIV+ and HIV- men who have sex with men.
Methods: CMV-specific T cell responses of 42 men (22 virologically suppressed HIV+, 20 HIV−; 21 frail, 21 non-frail) were assessed by flow cytometric analysis of production of IFN-γ, TNF-α and IL-2 in response to overlapping peptide pools spanning 19 CMV open reading frames. Frailty was assessed semiannually using the Fried criteria. To explore the relationship between cytokine-producing T cells and onset (in nonfrail men) and stability (in frail men) of frailty, men were categorized into tertiles of percentages of these cells. Times to onset or loss of frailty were compared by tertiles using Kaplan-Meier estimators and the nonparametric log-rank test.
Results: Cytokine production by T cells fell into three main patterns: IFN-γ+TNF-α+IL-2- (median: 51% vs 58% of CD4 vs CD8 cytokine-producing cells), IFN-γ+TNF-α-IL-2- (15% vs 34%), and IFN-γ+TNF-α+IL-2+ (11% vs 5%). IFN-γ-TNF-α+IL-2+ CMV-specific T cells were detected in only one man. Percentages of these subsets of cells did not differ significantly by HIV and frailty status. Over a median follow-up of 7 years, for HIV- men onset of frailty was associated with higher percentages of IL-2+ CD4 cells also producing IFN-γ and/or TNF-α, and of IFN-γ+TNF-α-IL-2- CD4 T cells ($p<0.001$). In contrast, for HIV+ men, onset of frailty was associated with lower percentages of the latter cells ($p<.05$). Lower percentages of these cells were associated with remaining frail for all men ($p<.05$ for HIV- and $p=0.06$ for HIV+ men).
Conclusion: Percentages of IFN-γ, TNF-α and IL-2-producing CMV-specific T cells did not differ significantly by HIV and frailty status. However, high percentages of IFN-γ+TNF-α-IL-2- CD4 T cells predicted onset of frailty in HIV- men, and low levels of these cells predicted both onset of frailty among HIV+ men, and maintenance of frailty in both HIV- and HIV+ men. Thus, this T cell subset may play different roles in onset and maintenance of frailty in HIV- and HIV+ men.

271 VULNERABLE TARGETS IN HIV-1 POL FOR ATTENUATION-BASED VACCINE DESIGN

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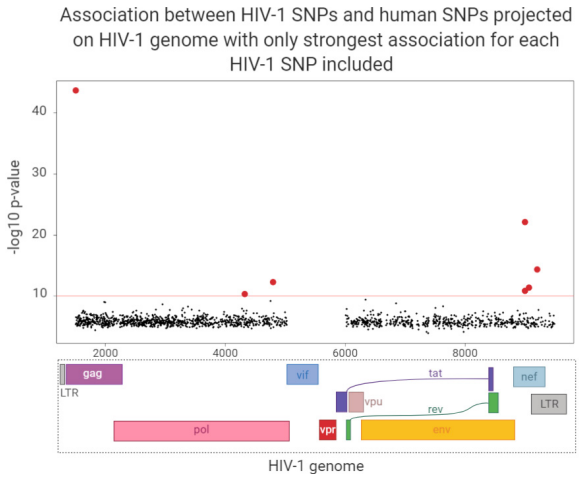
Background: Identification of viral immune escape mutations that compromise HIV's ability to replicate may aid rational attenuation-based vaccine design. Focussing cytotoxic T cell (CTL) responses on several epitopes where CTL escape compromises viral replication may delay escape and or attenuate the virus. We investigated immune-mediated attenuation in Pol, specifically reverse transcriptase (RT)-integrase
Methods: We generated 487 recombinant viruses encoding RT-integrase from individuals with chronic ($n = 406$) and recent ($n = 81$) HIV-1 subtype C infection and measured their in vitro replication capacities (RC) using a GFP-reporter T-cell assay. A codon-by-codon analysis was performed to identify amino acids associated with altered RC and mutagenesis experiments were performed to validate the effect of these mutations on RC.

Results: The polymorphisms V241I, I257V, P272K and E297K in RT and I201V in integrase, all relatively uncommon polymorphisms occurring in or adjacent to optimally-described HLA-restricted CTL epitopes, were statistically associated with the most pronounced decreases in RC, while RT polymorphisms E6K and A158S (both in CTL epitopes) were associated with modestly reduced RC. A subset of sequences (n=89) were mutated at the RT-integrase stop codon (*849Q), leading to the usage of a stop codon 17 residues downstream. These extended integrase sequences were significantly associated with reduced RC. Our mutagenesis experiments confirmed that RT mutants A158S, V241I, I257V as well as the integrase mutation *849Q significantly and negatively impact RC
Conclusion: In summary, the length of integrase influences Pol RC and RT-integrase variants in vital domains of the RT palm (158S) and RT thumb (241I and 257V) represent potential vulnerable targets for an attenuation-based vaccine. The relevant RT-integrase epitopes spanning these residues could be utilised in a vaccine construct to stimulate the CD8+ T cell responses, and in the event that the virus escapes these specific responses, this is likely to be accompanied by a replicative fitness cost

272 ASSOCIATION OF HIV AND HOST GENETIC VARIANTS IN ANTIRETROVIRAL THERAPY-NAIVE PERSONS

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Background: HIV-1 genetic diversity allows the virus to adapt and escape the host's immune response; conversely, certain sections of the host genome affect the replicative rate of the virus. The molecular specificity of the interplay between viral genetic escape and host genomic control remains poorly defined. Here, we associated viral genetic data with recently reported host genetic data from a demographically diverse cohort of ART naïve HIV+ participants in the Strategic Timing of AntiRetroviral Treatment (START) trial.
Methods: Two 3.6 kb amplicons (HIV-1 HXB2 genome regions 1,485-5,058 and 5,967-9,517) from viral genomes from plasma samples were sequenced on Illumina platform. Sequence alignment and single nucleotide polymorphism (SNP) calling were performed with BWA and Vardict software, respectively, using HXB2 genome as reference. Associations between HIV-1 SNPs and human SNPs and imputed human HLA types, respectively, were estimated with logistic regression models adjusting for age, sex and genetic structures in the viral and human population captured by principal component analysis. Bonferroni correction was used to set significance cut-offs.
Results: Human and viral genetic data was combined for 2,035 trial participants. Viral populations showed large diversity across the cohort (most common subtypes were B and C). We identified 1,461 HIV-1 SNPs for association analysis against 398,349 human SNPs and observed significant human SNP associations for a total of 7 HIV-1 SNPs ($p<8.6 \cdot 10^{-11}$; see Figure). All 408 associated human SNPs were in the HLA gene region. While the strongest association was observed in gag (1514C⟶A; rs41293883; $p=2.34 \cdot 10^{-44}$), 4 out of 7 significant HIV-1 SNPs were in nef (Nef downregulates CD4 and MHC class I molecules). Furthermore, we identified 15 imputed HLA alleles which were significantly associated with one or more of the 7 identified HIV-1 SNPs ($p<7.9 \cdot 10^{-5}$) using dominant logistic regression model. Most significant associations were 1514C⟶A HIV-1 SNP with B*57:01 ($p=9.99 \cdot 10^{-57}$) and C*06:02 ($p=5.42 \cdot 10^{-26}$) alleles, respectively.
Conclusion: These data suggest that human immunotypes impose selection on viral genotypes through viral epitope specificity. Alleles of HLA (B*57:01 and C*06:02) observed here to be associated with viral epitope selection have previously been found to be associated with viral load in the same cohort. Hence, the present finding provides independent confirmation of a genuine biological effect of variations in HLA gene region.



273 CXCR5 EXPRESSION ON HUMAN CD8+ T CELLS IS TIGHTLY REGULATED BY EPIGENETIC MECHANISMS

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Background: CD8+ T cells located in B cell follicles play an important role in viral and tumor control. However, only a small subset of CD8+ T cells called follicular CD8+ T cells express CXCR5, the chemokine receptor required for cell migration into B cell follicles. We investigated why most LN CD8+ T cells lack CXCR5 expression, and why there is reduced CXCR5 expression on CXCR5+CD8 T cells (fCD8s) relative to GCTfh.
Methods: We FACS-sorted CXCR5+CD8+ (fCD8s), CXCR5-CD8+ (non-fCD8s), naïve CD8+ T cells and GCTfh from lymph nodes of HIV-1 infected individuals and performed RNA-sequencing (RNA-Seq). DNA methylation was used to profile methylation pattern of the CXCR5 gene and the Assay for Transposase-Accessible Chromatin using Sequencing (ATAC-Seq) was used to quantify accessible genes and to identify epigenetic modules governing CXCR5 expression.
Results: RNA-seq data analysis of fCD8 and non-fCD8s identified 43 gene among the most differentially expressed genes (FDR<0.01) that are associated with epigenetic gene regulation. DNA bisulfite treatment and sequencing showed that 70% of CpG islands in CXCR5 gene were methylated whereas fCD8 had less than 7% methylation levels at equivalent sites. ATAC-Seq analysis revealed a closed chromatin conformation at the CXCR5 TSS in non-fCD8s whereas fCD8s had open chromatin at equivalent sites. Furthermore, analysis of nucleosomal footprinting around the CXCR5 TSS revealed greater nucleosomal occupancy in fCD8s compared to GCTfh, computational simulation indicated that the presence of nucleosomes at the TSS interfered with transcription efficiency resulting in attenuated expression of the CXCR5 gene.
Conclusion: We show that DNA methylation coupled with chromatin compaction at TSS prevent CXCR5 gene expression in non-fCD8s and greater nucleosomal occupancy down-modulate CXCR5 expression levels in fCD8s. Together, these data provide insights into both the underlying molecular mechanisms that repress CXCR5 in non-fCD8s and the molecular mechanisms responsible for the low CXCR5 expression in fCD8s, with implications for HIV cure strategy or eradication of B cell-derived tumors.

274 ADDITIVE DETRIMENTAL EFFECT OF B*35/39 TYPES IN A LARGE MEXICO/CENTRAL AMERICA COHORT

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Background

Polymorphism within the human leukocyte antigen (HLA) class I loci represents the strongest genetic modifier of HIV disease progression. In a cross-sectional Mexico/Central America (MEX/CAM) cohort, we have described both canonical and novel associations between specific HLA and HIV disease progression, from which the B*35 and B*39 subtypes featured several risk associations, including the Amerindian B*35:12/14 and B*39:01/05/06 alleles. As more than 6% of the MEX/CAM cohort expressed two alleles of the B*35 and/or B*39 subgroups, we investigated HLA additive effects and in the context of B*35-PX/PY grouping with HIV disease progression.

Methods: HLA sequence-based typing was performed on 3213 chronically HIV-1 clade B-infected, ART-naïve individuals from Mexico (n=1679), Guatemala (n=418), Nicaragua (n=254), Honduras (n=402), Panama (n=316), Belize (n=102), and El Salvador (n=42). Univariate and multivariate analyses were performed using the Generalized Linear Model (GLM) to evaluate additive effects between B*35/39 subtypes or between B*35-PX/PY groups. Associations were adjusted by age, gender and location of recruitment, included as possible confounders in multivariate analyses. For B*35-PX/PY analyses, only HLA-B heterozygous individuals were compared in order to exclude confounding effects resulting from HLA homozygosity.

Results: Both in univariate and multivariate analyses, expressing one or two copies of any B*35 or B*39 subtype (B*39:02 being the exception) was associated to significantly higher plasma viral load (pVL) and lower CD4 counts (in all cases p<0.05). pVL and CD4 linear regression coefficients were one-fold larger in individuals that co-expressed 2-copies of any B*35/39 in comparison with subjects that expressed 1-copy of any B*35/39, suggesting an additive detrimental effect. We confirmed the B*35-PX group association with poor HIV outcome (both with pVL and CD4), but also observed that B*35-PY alleles were associated to significant lower CD4 counts. Given its similarity with other PX members (B*35:02/03), the Amerindian B*35:12 allele represents a putative new member of the established B*35-PX HIV risk group.

Conclusion: Our results suggest an additive detrimental effect between B*35/39 subtypes, highly frequent in the Mesoamerican Mestizo population. Our results also challenge the B*35-PX/PY hypothesis, indicating that PY alleles can be disease-susceptible and also that differences exist in disease associations within PX/PY grouping.

275 NATURAL RESISTANCE TO HIV-1 CORRELATES WITH IFNA-CONTROLLED STEROL METABOLISM

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Background: The ER-associated enzyme cholesterol-25-hydroxylase (CH25H) is an Interferon stimulated gene (ISG) which is able to interfere with viral replication through the modulation of cholesterol metabolism. We therefore verified if natural resistance to HIV-1 infection in HIV-exposed seronegative (HESN) subjects is at least partially dependent on a peculiar regulation of sterol biosynthesis pathway mediated by IFN-induced CH25H expression.

Methods: Peripheral blood mononuclear cells (PBMCs) and monocyte-derived macrophages (MDMs) isolated from 15 sexually-exposed HESN, their HIV+ partners and 15 healthy controls were analyzed for: 1) percentage of IFNa-producing plasmacytoid Dendritic Cells (pDCs); 2) RNA expression of factors involved in lipoprotein signaling and cholesterol metabolism by Real Time PCR; 3) susceptibility to HIV-1 infection by p24 viral antigen quantification.

Results: The increase in IFNa-producing pDCs in both unstimulated and in vitro HIV-infected PBMCs from HESN was coupled with an augmented expression of cholesterol-25-hydroxylase (CH25H) (HESN vs HC: p<0.001 in both cases). The expression of several genes involved in cholesterol metabolism (LXR, ABCA1, SCARB, HMGCS1, PPARg) was modulated as well (>3 fold) in unstimulated as well as in in vitro HIV-1-infected PBMCs and MDMs from HESN. Notably, this resulted in a significantly reduced susceptibility to in vitro HIV-1-infection in PBMCs and MDMs of HESNs (p<0.01).

Conclusion: The observation that CH25H, an oxysterols-producing enzyme, is up-regulated in HIV-exposed cells from HESN, is particularly intriguing. This could be related to the activation of the IFNa pathway, resulting in a reduced susceptibility to in vitro HIV-1 infection. Further analyses are needed to ascertain the cholesterol pathway involvement in natural resistance to HIV-1 infection. These results, nevertheless, suggest a possible basis in novel preventive and therapeutic approaches against HIV-1 infection

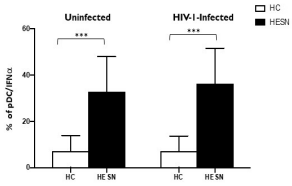


Figure 1 Evaluation of IFNa- producing -pDCs percentage on PBMCs of HESN compered to Healthy Controls. The percentage of IFNβ-producing PBMC was evaluated in PBMC isolated from 10 HESN and 10 HC. PBMCs from HESN showed a higher percentage of IFNβ- producing -pDCs in HESN compared to HC in both unstimulated and in 3-days post in vitro infection in vitro HIV-1 infected PBMCs. Mean values and ES are shown. ***= p< 0,001.

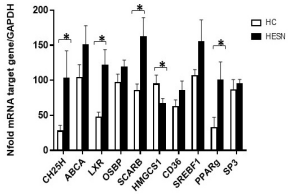


Figure 2 Evaluation of cholesterol metabolism gene expression in 7-days HIV-infected MDMs from HESN and HC by QPCR. the expression of several genes involved in sterol metabolism was altered in MDMs from HESN compared to HC. In particular, the expression of CH25H, ABCA1, LXRa, SCARB1 and PPARg was significantly increased compared to HIV-1 infected MDMs from HC (p<0,05 for all targets) while the expression of HMGCS1 (p< 0.05) was reduced . Mean values and ES are shown. *= p< 0,05.

276 BASELINE INDUCIBLE HIV p24 INFORMS VIRAL CONTROL DURING INTERFERON-A MONOTHERAPY

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Background: Pegylated (peg) IFNα monotherapy after ART interruption results in increased HIV control in association with NK cell activation. The relationship between inducible or other HIV proviral reservoir measurements with subsequent time to rebound during ART interruption and Peg IFN-α monotherapy are unknown.

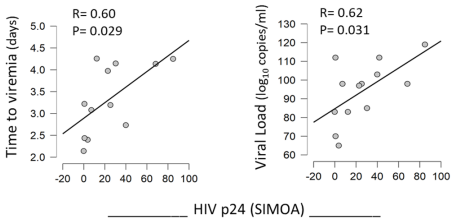
Methods: 13 individuals randomized to arm 1 of the BEAT-HIV study (NCT02227277: HIV VL < 50 copies/ml on ART, CD4 count > 450/µl) receiving 1 µg/kg of peg-IFNα-2b (Pegintron, Merck) for 20 weeks, interrupting ART at week 4 and resuming it upon viremia (VL > 50 copies/µl, bi-weekly evaluations) or at week 20.

P24 SIMOA (iP24) was measured in CD4+ T cells cultured for 16-hour with medium or PMA/Ionomycin using single molecule array (SIMOA). Intact, 5' defective, 3' defective and total proviral DNA were measured by Accelevir, Inc. on CD4+ T cells; Integrated HIV proviral DNA was assessed using Alu-gag RT-PCR on CD4+ T cells. Time to viremia was first VL > 50 copies/ml after stopping ART. HIV-specific responses in PBMC: a) T cell - 6-hour cultures of PBMC with of 15-mer gag peptides. B) NK ADCC: 4-hour co-cultures with anti-HIV sera with gp120-coated CEM NKres targets. Multicolor flow cytometry was used to assess HIV-specific degranulation and cytokine production.

Associations were tested with Pearson or Spearman tests, and linear regression models.

Results: 12 of 13 participants became viremic during ART interruption, one remained suppressed and was imputed to week 20. ip24 was positively associated (p<0.05) with time to viremia (effect estimate 0.362; p= 0.029; Adj R2 = 0.305), first detected VL (Fig 1), and Fc receptor-dependent expression of intracellular MIP1β in CD56dim/CD57neg NK cells, but not with T-cell responses to Gag peptides. Proviral measures were correlated to each other, as expected, but not with time to viremia or level of first VL measured.

Conclusion: In vitro-inducible HIV proteins (i.e.: p24 SIMOA), but not total proviral HIV DNA measures, are associated with level of first viral load and time to viremia during peg-IFNα-2b mono therapy. In contrast to expectation that higher latent reservoirs would lead to shorter time to viremia, the immune correlates measured are consistent with NK ADCC response and chemokine responses contributing to viral control off ART



277 LOSARTAN DOES NOT IMPROVE LYMPHATIC TISSUE FIBROSIS OR T-CELL RECOVERY IN HIV

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Background: Incomplete immune recovery despite HIV viral suppression is associated with excess clinical risk, and is, in part a consequence of fibrosis within secondary lymphoid tissues. We hypothesized that the angiotensin receptor blocker losartan would inhibit fibrosis and improve T-cell recovery within lymphatic tissue, given its established effects in blocking TGF-b.

Methods: We pooled data from two randomized (1:1), double-blind, placebo-controlled trials of losartan (100mg) versus placebo among persons with HIV on ART with plasma HIV RNA <200 copies/mL. Participants underwent an inguinal lymph node (LN) biopsy at baseline and after 12 months. The percent area of collagen and CD4+ T-cells were quantified in the LN parafollicular T-cell zone, using quantitative image analysis. Fibrosis biomarkers in blood were measured using ELISA and electrochemiluminescence (Table). Baseline associations estimated the difference in LN percent area collagen associated with a 1-SD difference in T-cell measures. The treatment effect was defined as change on losartan minus change on placebo over 12 months.

Results: Forty-eight participants had LN tissue available for analysis at both baseline and month 12 (n=23 on losartan; n=25 on placebo). Median age was 55 years, years of HIV diagnosis was 17, and current and nadir CD4+ count were 450 and 59 cells/mm_3, respectively; 97% were male, 59% white. The table reports baseline and month 12 levels of study measures. LN collagen was inversely associated with LN CD4+ T-cells (est: -3.8, p<0.001), though did not reach significance with blood CD4+ count (est: -1.3, p=0.18), and was positively associated with blood CD8+ count (est: 2.5, p<0.01). Losartan treatment was not associated with a significant difference in change of LN collagen, LN CD4+ T-cells, or blood measures of fibrosis activity or T-cell recovery over 12 months (Table). Neither LN collagen nor LN CD4+ T-cells changed over 12 months within losartan or placebo groups.

Conclusion: Among older persons with longstanding HIV disease, losartan did not alter lymphatic tissue fibrosis or T-cell immune recovery over one year. Future research is needed to identify treatments that reduce lymphatic tissue fibrosis and/or improve the associated T-cell immune depletion, given the importance for restoring health among persons living with HIV.

Measurements	Losartan Baseline, Mean (SD)	Losartan Month 12, Mean (SD)	Placebo Baseline, Mean (SD)	Placebo Month 12, Mean (SD)	L vs. P[c] Difference in Change (95% CI)	L vs. P p-value[c]
Lymph Node Tissue						
Collagen, % area[a]	23.6 (6.97)	24.4 (8.16)	23.1 (8.72)	25.4 (8.01)	-1.2 (-5.4, 3.1)	0.58
CD4+ T-cells, % area[b]	28.8 (6.26)	26.5 (8.28)	28.5 (8.19)	27.1 (5.35)	-0.62 (-5.4, 4.2)	0.79
Blood Specimens						
Hyaluronic Acid (ng/mL)[d]	29.1 (25.5)	23.9 (16.3)	25.1 (21.1)	32.3 (31.4)	-10 (-21, 1.5)	0.09
Beta-crosslaps (ng/mL)[d]	0.464 (0.191)	0.41 (0.189)	0.364 (0.122)	0.358 (0.112)	-0.016 (-0.078, 0.046)	0.60
CD4+ T-cell count (cells/μL)	489 (147)	499 (127)	469 (140)	477 (179)	5.9 (-56, 68)	0.85
CD8+ T-cell count (cells/μL)	787 (292)	747 (291)	838 (408)	772 (413)	27 (-66, 120)	0.56

[a]n=47 available for collagen analyses; [b]n=37 available for CD4 tissue analyses; [c]comparison of baseline to month 12 change on losartan versus change on placebo adjusted for baseline value and study; [d]Results for the difference in change were similar when measures were analyzed on log-2 scale

278 IL-21 ALTERS TFH DYNAMICS, IMPROVES FLU VACCINE RESPONSE IN OLD SIV+ NHPS UNDER ART

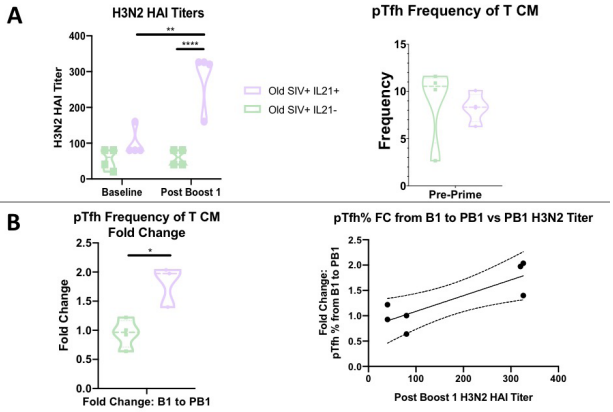
Daniel Kvistad[1], Suresh Pallikkuth[1], Tirupataiah Sirupangi[2], Kyle Russell[1], Rajendra Pahwa[1], Constantinos Petrovas[3], Francois Villinger[2], Savita Pahwa[1]

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Background: HIV/aging contribute to inflammaging (chronic low-grade systemic inflammation) and immune senescence (accelerated aging of the immune system). Immune dysfunction, in the form of impaired antibody (Ab) responses to vaccines such as influenza (flu) vaccination, is observed in aging and HIV infection. Given the central role of IL-21 in Ab responses we hypothesized that administration of IL-21 as a flu vaccine adjuvant in aged, ART treated, SIV+ Rhesus Macaques (RM) would result in significant improvement in the quality of pTfh and B cell function alongside improved germinal center reactions, resulting in improved Ab responses to vaccination. **Methods:** In this study flu vaccination was administered with (N=4) and without (N=4) subcutaneous IL-21 in a prime, boost, boost series at 3-month intervals to old ART treated, SIV+ (IV SIVmac239) RM. IL-21 was given (50μg/kg) on d-2, d0, d5 post each vaccine dose. Blood was collected on d0, d5, d14 and d42; and lymph node tissue was collected on d14 after each vaccine dose. Serum was analyzed for flu Ab titers, and PBMC with multicolor flow cytometry using panels for detailed phenotypic characterization of peripheral blood T follicular helper (pTfh) cells and CD4 memory populations.

Results: In results analyzed to date, pre-prime H3N2 HAI titers of controls (mean=1:55) did not differ from IL-21 treated animals (mean=1:100). Titers increased significantly (p=0.0018) in IL-21 treated animals from 1:100 at baseline to 1:283 post boost 1 (PB1) and were significantly higher (P=<0.0001) than the PB1 control mean titer of 1:60 (Fig. 1A). We did not observe baseline differences in pTfh frequency between groups (Fig. 1A). IL-21 treated animals had significant (p=0.0118) expansion of pTfh, as measured by the fold change of pTfh frequency from day of Boost 1 (B1) to 14 days PB1, correlating with H3N2 HAI titers 14 days PB1 (R2=0.6978, P=0.0193, Fig. 1B). We also observed that the frequency of PD1+ pTfh cells was significantly higher (p=0.0188) in IL-21 treated animals (mean=27%) compared to controls (mean=16.7%) on the day of B1 and correlated with H3N2 HAI titers 14 days PB1 (R2=0.728, P=0.0146).

Conclusion: These findings suggest IL-21 has a significant adjuvant effect, improving flu vaccine titers in old, ART treated, SIV+ RM. As no baseline pTfh differences were observed, these results highlight that IL-21 may be directly or indirectly inducing a shift in pTfh cell kinetics and phenotype, warranting further investigation as a potential vaccine adjuvant.



279 BUTYROPHILINS: NOVEL IMMUNE CHECKPOINT TARGETS FOR HIV

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Background: Overexpression of immune-checkpoint receptors (IRs) has been associated with T-cell exhaustion and overall dysfunction in HIV. CD4 T-cells expressing IRs (e.g, PD-1, CTLA-4, LAG-3) enrich for integrated provirus and likely contribute to viral persistence during ART suppression. We identified a class of IRs, buytrophilins (BTNs), with high homology to B7 family members (e.g., PD-L1 and PD-L2) and the capability to modulate T-cell activation and HIV expression. We postulate BTNs can be exploited to induce both latent virus reactivation and/or T-cell function and serve as novel immunomodulatory targets for HIV cure research.

Methods: An aptamer screen was performed to identify proteins enriched on primary CD4 T-cells infected with HIV. Target enrichment was confirmed by flow cytometry as well as immuno-pulldown in CD4 T-cells from ART-suppressed donors using qPCR and ELISA. Functional assays were performed using recombinant BTN proteins or antibodies to demonstrate the impact of target modulation on HIV latency reversal and T-cell activation. Viral reactivation in a human latency model was measured by GFP or luciferase reporter virus and T-cell activation was evaluated concomitantly via IFNg release in the culture supernatant.
Results: BTN immune checkpoint receptors were identified as cell surface proteins overexpressed on in vitro infected HIV+ CD4 T-cells relative to uninfected cells as determined by aptamer screen and flow cytometry. Antibody-pulldowns in CD4 T-cells from ART-suppressed participants demonstrated BTN3A-expressing cells enrich for HIV integrase RNA (4 of 8 participants), LTR DNA (4 of 4), and p24 protein (5 of 8). Recombinant BTN-Fc fusion proteins inhibited activation of human CD4 T-cells following anti-CD3 antibody stimulation, verifying pathway function. In contrast, BTN3A-specific antibodies enhanced T-cell activation and reactivated HIV in response to anti-CD3 antibody; an activity blocked by recombinant BTN3A-Fc proteins. Novel antibodies were generated against three BTN3A protein isoforms using yeast display and characterized for modulation of HIV latency and T-cell activation. Work is ongoing to evaluate Gag-specific CD8 T cell response +/- BTN antibodies.
Conclusion: This data collectively implicates BTN3A family members as putative immune targets for HIV transcriptional regulation or T-cell activation. This novel finding warrants further investigation to determine if therapeutically modulating BTNs can impact the latent viral reservoir.

280 BISPECIFIC Au NANOPARTICLES FOR THE ENHANCEMENT OF THE NK IMMUNE RESPONSE AGAINST HIV

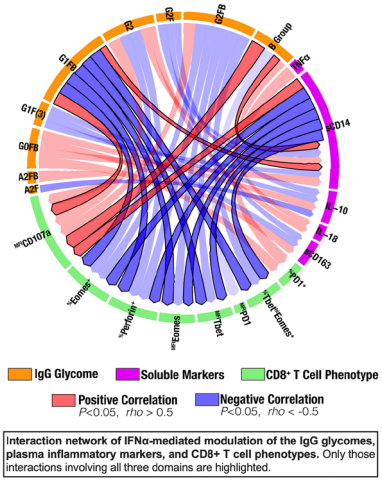
Antonio Astorga Gamaza[1], Mireya L. Borrajo[1], Carla Serra Peinado[1], Laura Luque-Ballesteros[1], Oscar Blanch-Lombarte[2], Julia G Prado[2], Juan Lorente[3], Félix Pumarola[3], Marc Pellicer[3], Vicenç Falcó[3], Meritxell Genescà[1], Víctor Puntes[1], María J. Buzón[1]
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Background: An efficient immunological synapse is required for Natural Killer (NK) cells to kill viral infected cells. HIV infection promotes the appearance of dysfunctional NK cells with diminished capacity to kill infected cells. Thus, new tools to reinvigorate and redirect NK-mediated immune effector functions will help to eliminate HIV.
Methods: We have developed bispecific gold nanoparticles (BiAb-AuNPs) containing two different polarized antibodies at their surface. BiAb-AuNPs were prepared by conjugating AuNPs with IgG anti-HIVgp120 (A32) and IgG anti-CD16 (3G8) antibodies following a novel controlled, linker-free and polarizing conjugation method. Validation was performed by transmission electron microscopy (TEM), UV-Vis Spectroscopy, Dynamic Light Scattering (DLS) and Zeta-potential measurements. The ability of BiAb-AuNPs to promote specific cell contacts was evaluated by flow cytometry and confocal microscopy. Functionality of BiAb-AuNPs was measured by ADCC assays and cytotoxicity assays performed in tonsil histocultures after ex vivo infection with HIV (n=8). In addition, the killing of viral reactivated cells promoted by BiAb-AuNPs was assessed in a primary cell model of HIV latency (n=5). In all assays we included irrelevant bispecific BiAb-AuNPs as a control.
Results: BiAb-AuNPs increased the number of NK-HIV+CD4 T cell doublets by over 7-fold compared to control medium (median %doublets 16.0% vs. 2.5%) (p=0.0143; paired t test). Direct contact zipped by BiAb-AuNPs was confirmed by confocal microscopy. In addition, BiAb-AuNPs increased the percentage of NK cells producing IFN-g and CD107a (median 22.5% vs. 4.9% of medium control) (p<0.05; Friedman test) and triggered a potent cytotoxic response against HIV-expressing cells (median 29.1% vs. 14.9% or 12.7% for irrelevant BiAb-AuNPs and A32, respectively) (p=0.0313 for both comparisons; Wilcoxon test). Moreover, BiAb-AuNPs entered tonsil blocks, measured by the loss of detection of CD16 molecules in NK cells (p=0.0078; Wilcoxon test) and significantly impacted HIV infection in this lymphoid tissue, reaching up to 50% of reduction in some cases (p=0.0313; Wilcoxon test). Furthermore, BiAb-AuNPs enhanced the killing of latent-HIV-infected cells after viral reactivation, inducing a median of 51.5% killing (p=0.0163; One sample t test).
Conclusion: BiAb-AuNPs are a novel molecularly-targeted nanotool that potentiates NK-immune response against HIV.

281 INTERFERON-A MODULATES THE HOST GLYCOSYLATION MACHINERY DURING TREATED HIV INFECTION

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Background: A comprehensive understanding of host factors modulated by the key antiviral cytokine interferon-α (IFNα) is imperative for harnessing its beneficial effects while avoiding its detrimental side-effects, during chronic diseases such as HIV infection. Cytokines modulate host glycosylation, and the host glycome (circulating glycans and cell-surface glycans) plays a critical role in mediating several cellular processes and immunological functions. However, the impact of IFNα on host glycosylation machinery has never been characterized.
Methods: We assessed the impact of pegylated IFNα2a therapy on circulating IgG glycomes and isolated CD8+T and NK cell-surface glycomes of 18 HIV-mono-infected individuals on suppressive antiretroviral therapy, using capillary electrophoresis and lectin microarrays. Plasma levels of sCD14 and sCD163 were measured by ELISA. CD8+T cell and K562-stimulated NK cell phenotypes were profiled using flow cytometry. Integrated HIV DNA in CD4+T cells was measured by qPCR. Wilcoxon test and Spearman's correlations were used for statistical analysis. False discovery rates (FDR) were calculated to account for multiple comparisons.
Results: Interactome analysis highlighted significant interactions that support a model in which a) IFNα increases the proportion of pro-inflammatory, bisected GlcNAc glycans (known to enhance FcγR binding) within the IgG glycome (FDR<0.02), which in turn b) increases inflammation (as measured by sCD14 and sCD163; p<0.03), which c) leads to lower levels of CD8+T cell functionality (perforin, Eomes, and TNFα expression) but higher degranulation (CD107) (p<0.02, Figure). IFNα-mediated induction of bisected GlcNac associated with a poor reduction of HIV integrated DNA (p=0.02, rho=-0.8). Examining cell-surface glycomes, IFNα increases the levels of T antigen (Gal-GalNAc) on CD8+T cells (FDR=0.01). This induction is associated with lower CD8+T degranulation (p<0.02, rho<-0.8). Last, IFNα increases the levels of fucose on NK cells (p<0.05). This induction is associated with higher expression of Eomes, T-bet, and IFNγ upon K562 stimulation (p=0.048, rho>0.8).
Conclusion: IFNα causes host glycomic alterations that are known to mediate inflammatory responses. These alterations are associated with mainly detrimental, but also beneficial, consequences of IFNα on innate and adaptive immune functions. Manipulating glycan-lectin interactions may represent a strategy to enhance the impact of IFNα on immunity while avoiding its detrimental side-effects.



Interaction network of IFNα-mediated modulation of the IgG glycomes, plasma inflammatory markers, and CD8+ T cell phenotypes. Only those interactions involving all three domains are highlighted.

282 PHASE I/II RANDOMIZED STUDY: THERAPEUTIC DENDRITIC CELL VACCINE PLUS PEGYLATED INF-A

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Palomino[2], Carlos Nicolau[1], Jose M. Gatell[3], Felipe Garcia[1], Montserrat Plana[2], for the DCV-3/RISVAC04 Study Group
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Background: A double-blind placebo-controlled randomized therapeutic vaccine trial with myeloid derived-dendritic cells (MD-DC) loaded with heat-inactivated autologous HIV-1 (HIAH) plus pegylated Interferon-alpha (pIFN) in HIV-1 chronic infected patients on antiretroviral treatment (ART) to achieve functional cure was performed.
Methods: 36 patients on successful ART with CD4+ ≥450 cells/mm_3 were randomized 1:1:1:1 and 29 received at w0, 2 and 4 an ultrasound-guided inguinal intranodal dose of: 1) vaccine (V) 107 MD-DC pulsed with 1010 HIAH (n=8); 2) V plus 3 doses of pIFN (VpIFN) at w4, 5 and 6 (n=6); 3) placebo (P) (n=7); and 4) P plus 3 doses of pIFN (PpIFN) at w4, 5 and 6 (n=8). ART was interrupted (ATI) at week 4. The primary end-points were safety and proportion of patients with undetectable VL 12w after ATI (w16). Secondary end-points were DVL set-point (set-point ATI-preART), and DHIV-1 specific T cell responses (IFN-γ Elispot) (w16-w0).
Results: All participants were male. The procedure was safe and well tolerated. All patients had detectable VL at w16. DVL set-point [log_{10} mean (SE) copies/ml) was: 1) V 0,20 (0,21) 2) VpIFN -0.44 (0,38) 3) P -0,19 (0,23) 4) PpIFN -0,17 (0,20) (p=0.37). A decrease >1log_{10} in VL set-point was seen in 0, 3, 1 and 0 patients in V, VpIFN, P and PpIFN, respectively (p=0.05 and p= 0.06 for the differences between VpIFN vs V, and VpIFN vs PpIFN, respectively). At baseline, HIV-1 specific T-cell responses were lower in vaccines vs placebo groups [mean (SE) 900 (200) vs 2259 (535) SFC/10^6 PBMC, p=0.028). No significant differences in DHIV-1 specific T-cell responses were observed between vaccine and placebo groups (p=0.09). No effect on T cell responses was observed with pIFN administration. A trend to significative negative correlation between DVL and DHIV-specific T-cell responses (w16-w0) was observed in vaccine and not in placebo groups (r=-0.56, p=0.09; r-028, p= 0.43; vaccine and placebo groups, respectively).
Conclusion: The combination of a MD-DC therapeutic vaccine and pegIFNα was safe. A very modest decrease in VL was observed in vaccine recipients and was correlated with an increase of HIV-1 specific T-cell responses.
Clinical trial.gov EudraCT 2015-001795-22

283 PERSISTENT ANTIVIRAL EFFECT INDUCED BY TYROSINE KINASE INHIBITORS

Lorena Vigón[1], Sara Rodríguez-Mora[1], Elena Mateos[1], Valentín García[2], Juan Ambrosioni[3], Virginia Sandonís[4], Guiomar Bautista[5], Pilar Pérez-Romero[1], José Alcamí Pertejo[1], Juan Luis Steegmann[6], Jose M. Miro[3], Vicente Planelles[7], María Rosa López-Huertas[1], Mayte Coiras[1]
[1]Institute of Health Carlos III, Madrid, Spain, [2]Hospital Ramón y Cajal, Madrid, Spain, [3]IDIBAPS, Barcelona, Spain, [4]Hospital Universitario 12 de Octubre, Madrid, Spain, [5]Hospital Puerta de Hierro, Madrid, Spain, [6]Hospital Universitario de La Princesa, Madrid, Spain, [7]University of Utah, Salt Lake City, UT, USA

Background: Tyrosine kinase inhibitors (TKIs) are used in clinic to treat chronic myeloid leukemia (CML). TKIs should be taken for life but some patients stop treatment due to antileukemic deep molecular response (DMR). Some TKIs may also induce a potent immune response against CMV and our group described an inhibition of HIV infection in vitro and in vivo. Many mechanisms define TKIs activity against HIV: 1) cytostatic effect and inhibition of cytokine-dependent proliferation, possibly affecting reservoir establishment and replenishment 2) maintenance of SAMHD1antiviral activity 3) sustained cytotoxic activity to control the growth of cancerous cells even after withdrawal. Objectives: 1) to analyze cytotoxic effect in CML patient cell populations during TKI treatment and after withdrawal; 2) to determine the susceptibility to HIV infection of CD4 T cells from CML patients off TKI treatment.
Methods: PBMCs from CML patients on TKI treatment for avg. 3.8±0.5y (dasatinib n=20; imatinib n=11; nilotinib n=9; bosutinib n=5; ponatinib n=1), CML patients off TKI treatment for avg. 2.3±0.3y due to DMR (last TKI: dasatinib=4; imatinib=7; nilotinib=6) and healthy donors (n=30) were analyzed by flow cytometry. IFNg synthesis was analyzed by flow cytometry and proviral integration by Alu-qPCR.
Results: 1) Active NK cells CD56+CD16+CD107a+ were increased >6-fold in patients on treatment with all TKIs except imatinib, compared to control. This population remained >5-fold enhanced after withdrawal. 2) CD8±TCRgd+ lymphocytes were increased >2-fold in patients on treatment and remained >3-fold greater in patients off treatment. 3) Synthesis of IFNg in response to in vitro CMV pp65 peptide was increased >2-fold in CD8+CD69+ T cells from patients off treatment. However, no CD8 reactivation was detected in patients on treatment probably due to the potent cytostatic effect of TKIs. 4) In vitro treatment with TKI dasatinib and IL-15 increased >2.5-fold the IFNg secretion from NK cells. 5) PBMCs from patients off treatment showed <12-fold proviral integration after in vitro infection
Conclusion: TKIs induce mechanisms with antiviral activity that may be used against HIV infection. Populations of active NK cells and IFNg-secreting CD8 cells may persist in CML patients even after treatment withdrawal, as well as CD4 cells resistant to HIV infection. These results suggest a possible transient use of TKIs in HIV-infected patients to establish a persistent antiviral activity

284 RATIONAL DONOR FECAL MICROBIOTA TRANSPLANTATION IN HIV (REFRESH STUDY)

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Background: It is unknown whether oral fecal microbiota transplants (FMT) can affect the gut microbiota and systemic immunity of HIV-infected individuals.
Methods: Thirty ART-treated HIV-infected subjects with a CD4/CD8 ratio <1 were allocated to receive either weekly oral fecal microbiota capsules or placebo for 8 weeks (10 capsules at week 0; 5 capsules/week from weeks 1-7). Three stool donors were selected from a universal donor stool bank based on bacterial abundance of Fecalibacterium and Bacteroides (high) and Prevotella (low) and high fecal butyrate concentrations. We assessed 48-week safety and efficacy, including changes in CD4/CD8 T cells, microbiota engraftment using Illumina 16S rDNA sequencing, T cell activation/senescence, inflammation (sCD14, sCD163, sTNFr-2), bacterial translocation (LTA, LBP) and intestinal damage (FABP2) markers.
Results: Twenty-nine participants, with a mean CD4 count of 641±286 cells/μL completed the 48-week follow-up. FMT was well tolerated, with no grade 3-4 related adverse events. No significant changes were observed in CD4/CD8 T-cells, in T-cell activation/senescence or levels of the inflammation/bacterial translocation markers. Significant between-group differences were observed in FABP2, with higher fold change decrease at week 4 in the FMT arm (0.52 vs. 0.95, p=0.045). Alfa diversity significantly and incrementally increased until week 6 in the FMT arm (FMT vs. placebo arm, p=0.013) and returned to baseline levels at week 48. Unifrac distance trajectories indicated mild engraftment of donor's microbiota that persisted until week 36 and greater engraftment among the 4 subjects who had received antibiotics in the 12-week period before FMT. LEfSe analyses showed an incremental engraftment of different taxa in the active arm, being Lachnospiraceae family and Faecalibaculum, Faecalicoccus, Fusicatenibacter, Anaerostipes and Ruminococcus genus the taxa more robustly engrafted across time-points.
Conclusion: Repeated oral capsular FMT was safe in HIV-infected subjects on ART and introduced incremental compositional changes in the microbiota. While it is unclear whether this strategy will help to attenuate systemic inflammation, our results indicate that manipulation of the gut microbiota using a non-invasive and safe strategy of FMT delivery is feasible.

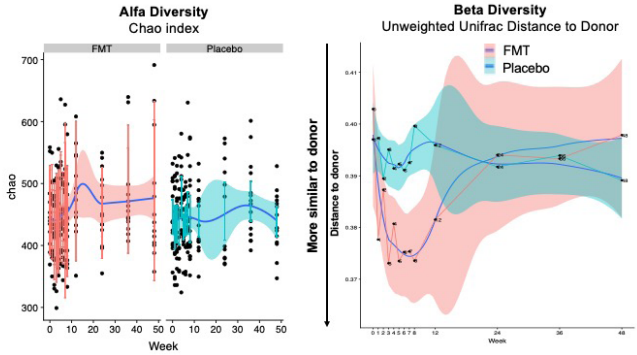


Figure. Changes in alpha diversity (Chao Index) and beta diversity (Weighted Unifrac distance to donor). For each control, the distances against the randomized donor are represented. Between-group differences in linear trajectories statistically significant in linear mixed models.

285 METHOTREXATE BLOCKS PROLIFERATION NOT INFLAMMATION TO MODULATE IMMUNITY

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Background: Inflammation associated with increased risk of comorbidities persists in people living with HIV (PLWH) on combination antiretroviral therapy (ART). Low-dose methotrexate (MTX) is an anti-inflammatory treatment for rheumatological disorders. A recent placebo-controlled trial (ACTG A5314) of low-dose MTX in PLWH found no changes in plasma inflammatory indices, but numbers of total and cycling (Ki-67+) CD4 and CD8 T cells decreased in the low-dose MTX arm.

Methods: Effects of MTX (up to 100nM) on the release of IL-1ß, IL-6, IFNγ TNF, and IL-2 by PBMCs from PLWH (n=6) or HIV-uninfected controls (n=6) was measured by ELISA in culture supernatant following exposure to LPS, flagellin, antibodies to CD3 and CD28 (anti-CD3/CD28), or medium control. Effects of MTX on T cell proliferation (CellTrace Violet dilution), activation (CD69 and CD25 expression), and numbers from PLWH (n=6) or HIV-uninfected controls (n=11) were measured by flow cytometry following stimulation with anti-CD3/CD28, IL-2, IL-7, IL-15, or medium control.

Results: At concentrations up to 100nM, MTX treatment did not inhibit IL-1ß and IL-6 release in response to LPS or flagellin; IFNγ, TNF, and IL-2 release in response to anti-CD3/CD28; or T cell activation (CD69 and CD25 expression) in response to stimulation with anti-CD3/CD28, IL-2, IL-7, or IL-15. T cell proliferative responses to anti-CD3/CD28 were inhibited by MTX (median $IC_{50} = 42.07$nM), but IC_{50}s were similar among cells from PLWH and controls ($P = 0.099$), with similar results seen for IL-2, IL-7, and IL-15. MTX treatment during anti-CD3/CD28 stimulation also resulted in a significant decrease in T cell numbers, suggesting activation-induced cell death. Addition of folinic acid (1µM) restored T cell proliferation to anti-CD3/CD28 stimulation, but did not rescue cell numbers.

Conclusion: Our findings indicate that MTX at concentrations up to 100 nM does not inhibit expression of IFNγ, TNF, and IL-2 in response to T cell receptor (TCR) stimulation or IL-1ß and IL-6 after stimulation with the TLR4 and TLR5 agonists LPS and flagellin in vitro. Proliferation of CD4 and CD8 T cells in response to TCR and common gamma chain cytokine stimulation is profoundly reduced by MTX and is associated with cell death in vitro. Folinic acid could restore T cell proliferation, but did not fully rescue cell death. Our data are fully consistent with the in vivo effects of MTX in PLWH suggesting that the major effect of MTX on immune function is an inhibition of cellular proliferation.

286LB ENHANCED COMPLEMENT ACTIVITY DOES NOT IMPROVE PROTECTION IN SHIV-CHALLENGED MACAQUES

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Background: Fc modified bNAbs are being developed for prophylactic and therapeutic treatment of HIV. Extended half-life and reduced immunogenicity modifications have proven effective, but attempts to improve bNAb efficacy by enhancing affinity for Fcg Receptors alone have not worked in SHIV-challenged macaques. In this model, ablating FcgR binding reduced protection, but the role of complement appeared limited. We hypothesized improving bNAb Fc-mediated complement activity and increasing affinity for FcgR would strengthen protection.

Methods: We developed 10 Fc variant bNAbs with site mutations designed to increase CDC activity, C1q binding, and FcgR affinity and evaluated each for binding to FcgRs, C1q and infected cells plus functional CDC, ADCC and ADCP activity. MPER targeting 10E8v4 that weakly neutralizes SHIVSF162P3 (IC_{50} 30 mg/ml) and mediated Complement activity in vitro, but does not mediate ADCC was selected for macaque studies. Protection was evaluated with a single high dose intrarectal SHIVSF162P3 challenge 3 days after 5 mg/kg mAb infusion. Groups of 6 macaques received either unmodified 10E8v4, 10E8v4-LALA (Complement/FcgR dual knockout), 10E8v4-EFTAE, (>2-fold enhanced Complement deposition, viral lysis, and CDC, increased affinity for FcgRs with no ADCC or increased ADCP), or a control mAb. Blood draws monitored viremia, mAb kinetics, and neutralizing titers.

Results: Unexpectedly, mean plasma viral loads (PVL) were elevated in the EFTAE group compared to unmodified 10E8v4 ($P<0.0001$) and LALA groups ($P=0.0070$). Viremia was starkly increased in multiple lymphoid and gut tissues in the EFTAE group, over unmodified 10E8v4 ($P<0.0001$), LALA ($P=0.0270$), and control ($P<0.0001$) groups. EFTAE mutations led to lower serum concentrations and neutralizing titers at challenge and reduced serum half-life. Higher doses of 10 and 20 mg/kg EFTAE or unmodified mAb led to comparable PVL, suggesting neutralizing titers may mitigate effects of increased complement. Mechanistic studies show splenocytes treated with sub-neutralizing EFTAE increased infection over controls dependent on the presence of monocyte derived DCs.

Conclusion: Our studies imply enhancing CDC in vitro may not predict in vivo function and supports evidence that increased affinity for FcgRs may not enhance protection. Implications of complement opsonization of HIV inhibiting effector cell function warrant further study. Importantly, consequences seen here of modulating complement in HIV infection may forewarn clinical safety and therapeutic trials with modified Fc bNAbs.

287 THE RV144 VACCINE PRIMED IgG4 AND V1V2-ADCP RESPONSES IN HIV BREAKTHROUGH INFECTIONS

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Background: The RV144 vaccine efficacy trial showed a reduction in HIV infections that associated with stronger binding antibody (Ab) responses against Env variable loops V1V2. High levels of Ab-dependent cellular cytotoxicity (ADCC) together with low plasma levels of Env-specific IgA also correlated with decreased infection risk. Exact mechanisms of prevention remain unclear.

Methods: To better understand the effect of vaccine priming, we performed a systems serology analysis in breakthrough infections in 42 vaccine and 63 placebo recipients, using plasma samples collected 6, 12 and 36 months after HIV diagnosis. We analyzed Ab binding features corresponding to immunoglobulin (Ig) subclasses and nine variant Fc gamma receptors (FcgR) (tested against 51 HIV antigens (Ag) for a total of 896 immune variables) together with functional Ab responses: ADCC, Ab-dependent cellular phagocytosis (ADCP), trogocytosis, NK cell activation measured by ICS and neutralization. Machine-learning analyses included clustering, CART, LASSO logistic model, and Partial Least Squares (sPLS). We filtered redundant immune features to reduce the number of variables to 221, 286 and 284 at 6, 12 and 36 months, respectively.

Results: RV144 vaccination primed B cells responses post HIV-1 infection. Vaccinees were classified by a specific Fc binding profile with IgG4 responses as the strongest distinguishing feature dominating until 3 years after diagnosis. When effector functions were included, vaccinees were characterized by strong V1V2-specific Ab responses synergized with V1V2-specific ADCP responses, whereas placebo recipients had stronger IgG3 and gp120-specific responses. The development of neutralization breadth, which was linked to gp120/gp140 binding features, did not cluster with the vaccine group.

Conclusion: Our results showed that the RV144 vaccine primed a specific IgG4 and V1V2-ADCP-dominated profile post-breakthrough infection while it did not prime broad neutralizing responses.These findings substantiate the importance of V2-specific binding Abs which were previously identified as a correlate of decreased risk of HIV infection in RV144 and show that vaccine-induced responses had consequences post HIV infection. By contrasting the immediate (post-vaccination, pre-infection) and long-term (post-infection) impact of vaccine priming, we can obtain a novel understanding of vaccine-elicited immunity, with characteristic features that can be harnessed to design more efficacious vaccine strategies.

288 PHASE I/IIA TRIAL OF HIV CLADE C DNA WITH MF59- OR AS01B-ADJUVANTED CLADE C PROTEIN

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Background: After RV144, the Pox Protein Public Private Partnership initiated multiple trials to evaluate a clade C bivalent protein (TV1.C and 1086.C gp120) vaccine with different adjuvants and priming agents to optimize the design of future vaccine regimens. We showed that substituting DNA (DNA-HIV-PT123) for ALVAC can improve immune responses. The aim of HVTN 108, a phase 1/2a randomized, placebo-controlled trial, was to evaluate the safety and immunogenicity of the DNA vaccine with several protein/MF59/AS01B adjuvant combinations.

Methods: We randomly allocated 334 HIV-uninfected participants from the US and South Africa to 7 intervention groups (T1-T7) or placebo. We assessed DNA prime at months (M)0, 1 with DNA/protein/adjuvant boosts at M3 and 6 (T1–T3), DNA/protein/adjuvant co-administration at M0, 1 and 6 (T4-6), and only low dose protein/AS01B at M0, 1 and 6 (T7). Protein was either adjuvanted with MF59 or AS01B. Safety was assessed by collecting reactogenicity and adverse events (AEs). We measured humoral and cellular immunogenicity at M6.5 by binding antibody multiplex assay and ex vivo intracellular cytokine staining.

Results: Blinded safety data revealed 48 grade 3, and three grade 4 reactogenicity events in 39 persons, and 30 mild or moderate related AEs. All intervention groups had high IgG response rates (>89%) and high magnitude responses to HIV-1 Env gp120 and gp140 proteins. Response rates for the AS01B-adjuvanted groups approached 100%. V1V2 IgG response magnitude, the correlate of decreased HIV risk in RV144, was higher in the AS01B group (Figure 1). Additionally, there was evidence of a higher IgG3 Env response rate in the AS01B group. CD4+ T-cell response rates and magnitudes to all Env peptide pools were higher in the AS01B-adjuvanted than MF59-adjuvanted regimens (all $p<0.01$), except for Env-2-ZM96. Furthermore, the AS01B-adjuvanted lower protein dose elicited higher magnitude responses than the higher protein dose regimen.

Conclusion: DNA/protein/adjuvant combinations demonstrated acceptable safety profiles, with unblinded analysis pending. All groups showed high IgG response rates to gp140 and gp120, and robust responses to Env V1V2. AS01B-adjuvanted groups showed improved CD4+ T cell, V1V2 IgG and Env IgG3 responses. Assessments of durability and antibody Fc effector functions are underway. These data highlight that substituting the MF59 adjuvant with AS01B could further enhance both humoral and cellular responses.

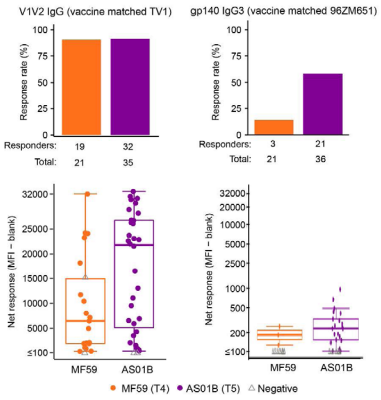


Figure 1. Adjuvant increases antibody responses associated with effective immunity. Comparison of IgG V1V2 magnitude (left) and IgG3 Env gp140 response rate (right) between DNA co-administered with bivalent clade C 100 ug/proteins used in HVTN 702 with MF59 (orange) vs. AS01B (purple).

289 MUCOSAL T AND B CELL RESPONSES INDUCED BY ALVAC-HIV/AIDSVAX B/E LATE BOOST STRATEGIES

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Background: The majority of HIV-1 infections occur across mucosal surfaces, hence mucosal immune responses including CTL, T-helper cells and IgA-secreting plasmablasts (PB) are part of the initial defense against infection. RV144 is still the only vaccine trial that demonstrated modest efficacy; however, mucosal responses were not characterized. Here we assess mucosal immune responses elicited after the ALVAC-HIV/AIDSVAX B/E prime boost regime used in RV144 followed by additional late boost strategies.

Methods: Sigmoid biopsies were collected two weeks after final vaccinations, either after the RV144 regimen, or after late boosts at 12, 15 or 18 months (mo) with ALVAC-HIV and/or AIDSVAX B/E. TH023- and Gag-specific CD4 and CD8 T cell responses as well as B cell responses were assessed by flow cytometry. Vaccine-specific IgG and IgA was measured in rectal secretions by binding antibody ELISA.

Results: Mucosal TH023- and Gag-specific T cell responses were readily observed with TNFa as the predominant cytokine produced followed by IFNg and IL-2. After the RV144 regimen, 30% of vaccine recipients developed TH023-specific CD4 T cell TNFa responses, which increased after the late boosts to 63% (12mo), and 100% (15/18mo). Similarly, the magnitude of TH023-specific CD4 T cell TNFa responses increased with a delayed boost interval from 0.01% post RV144, to 0.09% at 12mo, 0.98% at 15mo and 0.92% at 18mo boosts ($p=0.007$ by Kruskal-Wallis). Additionally, magnitude of mucosal TH023-specific CD8 T cell TNFa responses increased with later boost intervals (post RV144: 0.12%, 12mo: 0.09%, 15mo: 0.58%, 18mo: 0.83%; $p=0.03$ by Kruskal-Wallis). This is in contrast to univariate peripheral responses that were mainly CD4-mediated, appeared already after the RV144 regimen and were maintained after the late boosts. Although vaccine-specific IgA was not detected in rectal secretions, an increase in mucosal IgA-producing PB was observed with increasing late boost intervals (post RV144: 8.6%, 12mo: 7.7%, 15mo: 17.4%, 18mo: 17.0%; $p=0.04$ by Kruskal-Wallis).

Conclusion: Late boosts with ALVAC-HIV and/or AIDSVAX B/E induce robust mucosal vaccine-specific CD4 and CD8 T cell responses and increase the frequency of mucosal IgA-producing PB. These responses differ in quality and kinetics from peripheral responses, highlighting potentially different mucosal mechanisms in contributing to the defense against HIV-1 after vaccination.

290 CANDIDATE IMMUNOGENS DIFFERENTIALLY ENGAGE HIV BROADLY NEUTRALIZING PLASMA ANTIBODIES

Irene Abela[1], Teja Turk[1], Nikolas Friedrich[1], Claus Kadelka[1], Matthias Gloegl[1], Brano Ivan[1], Peter Rusert[1], Merle Schanz[1], Roger Kouyos[1], Huldrych F. Günthard[2], Alexandra Trkola[1], for the Swiss HIV Cohort Study

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Background: Deciphering factors that drive broadly neutralizing antibodies (bnAbs) induction remains critical to guide HIV-1 vaccine development. Including 4,484 patients with detailed demographic data alongside plasma samples, the Swiss 4.5K Screen had unique means to distinguish positive, independent drivers of breadth (viral load, infection length, viral diversity, black ethnicity) (Rusert et al. 2016). Here we report on the XbnAb cohort, a sub-cohort of the Swiss 4.5K Screen that includes bnAb inducers and matched non-neutralizing (nnAb) controls. Using the controlled setting of the XbnAb cohort we compared the capacity of candidate immunogens in binding naturally occurring Abs and assess their efficacy in predicting bnAb activity.

Methods: We defined within the Swiss 4.5K Screen the XbnAb cohort, which comprises all identified bnAb inducers (N=304) and matched nnAb controls (N=304; matched for HIV-1 subtype, length of infection, host demographics). Patient plasmas were assessed for binding antibodies (IgG1,2,3) against 47 HIV-1 envelope (Env) antigens (including 29 stabilized soluble Env trimer variants and candidate immunogens provided by lead investigators in the field) and 2 Gag proteins using an in-house Luminex bead assay. EC_{50} plasma Ab binding activity was established for each antigen and the prediction potential of antigens to distinguish bnAb activity assessed by univariate conditional logistic regressions.

Results: Confirming work from the Swiss 4.5K Screen (Kadelka et al. 2018) we found that IgG1 Env trimer reactivity is generally higher among bnAb inducers. However, levels of significance varied considerably ($p=10^{-3}$ to $p=10^{-16}$), highlighting substantial differences among candidate immunogens in engaging

natural occurring bnAbs. Comparison of wild type and CD4bs-knockout Envs allowed exploring the impact of CD4bs bnAb activity. Of note, IgG1 reactivity of trimeric CD4bs immunogens were good predictors of neutralization breadth, while the monomeric CD4bs tailored immunogens EOD-GT8 and RSC3 did not differentiate bnAb activity.
Conclusion: Focusing on closely matched bnAb and nnAb inducers, the XbnAb cohort captures the essence of the Swiss 4.5K Screen, providing means to derive population relevant information without the need to screen thousands of individuals. Highlighting the unique capacity of the XbnAb cohort we demonstrate a differential capacity of candidate antigens in engaging natural occurring Abs that needs to be considered when selecting immunogens for further development.

291 ACUTE INFECTION B-CELL DETERMINANTS PREDICT DEVELOPMENT OF NEUTRALIZATION BREADTH

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Background: Determining which immunological mechanisms contribute to the development of broadly neutralizing antibodies (bNAbs) during HIV-1 infection is a goal to inform vaccine design. It is not understood if factors during the acute stages of infection impact the generation of neutralization breadth years later.
Methods: Utilizing 178 longitudinal samples from 72 HIV-1 infected, ART-naïve individuals within the RV217 cohort, we identified 16 individuals who neutralized >70% of a panel of 34 viruses (broad neutralizers) and 12 individuals not able to neutralize >35% after 3 years of infection (non-broad neutralizers). Founder env genes were sequenced, and gp140 founder Env proteins were produced to characterize respective early autologous B cell responses. Founder Env+ and total B cell populations were phenotyped at pre-infection, peak viral load (day 11-18), month 1 (day 30-43), and chronic infection timepoints (day 391-2115).
Results: Reduced peripheral B cells starting at month 1 post-viremia were predictive of the development of bNAbs (HR=0.37, 95% CI: 0.18-0.76, p=0.007). Individuals with less than 160 B cells/mm$_3$ at month 1 were 42 times more likely to develop neutralization breadth. Reduced peripheral B cells were driven by a reduction in peripheral naïve B cells occurring at 14 days post-viremia. Naïve B cell frequencies at day 14 inversely correlated with frequencies of founder Env-specific (p<0.02), plasmablast (p<0.0001), and integrin beta7+ (p<0.001) B cell populations, suggesting early B cell engagement, differentiation, and migration to lymph nodes. Additionally, increased B cell engagement of respective founder gp140 Envelopes at 1 month predicted the development of bNAbs (OR=1.13, 95% CI: 1.02-1.28, p=0.035). Individuals with high engagement of their respective autologous founder Env at 1 month had a higher probability of developing neutralization breadth compared to individuals with low engagement of their autologous founder Env (p=0.02).
Conclusion: These data demonstrate development of neutralization breadth is influenced by early immunological mechanisms within the first month of acute infection. The reduction of peripheral naïve B cells in broad neutralizers and early, heightened engagement of the founder Env favored the development of broadly neutralizing antibodies, providing evidence that acute infection events lead to downstream functional outcomes.

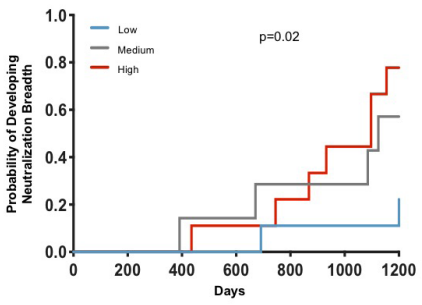


Fig. 1. Cumulative incidence curves indicating the probability of developing neutralization breadth using high, medium, or low frequencies of respective autologous founder Env gp140$^+$ specific-B cells 1 month (day 30-43) following initial viremia. Reported p-value by LogRank test.

292 TARGETING HIV ENV TO CD40 LEADS TO HIV-SPECIFIC POLYCLONAL B CELLS IN HUMANIZED MICE

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Background: Challenges in the development of HIV-1 vaccines are to more accurately direct protective immune responses and develop appropriate animal models.
Methods: Mice with a functional human immune system (HIS) were immunized with either anti-CD40 mAb in which the Fcgamma domains are fused to the HIV-1 envelop protein (gp140ZM96) (anti-CD40.Env gp140) with CpG-B (w0, w3, w5) (CD/CD group) or Nyvac-KC pox vaccine encoding gp140ZM96 with CpG-B (w0) followed by two injections of anti-CD40.Env gp140 with CpG-B (w3, w5) (N/CD group). B- and T-cell responses were studied at w6 in blood and spleens and compared to control animals (PBS or CpG-B only, C group). BCR diversity was analysed by single cell RNA sequencing (scRNAseq).
Results: As compared to C group, anti-CD40.Env gp140 vaccine induced a sustained CD40 expression on myeloid DCs and B cells. In both vaccine groups, gp140ZM96-specific CD4+ memory T cells and IgG-switched B cells were elicited at w6. Among these cells, gp140ZM96-specific IgG+ B cells were induced in the spleen and blood with a higher frequency in the N/CD group (7,360 cells/mL [4,022-13,640] and 1,421 cells/mL [1,023-2,830] in the spleen and 356 cells/mL [38-193] and 99 cells/mL [198-951] in the blood; P<0.05 for both comparisons). Increased frequency of blood ICOS+CXCR5+ Tfh-like cells significantly correlated with the induction of gp140ZM96-specific IgG+ B cells in vaccine groups (R=0.70, p=0.004). Analysis of Ig VH and Vk gene diversity showed a large diversity of IgV gene usage in non-specific memory B cells while an enrichment of VH3 and J(k) 4/5 family gene usage was observed in the gp140ZM96-specific IgG+ B cells. In the N/CD group, these cells exhibited a BCR with longer CDRH3 lengths (37% of clones with CDRH3 > 18 aa and up to 28 aa) and a higher rate of somatic hypermutations. Clonal evolution assessed by phylogenic trees was observed in both vaccine groups with a higher diversity in the N/CD group.
Conclusion: Our results showed that HIS-mice vaccinated with the anti-CD40. Env gp140 vaccine given as a prime or a boost of Nyvac-KC vector elicited T and B cell-specific responses with a diverse antibody B cell repertoire. Interestingly, gp140ZM96-specific IgG-switched memory B cells exhibit antigen-driven antibody maturation characteristics.

293 CD40-TARGETED VACCINE INCREASES MAGNITUDE OF HIV-ENV SPECIFIC RESPONSES

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Background: The development of DC-targeted vaccines aims to increase immunogenicity of proteins through improved delivery of the antigens to specific antigen-presenting cells playing a key role in inducing and regulating immune memory. CD40 signaling is essential for T cell-dependent humoral responses and targeting vaccine antigen to CD40 expressing APC seems therefore an attractive option to promote anti-HIV antibody development.
Methods: To determine the impact of DC targeting on immune responses, we analyzed cellular changes at immunization site. Twelve cynomolgus macaques were immunized with homologous prime-boost strategy by HIVgp140 protein fused with anti-CD40 targeting module or with IgG4 irrelevant control. Cellular trafficking was analyzed in injection site and draining lymph node by in vivo imaging after boost. Impact on immune responses was also evaluated over time.
Results: Combination of in vivo imaging techniques (near infrared imaging, probe-based confocal laser endomicroscopy and two-photon microscopy)

allowed the identification of the lymph nodes of interest that had drained the HIVgp140 protein. A significantly higher number of vaccine-targeted APC migrated in draining LN of NHPs immunized by anti-CD40.Env-gp140 (mean of 184 cells/mm^2) compared to control animals (mean of 69 cells/mm^2). Moreover, the magnitude of HIV-Env specific IFN-γ T cell response was correlated to the number of vaccine-targeted cells observed in vivo within the LN. HIV-Env specific T cell responses in anti-CD40 vaccinated animals was superior to the control group at the peak of response, 2 weeks post boost (1028 and 450 SFC/10^6 PBMC, respectively; mean of 6 animals). Specific antibody titers against Clade C Env proteins were also greater in anti-CD40 group (1700 and 202 EC_{50}, respectively) than in controls (840.8 and 77.5 EC_{50}, respectively) at 5 weeks post boost. Magnitude of the cellular response after a second boost was correlated to the durability of the response measured 30 weeks after immunization.
Conclusion: Altogether these results exhibited that CD40 targeting influences the early immune events within the draining LN then leading to stronger T and B cells responses. We also demonstrate that CD40 targeting in presence of adjuvant significantly improves vaccine immunogenicity without requiring priming with different type of vector or targeting strategy. The safety and efficacy of the CD40-targeted vaccine justify further development for future human clinical trials.

294 HARNESSING ORIGINAL ANTIGENIC SIN FOR PREVENTING MTCT OF HIV

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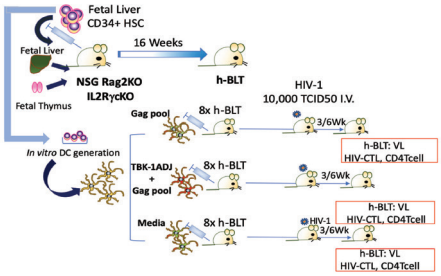
Background: Progress towards the elimination of pediatric HIV infection via mother to child transmission (MTCT) is limited by several factors, including inconsistent access and maternal adherence to ART. The development of a maternal vaccine that can synergize with current ART prophylaxis could overcome implementation challenges impeding achievement of an HIV-free generation. Both the epitope specificity of HIV envelope (Env)-specific antibody responses and autologous virus neutralization have been implicated in MTCT risk of HIV. Our goal was to evaluate the immunogenicity of a heterologous vaccine regimen to boost autologous HIV Env-specific antibody responses in SHIV-infected, ART-suppressed, female rhesus macaques (RMs).
Methods: Twelve female RMs were infected intravenously with SHIV.C.CH505.375H.dCT, and began a daily ART (TDF, FTC, dolutegravir) regimen at 12 weeks post-infection (wpi). Two weeks after ART initiation, RMs received 3 intramuscular doses of HIV b.63521/1086.c gp120 (n=6; vaccine group) or RSV (n=6; placebo group) vaccine with a TLR agonist adjuvant (StR8C) monthly. ART was discontinued after 12 weeks and RMs were monitored for viral rebound. Binding and functional antibody responses were also measured.
Results: HIV Env vaccination in the setting of ART did not delay viral rebound. HIV Env gp120 vaccinated RMs exhibited peak antibody binding responses at 20 wpi (2 weeks post 2nd immunization), with enhanced IgG responses against b.63521 and 1086.c vaccine immunogens; as well as the challenge virus Env, SHIV.C.CH505. Plasma autologous virus (CH505.TF) neutralization was similar between the two groups upon treatment interruption, while ADCC responses were markedly boosted in Env vaccinated animals. Vaccinated RMs exhibited greater breadth in IgG antibody responses against various Env epitopes, with V3- and V1V2- specific responses against both the vaccine and challenge virus antigens.
Conclusion: In conclusion, vaccination of SHIV-infected RMs in the setting of ART can boost IgG responses against the original infecting antigen, SHIV.C.CH505, and Env-specific antibody responses previously associated with low risk of MTCT. Our results suggest that a vaccine regimen administered to HIV-infected pregnant women could boost previously identified humoral correlates of reduced MTCT risk in humans.

295 TBK-1-DC VACCINE INDUCES POLYFUNCTIONAL T CELLS AND CONTROL OF HIV-1 IN THE BLT MOUSE

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Background: Dendritic cells (DC) are critical to induce protective antiviral T cell responses, but previous HIV-1 vaccine studies suggest that improvement of DC function is essential for boosting HIV-1 specific immunity. TANK-binding Kinase 1 (TBK-1) is a key regulator of DC maturation in response to HIV-1 and to prime polyfunctional specific T cells. Our objective is to evaluate the efficacy of a vaccine based on TBK1-engineered DCs controlling HIV-1 infection in vivo using the humanized bone marrow, liver and thymus (hBLT) mouse model.
Methods: A total of 24 humanized hBLT-mice were generated for the study. A fraction of autologous CD34+ hematopoietic stem cells (HSC) were used to differentiate DC in the presence of FLT3L, IL-7, SCF and GMCSF. Three separate groups of 8 humanized hBLT-mice were injected with HSC-derived DCs cultured in media (MED), gag peptides alone (GAG) or in combination with 2´-3´-c-AMP and Poly-I:C TBK-1 adjuvants (GAG-ADJ) and infected intravenously with 10,000 TCID50 of JRCSF HIV-1. Plasma HIV-1 viral loads, polyfunctional T cell responses from peripheral blood and lymphoid tissue and CD4+ T cell counts were assessed at 3 and 6 weeks post-infection. Presence of CD8+ T cells and p24+ infected cells was determined by immunofluorescence in lymphoid nodes. Statistical differences were calculated using a Mann Whitney or a Chi-square tests.
Results: All groups of hBLT-mice became infected with HIV-1, however animals vaccinated with autologous GAG-ADJ DCs exhibited a partial but significant reduction of HIV-1 plasma viral loads at 3 weeks p.i. compared to control groups (p=0.021). These differences were accompanied by higher polyfunctional profiles in circulating CD8+ T cells in the GAG-ADJ group (p=0.005), suggesting partial control of viral replication at early time points. At 6 weeks post-vaccination, plasma viral loads were similar across different groups of vaccinated mice, however Polyfunctional T cells were specifically observed in the spleen from GAG-ADJ and a less severe depletion of CD4+ T cell lymphocytes was detected in these animals compared to GAG mice (p=0.05 vs p=0.0078). Moreover, increased clusters of CD8+ T cells excluding infected HIV-1 p24+ cells from specific areas within the lymph node were also observed in these animals (p=0.001).
Conclusion: Engineered TBK-1 DCs are able to improve parameters of immune control of HIV-1 infection in the hBLT-mouse model and might be useful for subsequent vaccine studies.

TBK-1 engineered DC-based Vaccine in the BLT mouse model



296 CMV VACCINE VECTOR-INDUCED PROTECTION AGAINST SIV IN MAURITIAN CYNOMOLGUS MACAQUES

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Background: Strain 68-1 rhesus cytomegalovirus (CMV) vaccine vectors expressing simian immunodeficiency virus (SIV) antigens (RhCMV/SIV) prime broadly-targeted, unconventionally MHC-II- and MHC-E-restricted CD8+ T cell responses that stringently control SIV replication in vaccinated rhesus macaques (RM). However, RM express many more MHC-II and MHC-E alleles than humans, and it remains unclear if the unprecedented cellular immunity and control of SIV observed in RhCMV/SIV-vaccinated RM is due to the unique immunogenetics of RM or species-specific functions of RhCMV itself. In contrast to RMs, Mauritian cynomolgus macaques (MCM) exhibit reduced genetic diversity with immunogenetics that more closely resemble those of humans. However, 68-1

RhCMV was unable to elicit unconventionally restricted CD8+ T cells in MCM suggesting a species barrier for viral vector function.

Methods: To determine if non-classical T cell priming and protection against mucosal SIV challenge is restricted to RhCMV-vaccination of RM or a universal phenomenon, we constructed a '68-1 like' cynomolgus CMV expressing SIV antigens (CyCMV/SIV). We vaccinated eight MCM with CyCMV/SIV and monitored multiple immune parameters in the animals including transgene-specific CD4+ and CD8+ T cell responses in blood and BAL. We challenged the eight vaccinated MCM and eight unvaccinated controls with repeated, limiting-dose, intrarectal SIVmac239 to assess vaccine-mediated protection.

Results: CyCMV/SIV vaccinated MCM generated unconventionally, MHC-II- and MHC-E-restricted T cell responses comparable to RhCMV/SIV vaccinated rhesus macaques. Upon challenge with SIVmac239, 50% of CyCMV/SIV vaccinated MCM stringently controlled SIVmac239 replication, defined as no plasma viremia and the development of T cell responses against SIV proteins absent from the vaccine. Acquisition and subsequent control of SIV was confirmed by cell-associated viral loads and adoptive transfer to naïve MCM of tissue biopsies from CyCMV/SIV-protected animals.

Conclusion: Thus, we have confirmed the distinct immunologic and protective phenotype induced by CMV vaccines in a second nonhuman primate species with immunogenetics reflective of humans, indicating that these results are not unusual species-specific traits of RM or RhCMV and that 68-1 like HCMV/HIV vaccines might similarly recapitulate unconventional T cell restriction and protect against HIV.

297LB SUPERIOR PROTECTION AGAINST SHIV INFECTION BY SAME SITE DNA-PROTEIN COIMMUNIZATION

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Background: We compared immunogenicity and protective efficacy of an HIV vaccine comprised of DNA (env and gag) and Env proteins by co-administration of DNA and Protein in the same muscle or by separate administration of the DNA and Protein components in contralateral sites.

Methods: Female rhesus macaques (20 animals/group) were immunized with a 6-valent vaccine including DNA plasmids expressing membrane-anchored gp145 Env sequentially isolated from a HIV-1 infected individual (CH505). The DNA was delivered by IM injection followed by in vivo electroporation. The vaccine also included a gp120 Env protein component matching the sequences encoded by the plasmid DNA and adjuvanted in GLA-SE. The DNA and protein vaccine components were administered in the same anatomical sites ('Co-administration') or in contralateral sites ('Separate Administration') After 6 vaccinations in 4-month intervals, the macaques were challenged by weekly intravaginal exposures with low dose T/F tier-2 SHIV CH505 stock.

Results: Only macaques in the co-administration vaccine group were protected against SHIV CH505 acquisition, with a 67% risk reduction per exposure after 15 weekly IVAG challenges. Macaques in the co-administration group developed higher Env-specific humoral and cellular immune responses. Non-neutralizing Env antibodies, ADCC and antibodies binding to Fc-gamma Receptor IIIa were associated with decreased transmission risk. These data suggest that simultaneous recognition, processing and presentation of DNA + Env protein in the same draining lymph node play a critical role in the development of protective immunity.

Conclusion: Co-immunization of DNA+Protein in the same muscle is superior for inducing protective immune responses against repeated tier-2 SHIV challenge. The advantage of co-immunization vaccine regimens targeting immunogens to the same draining LN could also be beneficial to other vaccine modalities and other pathogens.

298 DOLUTEGRAVIR INCREASES B CELLS AND RESTING MEMORY B CELLS IN RV254

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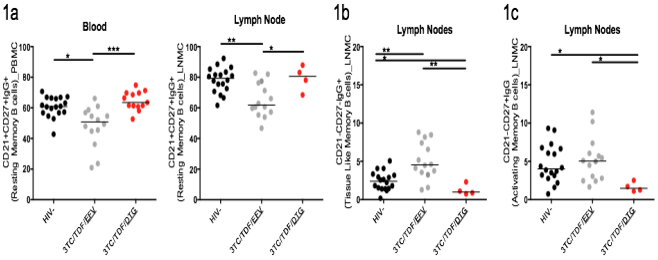
[1]Chulalongkorn University, Bangkok, Thailand, [2]SEARCH, Bangkok, Thailand, [3]Henry M Jackson Foundation, Silver Spring, MD, USA, [4]Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, [5]Henry M Jackson Foundation, Bethesda, MD, USA

Background: Early initiation of antiretroviral therapy (ART) in acute HIV infection (AHI) could help preempt evasion and damage of the immune system by HIV. Use of the integrase inhibitor Dolutegravir (DTG) and 2NRTIs is the new standard regimen. However, the influence of these drugs on the recovery of immune cells in blood and lymph node (LN) tissue has not been well studied. To address this, we assessed differences in B cell populations in Thai participants randomized to switch from 2NRTI+EFV to 2NRTI+DTG.

Methods: Cryopreserved peripheral blood mononuclear cells (PBMCs) and lymph node mononuclear cells (LNMCs) from 27 AHI treated Thai participants enrolled in the RV254 cohort were analyzed. Participants were grouped based on ART regimen: those randomized to switch from 2NRTI+EFV to 2NRTI+DTG (n=13; 6-22 mos EFV followed by 9-20 mos DTG) and those who remained on 3TC/TDF/EFV (n=14; range 6-22 mos). Eighteen uninfected individuals (HIV–) enrolled in RV304 were included for comparison. B cells were characterized by flow cytometry.

Results: The frequencies of CD19+ B cells were significantly decreased in PBMCs but not LNMCs of 2NRTI+EFV treated compared to HIV– participants ($p<0.05$), but were recovered in those who switched to DTG. The frequencies of resting memory B cells (RM; CD21+CD27+IgG+CD20+) were significantly decreased in both PBMCs and LNMCs of the 2NRTI+EFV group (Fig 1a), whereas the frequencies of tissue-like memory B cells (TLM) were significantly increased compared to HIV– participants ($p<0.05$; Fig 1b). 2NRTI+DTG treated participants had recovered frequencies of RM B cells, but lower frequencies of TLM and activated memory B cells (AM) compared to HIV– participants and non-switched EFV-treated participants ($p<0.05$; Fig 1c).

Conclusion: Our data show that switching from 2NRTI+EFV to 2NRTI+DTG could aid in recovery of B cell populations in the blood and LN, although the number of LNMC samples in the 2NRTI+DTG group in the present study limits definitive conclusions for this compartment. We observed higher frequencies of B cells and RM B cells in both PBMCs and LNMCs after switching from 2NRTI+EFV to 2NRTI+DTG. Further, 2NRTI+DTG treated participants had fewer AM and TLM B cells, the latter of which have an exhausted phenotype. These data suggest that switching from EFV to DTG may be beneficial to limit activation and exhaustion in the B cell compartment of participants who initiated treatment in AHI.



299 CHARACTERIZING ANTIBODY RESPONSES IN ART-TREATED INDIVIDUALS

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Background: Although suppression of HIV has become possible through antiretroviral therapy (ART), ART-treated individuals must maintain therapy to avoid rebound from a viral reservoir. Strategies to limit or clear this reservoir are urgently needed. Research has shown that individuals infected for longer prior to receiving ART harbor greater reservoir diversity, but may also have higher anti-HIV antibody titers. The roles that infection length and viral diversity play in the humoral response must be further studied to inform approaches to clearing infection. Here, we aim to clarify a role, if any, for autologous antibodies in these treatments by characterizing their function in individuals on different lengths of ART.

Methods: Plasma was collected from 8 HIV+ males on ART. Bulk IgG was isolated and normalized concentrations were tested for binding to gp41 and

gp120 proteins. IgG was then tested for breath and potency of neutralization against a global HIV panel as well as autologous outgrowth viruses derived from each individual.
Results: Binding against gp41 was highly correlated with gp120, and these binding titers were correlated with neutralization potency against the global panel. On average, participants exhibited low-potency neutralization of 8 of 12 viruses on the panel. Interestingly we did not observe potent autologous neutralization of outgrowth virus, and in fact 2 of 8 people harbored completely resistant virus at the highest level of IgG tested. 5 of the 8 individuals had a documented HIV-negative date, and therefore antibody functionality could be correlated to estimated length of infection before ART and duration of ART. We observe that length of infection is not correlated with autologous neutralization, but we do observe a trend toward more potent neutralization of the global panel by individuals infected for longer periods of time.
Conclusion: Our findings agree with published studies of untreated individuals that length of infection is related to neutralization breadth. By contrast, we found that duration of ART treatment was not associated with differences in neutralization – either heterologous or autologous. Overall, these data suggest that the inducible reservoir is relatively resistant to autologous antibodies whether the individuals are ART-suppressed early or late after diagnosis.

300 NEAR NORMALIZATION OF IMMUNE ACTIVATION IN PLWH ON LONG-TERM SUPPRESSIVE ART

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Background: In HIV-infected patients, chronic immune activation and inflammation persist after suppressive combination antiretroviral therapy (cART). We compared gene expression and biomarkers in peripheral blood between HIV-infected patients on long-term suppressive cART (HIV-group) and age-matched healthy controls (HC-group).
Methods: Cross-sectional study of 22 subjects in HIV-group with HIV-RNA <50 copies/ml and CD4+ T-cells ≥500 cells/mm_3 for more than one year before sampling, and CD4/CD8 ratio ≥1 at sampling. RNA-sequencing of polyA-RNAs was performed from peripheral blood mononuclear cells (PBMCs). Thirteen T-cell subsets were evaluated by flow-cytometry and 32 plasma biomarkers by immunoassays. All p-values were corrected by the false discovery rate (q-values).
Results: Only the serine/arginine repetitive matrix 4 (SRRM4) gene was differentially expressed between HIV and HC groups (q-value≤0.05 and fold-change≥2). However, 147 differentially expressed genes were found with a more relaxed threshold (p-value≤0.05 and fold-change≥1.5). Sixty-seven of them, with values of variable importance in projection (VIP)≥1, were selected for pathway analysis. Significant Ribosome-related pathways were represented by six ribosomal genes (RPs): S27 (RPS27), L18a (RPL18A), L8 (RPL8), L26 (RPL26), L4 (RPL4), and S21 (RPS21), all of them downregulated in the HIV-group. T-cells subset and plasma biomarkers were also analyzed, but none of them were significant (q-value>0.05). However, non-corrected p-values showed higher values of CD4+ Treg cells (CD4+CD25+CD127-/low), MCP-1, and sVEGF-R1 in the HIV-group (p-value≤0.05). Correlation patterns between RNA-seq expression and peripheral biomarkers (T-cells and plasma) were different between HC and HIV groups.
Conclusion: Immune activation and inflammatory biomarkers were close to normalization in HIV-infected patients on long-term suppressive cART, compared to HC-group. However, residual alterations remained at the gene expression of PBMCs, which still reveal the impact of HIV infection in these patients.

301 REVERSION OF CD4+ T-CELL EXHAUSTION MEDIATED BY PLASMACYTOID DENDRITIC CELLS

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Background: T-cell exhaustion is not reverse by effective ART. T-cell exhausted cells have been associated with HIV persistence during ART. The plasmacytoid dendritic cells (pDCs) sense viral and bacterial products through Toll-like receptors (TLR)-7 and -9 and translate this sensing in IFN-α production and T-cell polarization. It is unknown whether pDCs can reverse T-cell exhaustion in HIV-infected patient on long-term suppressive ART. The aim of the present study was to analyze, through a pDC/T-cell co-culture, whether pDCs after stimulation with different TLR agonist were able to reverse T-cell exhaustion.
Methods: Patients on suppressive ART (ART, n=5) were compared with healthy donors (HD, n=5) and viremic patients naïve for ART (VIR, n=4). pDCs, CD4+ and CD8+ T-cells were isolated from 450mL of whole blood using by negative selection. After pDC overnight stimulation with HIV inactivated with aldritiol (AT-2-HIV), CpGA, CpGC, and GS9620 or no stimuli, stimulated pDCs were cocultured for 6h with autologous CD4+ or CD8+ T-cells. The expression of PD-1, TIGIT, TIM-3 and LAG-3 in different T-cell subsets was quantified ex vivo and in vitro by multiparametric flow cytometry.
Results: Ex vivo the expression of PD1, TIGIT, TIM3 or LAG3 were increased in several CD4+ T-cell memory subsets from ART compared to HD (e.g.:PD1+TIGIT+TIM3+LAG3-CD4+CD45RA-CD27+,p=0.002). After the coculture, we observed a trend to decrease in the expression of these markers after AT-2 and CpG-A pDC stimulation (p=0.047 and p=0.06, respectively). This reversion in CD4+ T-cell exhaustion phenotype was specially patent after CpG-C and GS9620 pDC stimulation with normalization compared to HD (p=0.117,p=0.144, respectively). This decrease of CD4 T cells exhaustion markers occurs at the same time of an increase in the polyfunctionality of different CD4+ T-cell subsets in terms of cytokine production (e.g.: CD107a+IL2-IL17a+INFg+TNFαCD4+CD45RA+CD27- expression were significantly increased in ART respect HD after CpG-C and GS9620 stimulation p=0.047,p=0.037; respectively).
Conclusion: The modulation of the pDCs through TLR agonists reverses CD4+ T-cell exhaustion in HIV-infected patients on ART. These results may have important implications in the reduction of deleterious effect of pDCs and T-cells causing non AIDS events and may decrease HIV-reservoir levels.

302 CD8+ SUBSET-DEPENDENT OVEREXPRESSION OF TIGIT AND TIGIT+TIM3 BY HIV DESPITE ART

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Background: The expression of inhibitory Receptors (iRs) blocks CD8+ T-cell activity in HIV-1 infection. Consequently, the control of iRs is critical for recovering CD8+ T-cell function. The alterations of iR expression by HIV-1 infection are not fully delineated but are essential to identify future immunotherapeutic targets. With this aim, we performed a high-dimensional cytofluorimetrics of iRs, CD39, and CD8+ lineage markers in early and chronically suppressed HIV-infected individuals.
Methods: We selected PBMCs from early (Ei=24) and chronically HIV-infected individuals with longitudinal samples in a median of 3 (CiS1) and 10 years (CiS2) on suppressive cART (n=24). For comparisons, we selected PBMCs from healthy seronegative individuals (HC, n=24). We stained PBMCs using antibodies for iRs (TIGIT, PD1, LAG3, and TIM3), CD39, and CD8+ T-cell lineage (CD3, CD8, CD45RA, CCR7, and CD27). We analyzed multivariate datasets by FlowJo, SPICE, and R package. Also, we performed an unsupervised KNN algorithm for cell clustering and tSNE for visualizing single-cell data.
Results: Based on the expression levels of iRs and lineage markers, we identified 23 cellular clusters. From this analysis, we observed a remarkable heterogeneity of CD8+ T cells and detected four clusters with significant differences across CiS1 and CiS2 individuals (p<0.05). These four clusters were high on TIGIT expression and one of them was also high on TIM3 expression. Moreover, differentiated clusters had additional lineage markers indicative of memory or effector-like features. We confirmed the overexpression of TIGIT at a single level or combined with TIM3, LAG3, and CD39 in CiS1 and CiS2 by combinatorial profiling with SPICE. Single TIGIT was elevated on CM and TM (p<0.05) and TIGIT+TIM3 on CM and E (p<0.05). The combinations of four iRs, including TIGIT+TIM3 with LAG3 or CD39, were upregulated on CM or E (p<0.05). Also, we found a correlation between CD4 counts and the absence of iR expression in CiS2 (r=0.51, p<0.05).

Conclusion: HIV-1 infection drives irreversible overexpression of TIGIT alone or co-expressed with TIM3, and LAG3 or CD39 in a CD8+ T-cell subset-dependent manner. These results point towards the targeting of TIGIT in combination with TIM3, and LAG3 or CD39 to regain CD8+ T-cell subset specific function in HIV-infected individuals on cART.

303 DYNAMICS OF HIV-SPECIFIC T CELLS ON DURABLE ART DIFFER BY ANTIGEN RECOGNIZED & BY SEX

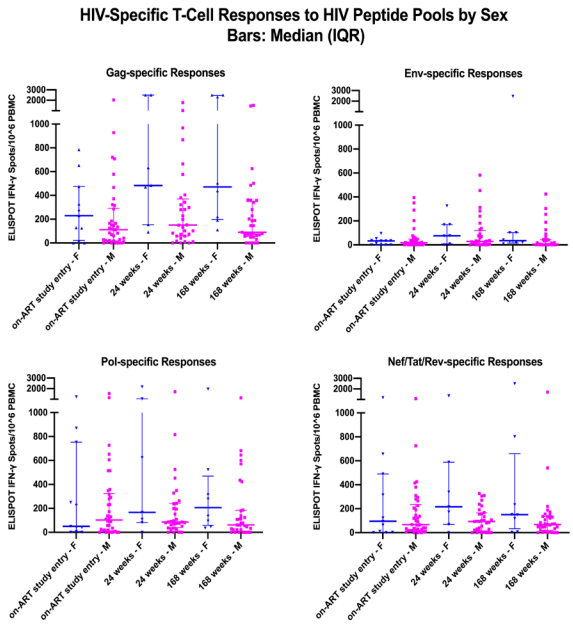
Eva M. Stevenson[1], Adam R. Ward[2], Thomas R. Dilling[1], John W. Mellors[3], Rajesh T. Gandhi[4], Deborah McMahon[3], Joseph J. Eron[5], Ronald Bosch[6], Christina Lalama[6], Joshua C. Cyktor[3], R. Brad Jones[1], for the A5321 Team
[1]Weill Cornell Medicine, New York, NY, USA, [2]George Washington University, Washington, DC, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA, [4]Massachusetts General Hospital, Boston, MA, USA, [5]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [6]Harvard University, Cambridge, MA, USA

Background: T-cell responses to HIV decay in the early stages of ART, with a half-life of 39 weeks. We previously demonstrated a direct correlation between levels of cell-associated HIV DNA (CA-DNA) and magnitudes of HIV-specific T-cell responses targeting early gene products Nef/Tat/Rev in the ACTG A5321 cohort. These results suggested that ongoing interactions with HIV-infected cells may shape HIV-specific T-cell responses in individuals on long-term ART; however, little is known about the dynamics of these responses.

Methods: We previously performed IFN-g ELISPOT assays on PBMCs from 49 participants (11 female) at study entry (on-ART timepoint 1): median (IQR) yrs on ART 7 (4, 8). We measured responses to pools of overlapping 15-mer peptides spanning the HIV gene products Gag, Env, Pol, Nef/Tat/Rev, as well as CMVpp65. Here, we applied this same assay to batched samples from week 24 & week 168 post-entry. Relationships were assessed between these responses and virologic/immunologic & clinical data provided by the ACTG.

Results: HIV-specific T-cell responses were stable on durable ART, with magnitudes differing by gene product & by sex (Figure). Responses exhibited long median half-lives, which also differed by sex: Gag 32.4yrs (F 75.1yrs, M 3.7yrs); Env 3.5yrs (F 2.5yrs, M 1.1yrs); Pol 12.1yrs (F no decay, M 6.1yrs); Nef/Tat/Rev 6.9yrs (F 5.3yrs, M 6.1yrs). F vs. M participants exhibited higher magnitudes of responses longitudinally for all HIV gene products, but not for CMV, before and after controlling for pre-ART HIV RNA & CD4 count (all $p<0.05$). Higher levels of CA-DNA at study entry were associated with lesser decay of Nef/Tat/Rev-specific responses between weeks 24 & 168 ($r=0.36$, $p=0.03$; $r=0.34$, $p=0.06$ controlling for pre-ART HIV RNA & CD4 count). Correlations were not observed between: i) CA-DNA & T-cell responses to other HIV gene products ($p>0.1$), nor ii) between the slopes of decay of any HIV-specific T-cell responses and CA-RNA, plasma HIV-RNA, %CD38+HLA-DR+ T-cells, age, or PD-1 expression.

Conclusion: Overall, HIV-specific T-cell responses were stable, demonstrating long half-lives, which differed by sex. Females also displayed higher magnitudes of HIV-specific T-cell responses. This result may help explain previous findings that females have a lower residual viremia in this cohort. Higher CA-DNA at study entry correlated with slower rates of decay in Nef/Tat/Rev-specific T-cell responses on long-term ART, consistent with some level of ongoing recognition of infected cells.



304 EXPRESSION PROFILING OF HIV LATENTLY INFECTED CELLS VIA NANOSTRING AND MASS CYTOMETRY

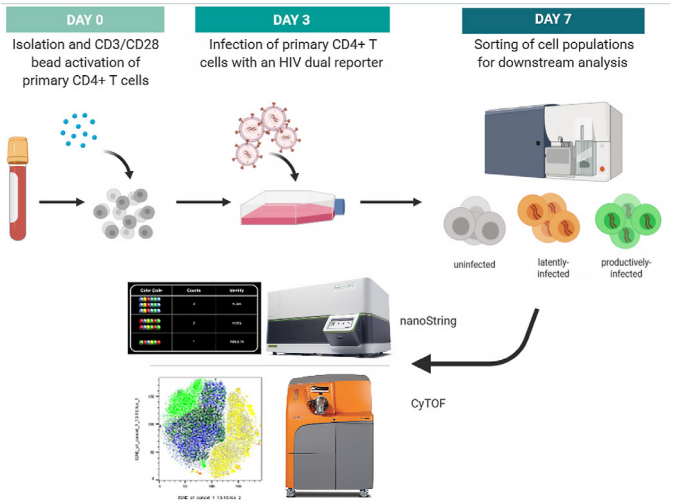
Hannah S. Sperber[1], Tongcui Ma[2], Nadia R. Roan[2], Satish K. Pillai[1]
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Background: The main barrier to an HIV cure is the latent HIV reservoir. Long-lived HIV latently-infected cells remain invisible to the host immune system and persist during antiretroviral therapy. In this study, we characterized latently-infected cells by implementing combined transcriptomic and proteomic profiling to identify unique expression signatures and reliable biomarkers that can be exploited to target and eliminate the latent reservoir.

Methods: Primary CD4+ T cells were purified from six healthy donors and were infected with a dual-reporter HIV construct that enables the isolation of HIV latently-infected and productively-infected cells by flow cytometry. The populations were then characterized using NanoString hybridization and fluorescence-based digital counting technology allowing for simultaneous detection of 770 mRNA and 30 protein targets, and mass cytometry (CyTOF), measuring 40 surface proteins. Target expression levels were compared between populations using false discovery rate (FDR<0.1), cellular pathways were analyzed using global significance scores, and upstream regulatory networks and causal relationships were deciphered using Ingenuity Pathway Analysis.

Results: The latent population displayed significant upregulation of CD73 protein and IL8 mRNA, and significant downregulation of CD39 mRNA compared to productively-infected cells and controls. Protein expression levels of T cell activation markers including CD25, PD-1, OX40, CD127, and GITR did not significantly differ between productively- and latently-infected cells, while ICOS, an inducible T cell costimulator, was significantly increased on latently-infected cells. The 'Pathogen defense' pathway was significantly suppressed in both HIV infected cell populations compared to uninfected controls. 'Antigen processing' was strongly suppressed in the latent population. Transcription factors FOXP1, FOXD1, and FOXJ1 were discovered as the top three master regulators in latent cells.

Conclusion: Our data suggest that HIV latently-infected cells exhibit distinct molecular features associated with an anergic and/or hypoxic T cell state, and may subvert antigen processing to remain immunologically invisible. FOXD1 and FOXJ1 likely repress HIV transcription in latently-infected cells through inhibition of NFkB and NFAT complexes. Our results warrant validation in vivo using clinical samples from ART-suppressed HIV-infected individuals, and mechanistic exploration ex vivo using targeted gene knockouts.



305 EPIGENOMIC CHARACTERIZATION OF A PRIMARY CELL MODEL OF HIV LATENCY

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Background: Transcriptional silencing of HIV in CD4 T cells generates a reservoir of latently infected cells that can reseed infection after interruption of therapy. As such, these cells represent the principal barrier to curing HIV infection, but little is known about the characteristics or regulation of the latent reservoir.

Methods: To further our understanding of the molecular mechanisms of latency, we employed a primary cell model of HIV latency in which infected cells adopt heterogeneous transcriptional fates with a subset of infected cells establishing viral latency. We characterized this model using assay of Transposon-Accessible Chromatin sequencing (ATACseq).

Results: We observed that loss of viral gene expression is a stable and heritable phenotype that is maintained through multiple rounds of stimulation and expansion, suggesting a role for epigenetic maintenance of latency. Using ATACseq we found that cells in which latency is established exhibit a significantly more closed chromatin conformation, both within the HIV genome and across the host cell genome, indicating that latency is correlated with a global process of epigenomic modification and heterochromatin expansion. We also observed that latency reversing agents (LRAs) induced distinct patterns of chromatin openning in both the HIV and host cell genomes. Furthermore, we observed that latently infected cells exhibited elevated levels of specific repressive histone modifications, including H3K27me3.

Conclusion: Altogether, these data demonstrate that latency establishment in primary CD4 T cells occurs preferentially in a subset of cells that exhibit expanded H3K27me3-associated heterochromatin, and that viral silencing is connected to global cellular epigenomic reprogramming. A deeper understanding of this process will likely lead to new therapeutic strategies for blocking the initiation or maintenance of latency.

306 SINGLE-CELL ANALYSIS SHOWS MOLECULAR SIGNATURES OF HIV LATENCY IN PRIMARY CELL MODELS

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Background: Primary cell models have greatly advanced our understanding of HIV latency. However, it is unclear what mechanisms underlie latency in these primary cell models. We hypothesized that molecular signatures can distinguish uninfected, latently- and productively-infected populations in these models.

Methods: We assessed 4 primary cell models [blood CD4T cells: models from labs of Eric Verdin, Alberto Bosque, and Warner Greene; tissue(tonsillar) CD4T cells: model from Warner Greene]. Single cells from each model (2 donors) were FACS-sorted into 96-well plates and multiplex RT-qPCR (BiomarkHD) was used to quantify 88 human RNAs previously implicated in HIV infection/latency and 8 HIV targets (5'LTR, Gag, Pol, Nef, MS Tat-Rev, U3-PolyA, and the IPDA assays for Env&Gag). We compared HIV-unexposed, HIV-exposed but uninfected, and latently- +/- productively-infected populations from each model to identify genes with ≥2-fold difference in median expression levels and P<0.05(*) or FDR-corrected P<0.05(**).

Results: As expected, multiple HIV targets(**) distinguished uninfected, latently-infected, and productively-infected cells. Each model differed in the cellular factors that distinguished populations, with some differences between donors. Compared to HIV-unexposed cells, latently-infected cells from the Verdin model showed higher expression of CXCR4(**), POL2RA(**), APOBEC3G(*), and STING(*) and lower expression of PRMT6(*), while latent cells from the Bosque model expressed higher levels of CGAS(**), and latent tonsil cells from the Greene model showed higher expression of CDK7, PBAF, RIG-I, and MDA5 (*for all). Compared to HIV-exposed but uninfected cells, latently-infected cells showed: 1) less CCR5(*), CD38(*), and NF-KBIA(*), but higher CD25(*) expression in the Verdin model; 2) less Cyclin L2(*) and more BCL6(*) in the Bosque model; and 3) no difference (except HIV targets[**]) in blood cells from the Greene model. Relative to productively-infected cells, latently-infected cells upregulated CTLA-4, BCL-11B, NFATC1, CDK7, HTATSF1, PAF-1, and PBAF expression (**for all) in the Verdin model, and exhibited lower expression of CD28, CTLA-4, PD-1, BCL-6, BCL-11B, FAS, Sp1, POLR2A, CREBBP, G9a, STAT1, and IRF9 (**for all) in the Greene tonsil model.

Conclusion: Our single cell analysis reveals multiple cellular factors that distinguish latently-infected cells from uninfected and productively-infected cells, that may provide a molecular signature necessary to discriminate this population in vivo.

307 PROVIRAL/HUMAN GENOMIC CROSSTALK IN CELLULAR MODELS FOR HIV INFECTION

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Background: Chronic HIV-1 infection is characterized by accumulation of proviral sequences in the genome of HIV target cells. Integration of viral-derived DNA is found at preferential loci, suggesting site-specific crosstalk between viral sequences and human genes. This crosstalk has been postulated to play a role in emergence of clonal infected cell populations. The molecular nature of this phenomenon is unclear. Paucity of HIV-infected cells in chronically infected individuals and lack of markers for HIV reservoir cells preclude functional studies in primary patient-derived cells.

Methods: CRISPR/Cas9-based homologous recombination was used to target HIV-derived reporter sequences to genomic sites in T cell-derived immortalized cells. Clonal lines were generated and multiple screening steps used to verify correct targeting. Cell models were analyzed for LTR inducibility and epigenetic regulation/ transcriptomic effects of LTR activity.

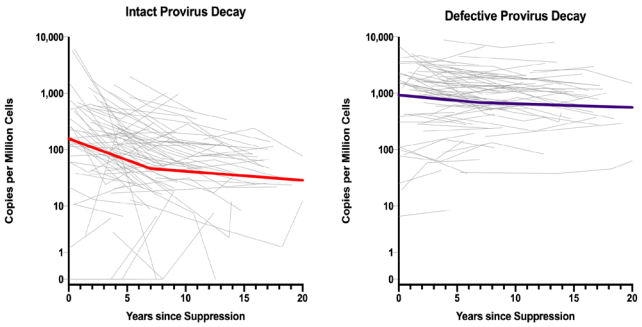
Results: We have established a workflow to generate cellular models for HIV infection that recapitulate proviral integration at selected genomic loci. Using this workflow, we have derived several BACH2-HIV-1 reporter models that mimic integration of proviral DNA in the BTB Domain and CNC Homolog 2 (BACH2) locus, which has been associated with recurrent integration and HIV-reservoir maintenance in chronically infected patients. We show that LTR transcriptional activity is repressed in BACH2 intronic regions associated with proviral-DNA integrations in vivo. This repression is not observed if proviral-sequences are targeted to regions that do not correlate with sites observed in patients. We demonstrate that these findings are reflected in epigenetic modifications on LTR regulatory regions. Furthermore, to study genome-wide effects of proviral/human crosstalk at the BACH2 locus, we have undertaken transcriptome analysis in different BACH2-HIV-1 models in latent as well as LTR-activating conditions for which results will be presented.

Conclusion: Our workflow is an adaptable tool for functional studies of proviral/human crosstalk. We show features of such crosstalk for the BACH2 locus, indicating that clustered BACH2 proviral integrations in vivo might be due to site-specific effects on LTR activity.

308 DIFFERENTIAL DECAY OF INTACT AND DEFECTIVE PROVIRUS IN INDIVIDUALS ON SUPPRESSIVE ART

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Background: The latent HIV-1 reservoir is established early in the course of infection and persists despite suppressive antiretroviral therapy (ART). The relative stabilities of the intact and defective HIV genomes over time during effective ART have not been fully characterized. Understanding variability in the rate of change of the reservoir size, correlates of this variability, and factors associated with rapid decay is likely to be useful in the design and interpretation of HIV cure interventions.
Methods: We used the intact proviral DNA assay (IPDA) to estimate the rate of change of intact and defective proviruses in HIV-infected adults on suppressive ART over several years. We used linear spline models with a knot at seven years; these included a random intercept and slope up to the knot. We also estimated the influence of covariates on levels at the start of suppression and rates of change.
Results: We studied 81 individuals for a median of 7.3 (IQR 5.9-9.6) years. In a model allowing for a change in the rate of decline, we found evidence for more rapid declines in intact genomes from initial suppression through seven years (16.0% per year decline; CI -23.0%, -8.4%) followed by a slower rate (3.6% per year; CI -8.1%, +1.1%). The estimated half-life of the reservoir was 4.0 years (CI 2.6-7.9) until year seven and 19.0 years (CI 8.2-infinite) thereafter. Intact provirus declined at a faster rate than defective provirus ($p<0.001$). There was substantial variability between individuals in the rate of decline until year seven. In multivariate models, individuals with higher CD4+ T-cell count nadir values had a faster rate of decline. A subset of individuals (n=7) were estimated to have very rapid declines (>30% per year).
Conclusion: These results demonstrate a non-linear decay of viral genomes over time. Intact proviral genomes decay more rapidly than defective ones. The mechanism for this difference is not clear, but could involve cells with intact genomes experiencing increased cytopathic effects or enhanced immune targeting due to virus protein production. These findings provide evidence that the biology of the replication-competent (intact) reservoir differs from that of the replication-incompetent (non-intact) pool of proviruses.



309 DISTINCT HIV RESERVOIR MEASURES CORRELATE WITH DEFECTIVE BUT NOT INTACT PROVIRAL DNA

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Background: A major priority for HIV cure strategies remains how best to measure persistence of HIV despite suppressive antiretroviral therapy (ART) in chronic HIV infection. Several assays have been developed to measure the HIV reservoir. We assessed the association between five distinct HIV measures on ART (intact and defective pro-viral DNA, integrated HIV DNA, integrated HIV Gag and Pol, and inducible RNA or p24).
Methods: Peripheral blood mononuclear cells (PBMC) from 20 HIV+ subjects chronically suppressed on ART at <50 HIV-1 copies/ml were assessed for a) intact and defective pro-viral DNA by IPDA (Accelevir), b) integrated HIV DNA by Alu-gag PCR, c) integrated HIV Gag and Pol by droplet digital PCR (ddPCR) following pulsed-field gel electrophoresis (PFGE), and d) latency re-activation in vitro measured by both cell-associated tat/rev induced limiting dilution assay (TILDA), and by HIV p24 single molecule array (Simoa). Spearman tests were used to test relationships between HIV measures.
Results: HIV DNA measures assessed by Alu-gag PCR or PFGE/ddPCR as well as in vitro latency re-activation assessed by TILDA or HIV p24 Simoa were positively associated with each other (e.g. HIV DNA measures assessed by Alu-gag PCR and in vitro latency re-activation assessed by TILDA: p=0.025, spearman's rho=0.541). On the other hand, intact proviral DNA did not correlate with any HIV measure. However, hypermutated and/or 5' deleted pro-viral DNA was positively associated with integrated HIV DNA assessed by Alu-gag PCR ($p<0.001$, spearman's rho=0.909) and total Gag by PFGE/ddPC R (p=0.008, spearman's rho=0.741), as well as with in vitro latency re-activation by HIV p24 Simoa (p=0.044, spearman's rho=0.627).
Conclusion: Alu-gag PCR or PFGE/ddPCR HIV DNA measures, as well as induced HIV p24 in HIV-1+ subjects chronically suppressed on ART best reflect hypermutated and/or deleted rather than intact pro-viral DNA.

310 RISK AND PREVALENCE OF RESIDUAL VIREMIA AFTER cART IN RESOURCE-LIMITED COUNTRIES

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Background: Tuberculosis, hepatitis B and C, sexually transmitted and tropical infections may contribute to higher residual viremia in virally suppressed people with HIV (PWH). The limited data describe residual viremia from low- and middle-income countries (LMIC). We assessed the prevalence, and factors associated with residual viremia in PWH, who were virally-suppressed on combination antiretroviral therapy (cART). We also compared residual viremia prevalence between the US and LMIC.
Methods: The last available sample among PWH on cART and virally suppressed with plasma HIV RNA <400 copies/mL for ≥3 years from ACTG A5175 and A5208 were tested by the HMMCgag single copy assay (SCA). Detectable residual viremia was defined as having ≥1 copy/mL.
Results: A total of 320 participants, 74 (23%) from US and 246 (77%) from LMIC, were analyzed. Median (IQR) age was 33 (28,40) years; duration of viral suppression 3.4 (3.1, 4.0) years and 48% were male (Table). In 85 participants with data available, 53% were subtype C, 42% subtype B and 5% other subtypes. Overall prevalence of residual viremia was 57% [95% CI, 52-63] with 51% [40-63] in US and 59% [53-65] in LMIC (Table). Among participants in LMIC, higher baseline RNA (r=0.29; $p<0.001$) and shorter virologic suppression duration (r= -0.19; p=0.002) were associated with higher SCA. There were no association between residual viremia and age, sex, race, prior AIDS-defining illness, HIV subtype, cART regimens and co-infection.The final multivariable model conducted in LMIC participants showed that higher baseline HIV RNA was associated with detectable residual RNA by SCA (OR 2.9, 95% CI 1.8, 4.6 for every $\log_{10}$increase, $p< 0.001$). After including both US and LMIC in the final model, baseline HIV RNA remained significant. No difference in SCA detectability was found between US and LMIC sites (OR 1.1 [0.6, 2.0], p=0.72) after adjusting for baseline RNA and parent study.
Conclusion: To our knowledge, this is the first study to compare residual viremia in long-term virally suppressed PWH between US and LMIC. The prevalence of residual viremia between both groups were not different and more than half of the participants had detectable viremia. Higher baseline HIV RNA was independently associated with residual viremia.

Table: Baseline characteristics and outcome of participants

	Total (N=320)	Site location: US (N=74)	Site location: LMIC (N=246)	P-value
Baseline characteristics				
Age (years), Median (IQR)	33 (28, 40)	38.5 (30, 47)	32.5 (28, 38)	<.0001 (a)
Male (n,%)	152 (48%)	60 (81%)	92 (37%)	<.0001 (b)
Baseline CD4 (cells/mm^3), Median (IQR)	166 (88, 230)	179 (71, 255)	162 (90, 224)	0.43 (a)
Baseline HIV-1 RNA (log_{10} copies/mL), Median (IQR)	5.0 (4.5, 5.3)	5.0 (4.6, 5.4)	4.9 (4.5, 5.3)	0.58 (a)
Co-infection* disease at the time of SCA (n,%)	99 (31%)	21 (28%)	78 (32%)	0.67 (b)
Duration of viral suppression (years), Median (IQR)	3.4 (3.1, 4.0)	4.4 (3.6,4.7)	3.3 (3.0,3.8)	<.0001 (a)
Outcomes				
Prevalence (95% CI) of detectable residual viremia (≥ 1 copy/mL) by SCA	57% (52,63)	51% (40,63)	59% (53,65)	0.28 (b)
Level of residual viremia among participants with detectable SCA (copies/mL), Median (IQR)	3.8 (2.2, 8.1)	3.9 (2.2, 7.9)	3.8 (2.2, 8.1)	0.88 (a)

(a) Wilcoxon Test
(b) Fisher's Exact Test
(c) Chi-Square Test
* Co-infection disease includes hepatitis B, hepatitis C, tropical infection, TB and sexually transmitted diseases
SCA: Single copy assay

311 A NOVEL DDPCR PROTOCOL TO ESTIMATE COPY NUMBERS OF POTENTIALLY INTACT HIV-1 PROVIRUS

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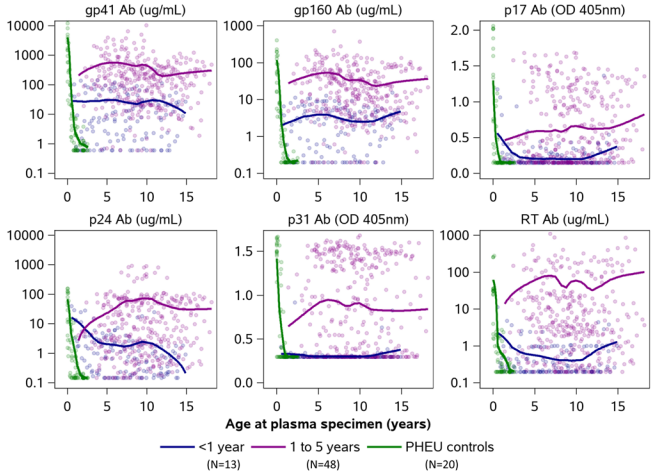
Background: Accurately quantifying the replication-competent HIV reservoir is essential for evaluating the efficacy of HIV cure strategies. Ideally, this should be achieved by a rapid turn-around high-throughput assay suitable for a clinical setting.
Methods: We designed a multiplex ddPCR protocol to quantify potentially intact provirus in CD4+ T cells in ART-suppressed people living with HIV (PLWH). Our multiplex ddPCR targets 5 regions in the HIV genome across 2 ddPCR assays, each with 2 unique and 1 common target. We chose the 5 targets by selecting conserved sequences but with documented deletions from the LANL database. Multiplex ddPCR allows us to assess potentially intact ("intact") proviral genomes by quantifying the number of droplets positive for all 3 targets. We developed a gentle DNA isolation method for cell and tissue samples, and also mathematically corrected for residual shearing, measured by two RPP30 targets. We normalized results to number of T cells, quantified by RPP30 (all cells) minus copies of a region in TRD that is deleted during TCR rearrangement and quantifies non-T cells.
Results: Our method results in minimal shearing of DNA isolated from blood samples (mean: 90% un-sheared, SD: 6%), has a low limit of detection (96.1 copies/million T cells by probit analysis with 95% confidence), and high sensitivity (detection: 1-5 copies/million), specificity (100%, n=150 negative control tests) and reproducibility (CV of positive control aliquots tested 23x over 1-year: 42.8%). The final estimate of intact provirus is the lower of the 2 assays. In blood CD4+ T cells from 14 ART-suppressed PLWH, we measured HIV by QVOA (range: 0.08-3.49 infectious units/million) and ddPCR (0-1,900 copies/million, undetectable in 2/14 samples). ddPCR averaged 99.2x (range: 0-557x) higher than QVOA. Longitudinal CD4+ T cell samples from 6-8 blood draws over 4.5-10 years in 20 ART-suppressed PLWH showed median reservoir half-lives of 55 months (range: 22-∞), consistent with previous studies. To relate the mucosal tissue reservoir to HIV shedding, we tested 6 pairs of cervical biopsies (ddPCR) and vaginal secretions (HIV RNA). 3/6 were positive for intact provirus in tissues and viral RNA in secretions, 2/6 were negative for both, and 1/6 was positive by ddPCR but negative for viral RNA.
Conclusion: Our protocol to quantify potentially intact HIV provirus is specific, sensitive, reproducible, and applicable to cell and tissue samples.

312 QUANTITATIVE HIV-1 SPECIFIC ANTIBODIES AS PREDICTORS OF BLOOD HIV-1 DNA LEVELS

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Background: Antiretroviral therapy (ART) reduces HIV-1-related morbidity and mortality in children but does not prevent the establishment of a persistent replication-competent HIV-1 reservoir. Achieving low reservoir size is favorable for HIV-1 eradication efforts and sustained virologic remission. We evaluated the utility of using HIV-quantitative antibodies as a screening test for low circulating cell-associated HIV-1 DNA levels in children and adolescents with perinatal HIV-1 infection.
Methods: This study utilized 514 longitudinally-collected plasma specimens from 61 perinatally-infected study participants living with HIV and enrolled in the Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol (PHACS AMP). We included participants who achieved sustained virologic suppression (VS) with HIV-1 plasma levels <400 copies/mL at or before 5 years of age on ART and maintained virologic control (allowing for isolated viral loads ≥400 copies/mL). Antibody levels to HIV-1 envelope (gp160, gp41), gag (capsid, p24; matrix, p17); RT (p66/51), and integrase (p31) were quantified by ELISA; PBMC HIV-1 DNA levels were measured by droplet digital PCR. Receiver operator curve (ROC) analyses and the random forest method were used to identify the most predictive antibodies for low HIV-1 DNA levels (<100 and <10 copies per million PBMCs). We also utilized ROC analysis to inform the stepwise building of a GEE model for low HIV-1 DNA levels that included all antibody levels as predictors.
Results: Among the 13 children with VS by 1 year of age, antibodies to p17, p24, and RT decreased throughout follow-up and antibodies to gp160 and gp41 were low and remained low; antibodies to p31 were either exceedingly low or undetectable (Figure). In contrast, among the 48 children with late VS after 1 year of age (between 1-5 years), antibody levels to all six HIV-1 proteins were high and remained high or increased longitudinally. The stepwise model suggested that gp41 and gp160 were useful predictors of low HIV-1 DNA levels; c-statistics including all antibodies ranged from 0.75 to 0.77. The random forest method also identified gp41 and gp160 as important predictors of low HIV-1 DNA; area under the curve estimates using all HIV-1-specfic antibodies ranged from 0.70 to 0.81.
Conclusion: HIV-1 antibody levels to gp41 and gp160 may be useful to identify virologically-suppressed children on ART with low circulating cell-associated HIV-1 DNA levels for inclusion in clinical trials aimed at remission.

Figure. LOESS trajectories of ELISA results by antibody and age at sustained virologic suppression



313LB LONGITUDINAL QVOA AND IPDA MEASUREMENTS IN CD4 T CELLS FROM ART-SUPPRESSED DONORS

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Background: The intact proviral DNA assay (IPDA) is a novel method to quantify intact, latent provirus using minimal cell input relative to the gold standard quantitative viral outgrowth assay (QVOA). As IPDA sensitivity may be affected by viral diversity, prior to implementation in experimental medicine trials it is critical to evaluate the relationship between IPDA and QVOA measurements across different participants. As latent provirus can decay over time, a comparison of the IPDA to QVOA longitudinally is also needed.
Methods: We conducted the IPDA on stored resting CD4 T cells from a cohort of 68 ART-suppressed individuals in whom QVOA had been measured. In 25 of these individuals, we performed the IPDA on two to six longitudinal samples, with matched QVOA data. Longitudinal sampling spanned a range of 1 to 33 years after ART initiation.

Results: The IPDA moderately correlated with QVOA measurements (Spearman r = 0.661, p < 0.0001). For 4/68 participants, no IPDA signal was observed despite moderate QVOA levels. For longitudinal measurements, there was significant interparticipant variability in the correlation between QVOA, intact DNA, and defective DNA measurements. In general, however, we observed a significant decay of both IPDA and QVOA measurements in the first 1 to 4 years following ART-initiation. After 4 years of ART, both IPDA and QVOA measurements generally remained stable or decayed more slowly. Packaging Signal (PS)- and Rev Response Element (RRE)-defective proviral DNA frequency tracked with intact and QVOA changes (or lack thereof) in most participants (17/25). However, in some participants there appeared to be expansion and/or decay of defective DNA species over time (8/25).
Conclusion: This study provides a key comparison of QVOA and IPDA measurements longitudinally in a large cohort of ART-suppressed participants. In general, intact proviral DNA measurements correlated with QVOA measurements over time; some correlation was also seen in measurements of defective DNA species. The precision of correlation of IPDA with QVOA may vary across individuals. The recent description of proviral clones that contract and expand over time may explain some changes seen in IPDA over time. These findings suggest an advantage for the IPDA over traditional single-target assays that measure predominantly defective DNA. The utility of IPDA to monitor cure interventions designed to deplete persistent infection deserves further study.

314 HIV TRANSCRIPTION PROFILE IN BLOOD, GUT, LIVER, AND GENITAL TRACT IN SUPPRESSED WOMEN

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Background:
Sex-specific differences affect various aspects of HIV infection. However, few studies have quantified levels of HIV infection or expression in tissues from women. Here, we measured the extent of HIV infection and progression through the HIV transcriptional blocks in blood, gut, liver, and genital tissues from HIV-infected ART-suppressed women.
Methods: Peripheral blood mononuclear cells (PBMC), liver, gut (ileum, colon, rectosigmoid), and genital tract biopsies (cervix, endometrium), and endocervical curettage (ECC) samples were collected from 5 women with plasma HIV RNA<200 copies/ml (median 10.4 years). Total and intact (IPDA) cell-associated HIV DNA and levels of read-through, initiated (TAR), 5'elongated, polyadenylated, and multiply-spliced HIV transcripts were measured by ddPCR. Phenotyping of immune cells was conducted by CyTOF. Results were analyzed using the Wilcoxon signed-rank test.
Results: Total HIV DNA was detected in all tissues, with levels being comparable between the gut, liver and genital tract tissues. Intact HIV DNA was detected in PBMC, ileum, colon and cervix. HIV transcriptional initiation (TAR RNA per provirus) tended to be higher in PBMC and endometrium than in ileum, colon, rectosigmoid, cervix, and ECC (all p=0.06), and higher in rectum than either ileum or colon (p=0.06). Likewise, levels of elongated HIV transcripts per provirus were comparable in PBMC and endometrium, but higher than the gut and cervical samples (p=0.06). Polyadenylated HIV transcripts were detected in PBMC from all 5 individuals but were rarely detected in the tissues. Multiply-spliced HIV transcripts were detected in PBMC from 2 of 5 individuals, but not detected in any tissue. The phenotypes of CD4+ T cells were distinct between the blood, genital tract, and gut.
Conclusion: The gut, liver, and genital tract are all sites of HIV persistence in women. The female genital tract contains a large pool of HIV-infected cells, with HIV DNA levels/million tissue cells that are similar to the gut. HIV-infected cells in the blood and endometrium showed higher levels of HIV transcription per provirus, while much lower levels were observed in the gut, cervix and liver. These results suggest tissue-specific differences in the mechanisms that govern HIV latency, with greater suppression of HIV transcription in most tissues than blood. Therapies aimed at disrupting latency, such as latency-reversing or latency-silencing agents, will be required to penetrate into multiple tissues and affect different blocks to HIV transcription.

315 INTACT PROVIRUSES FROM NAIVE AND EFFECTOR MEMORY T CELLS MATCH PERSISTENT VIREMIA

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Background: Genetically intact, and potentially replication competent, proviruses are a likely source for viremia during antiretroviral therapy (ART). Identifying the CD4+ T cell subsets that harbour these proviruses within different anatomic sites is important for future eradication strategies.
Methods: Near full-length proviral sequences were obtained from naïve (NV), central (CM), transitional (TM) and effector memory (EM) CD4+ T cells (sorted based on their expression of CD45RA, CD27 and CCR7), which were isolated from both the peripheral blood (PB, 13 participants) and lymph nodes (paired LN, 5 participants), using the Full-Length Individual Proviral Sequencing Assay (FLIPS). Proviral sequences were identified as genetically intact if they lacked inversions, stop codons/hypermutation, insertions, deletions or frameshifts. Genetically intact proviruses from 10 participants were compared to on-therapy plasma RNA (p6-RT region obtained by single-genome sequencing (SGS)).
Results: We sequenced 1913 proviruses, and genetically intact proviruses were found in all cell subsets except for LNEM (n=3). We found that the infection frequency of genetically intact proviruses differed across the subsets in both PB and LN (P<0.001). In PB, the order of intact genomes was found to be EM>TM/NV>CM (all P<0.02), while in the LN the trend was NV>TM>CM>EM, with evidence for NV>CM (P=0.01). All 22 intact LN sequences were genetically unique. For the subsets that had more than 10 genetically intact DNA sequences (PBEM, PBNV and LNNV), we compared the genetically intact proviruses obtained by FLIPS to the on-therapy plasma RNA p6-RT sequences obtained by SGS. PBEM had the highest frequency of genetically intact DNA sequences matching 100% to the on-therapy RNA sequences (13/23, 57%). This was followed by PBNV, with 6/19 (32%) DNA sequences matching RNA, and LNNV, with 3/16 (19%) DNA sequences matching RNA.
Conclusion: The distribution of genetically intact proviruses differs between PB and LN. For the five participants with paired PB and LN cells available, NV cells had the highest frequency of intact proviruses in LN. In PB, however, the highest levels of intact genomes were found in EM cells. PBEM, PBNV and LNNV also had a high frequency of genetically intact proviruses matching to on-therapy plasma RNA p6-RT sequences, suggesting that the intact proviruses within these T cell subsets from different anatomic sites may contribute to ongoing viremia during ART.

316 HIV Gag p24 PERSISTS IN TISSUE AND CORRELATES WITH IMMUNE RESPONSE

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Background: Gut tissue and lymph nodes (LN) harbor HIV DNA and RNA during antiretroviral therapy (ART)–mediated viral suppression, but less is known about HIV protein expression. The goal of this study is to apply a sensitive immunoassay for detecting HIV p24 antigen in lymphoid tissues during ART and to assess the relationships between immune phenotypes and HIV control to inform on HIV cure strategies.
Methods: HIV gag p24 protein was measured by an in house optimized digital ELISA in cells isolated from either rectal tissue, LN biopsies, or LN fine needle aspirates from HIV participants in the UCSF and University of Minnesota cohorts. HIV gag protein was assessed from study participants with variable levels of plasma viremia levels, ranging from fully suppressed to viremic, either naturally controlling or on ART.
Results: HIV gag p24 protein persists in lymph node and rectal biopsies in well-suppressed participants. HIV p24 levels in rectal and peripheral blood CD4+ T cells were moderately correlated among all participants (r: 0.54, P=0.0169); Rectal p24 levels discriminated between viremic, ART-suppressed, and HIV-uninfected participants much better than peripheral blood p24 levels.

Furthermore, ART-suppressed immunological non-responders (INR) had significantly higher median rectal p24 levels than immunological responders (IR (0.024 vs 0.009 pg p24 per million rectal CD4+ T cells, P=0.009). Rectal tissue from viremic and elite controllers also had measurable p24 pre-ART that declined significantly following ART. Among all ART-suppressed participants, higher rectal p24 levels were associated with lower CD4 counts and among the controllers, rectal p24 levels are better predictors of HIV-specific CD107a+ CD8 response than HIV RNA. p24 was also detected in aviremic FNA LN samples and early data suggests associations with PD1, CXCR5+ PD1 and Tfh CD4+ cells.
Conclusion: HIV gag p24 was detected in most rectal and lymph node biopsies from ART-suppressed donors and controllers suggesting a higher burden of p24 in tissues than blood. The capacity to measure and characterize HIV reservoir at the level of viral protein and assess the relationship between immune phenotype revealed p24 correlates with immune function and will be important for immune-based clearance strategies.

317 LACK OF COMPARTMENTALIZATION IN THE LATENT RESERVOIR OF BLOOD AND LYMPH NODES

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Background: There are conflicting reports on the similarity of the HIV-1 latent reservoir (LR) in the lymph node (LN) compared to the peripheral blood (PB). Characterizing the composition and any possible differences in anatomical compartments remains a crucial step to understanding the barriers to HIV cure.
Methods: HIV+ individuals on ART with suppressed viral loads who were undergoing solid organ transplantation consented to have LN removed at the time of transplant, and PB and LN mononuclear cells (MC) were collected and isolated (n=10). CD4+ cells from matched PBMC and LNMC samples were plated in a novel quantitative viral induction assay (QVIA). Sequence data was obtained from positive wells using a validated site-directed next-generation sequencing based assay that amplified the gp41 region of the viral envelope to identify the prominent induced viral variants (>2.5% of amplicons; Illumina Inc.). Subjects who had sequences obtained from >75% of the positive wells in both compartments were used to examine for compartmentalization. Neighbor-joining trees of all prominent patient sequences were inferred (Geneious prime), and identical variants were classified as 'replicates'. A Bayesian model (IUPMBayes) was used to estimate the relative size of the LR for each participant, as well as the proportion of the LR made up by each variant for their respective compartments. Compartmentalization was assessed on samples using a Hudson based test for panmixia (non-parametric) and a branch length tree correlation coefficient (parametric).
Results: In four individuals with sufficient sequences, a median of 29 induced variants were identified in PB (IQR=54.8-16.0), as compared to 26 in LN (IQR=27.8-21.3). The estimated frequency of latently infected cells was 10.4 induced proviruses per million cells (IPPMC) in PB (IQR=16.5-7.5) and 8.4 IPPMC in LN (IQR=13.2-6.8). Replicant variants and variants with unique sequences were found in both compartments in all patients. The estimated proportion of the LR made up of variants that were replicated in the patient's matched compartment varied between compartments and between patients [median % LR shared for PB=37.1% (IQR=40.1-20.5%) and LN=42.4% (IQR=57.9-29.8%); Figure]. There was no significant compartmentalization between PB and LN across all patients.
Conclusion: These data provide further evidence of intermingling and limited compartmentalization between the LN and PB, and support previous data that the LR found in the blood can be a good representation of the LR in the lymph node

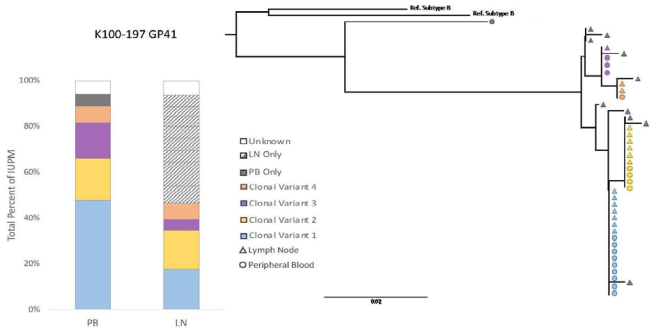


Figure: Neighbor-joining tree of distinct and replicate viral gp41 prominent species between PB and LN compartments from induced viral RNA populations from QVIA positive wells of one representative patient. Bar graph coloring shows percent of the LR made up by each variant. Replicate sequences shared between sites are shown with matched colors, solid grey sequences were detected only in PB and striped grey were found only in LN. The percentage shared variants for this patient is PB= 93.98%, LN=54.0%.

318 CHARACTERIZATION OF CD8+ TRM TOWARD THE CONTROL OF THE HIV RESERVOIR IN CERVIX

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Background: In tissues, resident memory CD8+T cells (TRM) are most likely necessary to eliminate remaining cellular HIV-1 reservoirs. However, TRM signature includes expression of molecules associated to exhausted phenotypes during chronic viral infections. Here we addressed the functional capacity of CD8+TRM from the cervical mucosa of HIV-infected women on ART to determine the most effective phenotypes at limiting viral persistence.
Methods: CD8+T cells from cervical tissues were phenotyped based on CD69 expression to determine TRM signature (n=6-9). Frequency and activation of CD103+/-CD8+TRM subsets were compared between healthy (n=9) and ART-suppressed HIV+ women (n=18). In a subset of these patients, we determined total vDNA in blood and cervix (n=7). A functional assay was established to determine suppression of viral reactivation by CD8+TRM in ART-suppressed HIV+ women.
Results: Cervical CD69+CD8+T cells protein profile was compatible with >90% belonging to bona fide CD8+TRMs, as determined by CCR7, S1PR1, T-bet, Eomes, Hobit, α1 and PD-1 expression. Further, CD8+TRMs expressed more frequently CXCR3, CCR5, CCR2 and CD161 compared to non-CD8+TRMs, and less frequently α4, CD122 and gdTCR ($p<0.05$). Cervical samples from ART-suppressed patients were enriched in total CD8+T cells compared to uninfected women, including higher frequencies of non-TRMs ($p<0.01$) and TRMs ($p<0.05$), and higher expression of HLA-DR ($p<0.01$). Importantly, the frequency of cervical CD8+TRMs correlated with proviral HIV-1 DNA in cervix ($r=-0.82$; $p=0.03$) and tissue CD8+TRMs showed better control of the reservoir in reactivated cells than effector circulating CD8+T cells.
Conclusion: Alterations of the CD8+T cell compartment within the cervical mucosa remain in HIV+ women even after several years of effective ART-suppression. The association between higher proportion of CD8+TRM in cervix and less proviral HIV-1 DNA, together with data showing higher control of virally-reactivated infected cells by CD8+TRM, indicates that these cells may be critical to control persisting virus in tissues.

319 FACTORS ASSOCIATED WITH VIRAL CONTROL AFTER STRUCTURED TREATMENT INTERRUPTION

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Background: ACTG A5068 was a RCT of people with chronic HIV infection (18% females) receiving continuous ART versus intermittent structured treatment interruptions (STIs) with or without administration of a therapeutic HIV vaccine. In the CHAMP study, HIV post-treatment controllers (PTCs) were clustered among

individuals who were subjected to STIs prior to a prolonged analytical treatment interruption (ATI). We aimed to identify virologic determinants of post-treatment control in the participants of A5068 who underwent multiple TIs.

Methods: A5068 participants in the STI arms underwent two short (~4 weeks) TIs (STI 1 and 2) and a subsequent extended ATI. Both STI 1 and 2 were followed by 16 weeks of antiretroviral therapy. We compared plasma viral load (pVL) dynamics after each STI between PTCs and post-treatment non-controllers (NCs). Single-genome sequencing (SGS) of the pol region from plasma HIV RNA was performed for 6 PTCs and 7 NCs. Confirmatory long-range SGS of the pol-env region was performed for a subset of time points. Viral diversity was calculated by the average pairwise distance at one time point and viral divergence was calculated by the average pairwise distance between sequences of different time points.

Results: pVLs were significantly lower during STI 2 compared to STI 1 for both PTCs (n=6) and NCs (n=27). For both the first and second STI, PTCs had significantly lower peak pVLs compared to NCs (median pVL [Q1, Q3] for PTCs vs. NCs at the first STI: 1,270 [536, 5,593] vs. 37,506 [1,643, 66,579] HIV-1 RNA copies/mL, p=0.001; and second STI: 199 [<50, 424] vs. 14,562 [7,870, 33,031] HIV-1 RNA copies/mL, p=0.001). An algorithm that used a combination of peak pVL<10,000 HIV-1 RNA copies/mL during STI 1 and peak pVL<1,000 HIV-1 RNA copies/mL during STI 2 accurately predicted that all 6 PTCs would achieve HIV control and that 26/27 NCs would not. In addition, we have generated >500 plasma HIV single-genome sequences for the PTCs and NCs during the STIs and ATI. Among all participants, higher plasma HIV diversity during STI 1 predicted higher viral diversity in ATI (Spearman r=0.67, p=0.02). Increasing viral divergence from STI 1 to ATI was associated with a higher peak pVL at ATI (Spearman r=0.69, p=0.02).

Conclusion: In participants undergoing STIs, lower peak pVLs during the first two short TIs may predict post-treatment control. Emergence of divergent viral populations during the third TI may compromise the ability to achieve viral control.

320 VIRAL REBOUND KINETICS FOLLOWING SINGLE AND COMBINATION IMMUNOTHERAPY FOR HIV/SIV

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Background: HIV infection can be treated but not cured with antiretroviral therapy, motivating the development of new therapies that instead target host immune responses. Three such immunotherapies were recently tested in non-human primates – a TLR7-agonist, therapeutic vaccine (Ad26/MVA), and broadly-neutralizing antibody (PGT121) – and cured a subset of animals by preventing or controlling viral rebound after antiretrovirals were stopped. The goal of this study was to use viral dynamics modeling to infer the mechanisms of action of these therapies and predict outcomes in human trials. In addition, we examined whether they reduced the pool of latently-infected cells versus boosted antiviral immunity, and whether they acted independently or synergistically.

Methods: Here we conduct a detailed analysis of the kinetics of viral rebound after immunotherapy. We introduce a new mathematical model of viral dynamics that incorporates both the stochastic and deterministic regimes of rebound and includes the action of adaptive immune responses. This model is fit to data from 99 macaques across three separate studies using a non-linear mixed-effects statistical approach. A rigorous model comparison procedure was designed to identify the effects of each intervention and quantify the impact on viral dynamics. To predict the impact of these immunotherapies in clinical trials, we calibrated the model to HIV rebound in human treatment interruption trials and simulated the effect of adding each immunotherapy.

Results: We find that the vaccine reduced reactivation of latent virus by 4-fold (95% CI [2,8]), and boosted the avidity of antiviral immune responses by 17-fold when alone [5, 67] and 210-fold [30, 1400] when combined with the TLR7-agonist. In the context of later initiation of antiretroviral therapy only (9 vs 1 week after infection), the TLR7-agonist reduced latent reservoir reactivation by 8-fold [4, 16], but also slightly increased target cell availability (1.5-fold). The antibody boosted immune response avidity 8-fold [3,16] and displayed no detectable synergy with the TLR7-agonist. In humans, the TLR7-agonist alone, TLR7+vaccine, and TLR7+antibody are expected to lead to control of rebound in some patients (~5%, 55%, 90% respectively), but often after a high peak viral load. Heterogeneity in rebound time and peak/setpoint viral loads between patients is predicted to be very high.

Conclusion: Overall, our results provide a framework for understanding the relative contributions of different mechanisms of preventing viral rebound and highlight the multifaceted roles of TLR7-agonists for HIV/SIV cure.

321 FREQUENCY OF POSTTREATMENT CONTROL VARIES BY ART RESTART AND VIRAL LOAD CRITERIA

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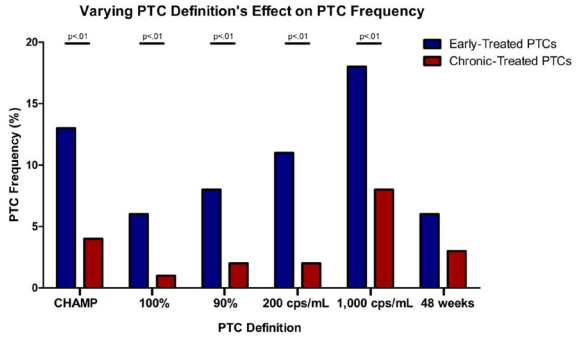
Background: Clinical trials including an analytic treatment interruption (ATI) are vital to evaluating the efficacy of strategies for HIV remissions. Determining the optimal ART-restart criteria that minimizes exposure to high-level viremia and maximizes detection of post-treatment controllers (PTCs) remains challenging. We present an interactive online tool for predicting viral rebound timing in ATI trials and describe the impact of PTC definitions on PTC frequency estimates.

Methods: The interactive viral rebound calculator (http://jonathanlilab.bwh.harvard.edu/rebound-calc/) was created with a pooled analysis of plasma viral loads (pVLs) of >700 participants from 10 ATI trials. The tool allows the user to set the ART restart criteria based on a single or multiweek pVL criteria and to customize results by the timing of ART initiation, ART regimen, and PTC frequency (default is the CHAMP study criteria: pVL<400 cps/mL at ≥2/3 time points for ≥24 wks post-ATI).

Results: We compared the impact of several commonly used ART restart criteria (1,000 pVL x 1 wk, 1,000 pVL x 2 wks, 1,000 pVL x 4 wks, and 50,000 pVL x 4 wks) on the ability of a hypothetical ATI trial to detect PTCs. Our calculator estimates that these criteria fail to identify 30%, 10%, 0%, and 0% of PTCs, respectively, due to premature ART restart. The sensitivity and specificity of PTC detection also varied by ART restart criteria. Of the 4 criteria, the 1,000 pVL x 1 wk criteria had high specificity (99%), but low sensitivity (43%), while the 50,000 pVL x 4 wks criteria had low specificity (15%), but high sensitivity (100%). The 1,000 pVL x 4 wks criteria achieved a balance with 91% specificity and 93% sensitivity for identifying PTCs. Using high pVL thresholds (≥10,000 cps/mL) for ART restart substantially reduces the specificity of PTC identification in early-treated participants, likely related to their overall lower pVL peaks compared to chronic-treated participants. The expected frequency of PTCs varied dramatically by the PTC definitions (Figure). In almost all scenarios, PTC frequency was significantly higher in early-treated individuals.

Conclusion: This calculator provides the first interactive tool for estimating viral rebound outcomes and supporting the design of ATI trials. A multi-week ART restart criteria of 1,000 pVL provides high sensitivity and specificity for PTC detection. However, the expected frequency of PTC identification in ATI trials can vary dramatically by the definition of post-treatment control.

Figure. Effect of post-treatment controller definitions on estimated frequency of control. "CHAMP" refers to the PTC criteria used in the CHAMP study: pVL<400 cps/mL at ≥2/3 time points for ≥24 wks post-ATI. "100%" criteria = pVL<400 cps/mL at 100% of time points for ≥24 wks post-ATI. "90%" criteria = pVL<400 cps/mL at 90% of time points for ≥24 wks post-ATI. "200 cps/mL" criteria = pVL<200 cps/mL at ≥2/3 of time points for ≥24 wks post-ATI. "1000 cps/mL" criteria = pVL<1000 cps/mL at ≥2/3 of time points for ≥24 wks post-ATI. "48 wks" criteria = pVL<200 cps/mL at ≥2/3 of time points for ≥48 wks post-ATI. Frequencies were compared using Fishers exact test.



322 NONSTRUCTURED TREATMENT INTERRUPTIONS CONTRIBUTE TO LATENT HIV-1 RESERVOIR IN PWID

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Background: Persons with a history of injecting drugs (PWID) often struggle to maintain stable viral suppression and experience ART non-structured treatment interruptions (NTIs). Injecting drugs has been associated with increased inflammation and alterations in T cell homeostasis. However, the long-term effects of NTIs or of injection drug use on the HIV-1 latent reservoir have not been defined.
Methods: We performed the intact proviral DNA assay (IPDA) on 108 HIV-1+ adult participants of the ALIVE cohort who at a minimum were on suppressive ART with plasma HIV-1 RNA <50 copies/mL at the time of sampling and at the study visit 6 months prior; a minimum of 5 HIV RNA measurements (2.5 years of observation) was required. Participants were selected based on self-report of current drug use: active heroin use (n=28), active cocaine use (n=23), combined cocaine and heroin use (n=29), and no reported drug use (n=28). Participants were further selected to include those with a history of stable viral suppression (n=36) and those with past periods of viremia due to NTIs (n=72).
Results: Participants were 71% male, 96% black, and median age was 53 years. No significant differences were observed by current patterns of drug use, with median frequencies of intact proviruses ranging from 1.95 to 2.44 $\log_{10}$ per 10^6 CD4+ T cells across groups, values comparable to those seen in other cohorts not selected based on illicit drug use (Figure, Panel A). However, we did observe notably higher intact provirus frequency among persons who had experienced NTIs (Figure, Panel B) compared to those with stable suppression (mean 2.15 vs. 1.50 $\log_{10}$ per 10^6 CD4+ T cells, respectively; P=0.0011). In multi-variable linear regression adjusting for demographics and drug use, NTIs were strongly associated with higher intact provirus (coef= 0.576; P=0.026).
Conclusion: We found no apparent long-term effect of injecting drugs on latent reservoir size as measured by IPDA. However, we found a notable increase in reservoir size for those with past periods of viremia due to NTIs compared to those with a history of more stable viral suppression. Our data have important implications for the field. First, they support the inclusion of PWID with stable suppression in cure studies. Second, they demonstrate that a history of viremia due to NTIs may have lasting effects on the size of the reservoir, and as such, virologic history should be considered when designing or analyzing HIV-1 cure studies.

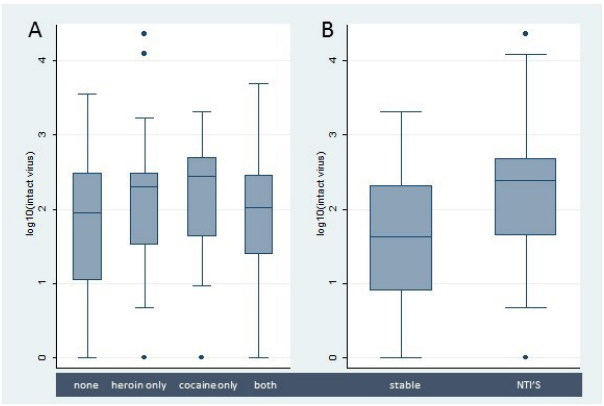


Figure. Box and whisker plot of the distribution of intact provirus (per 10^6 CD4+ T-cells), stratified by A) current drug use, and, B) stable viral suppression versus NTI's.

323 PRESENCE MACROPHAGE-TROPIC HIV-1 VARIANTS FOLLOWING ANALYTIC TREATMENT INTERRUPTION

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Background: HIV-1 persists in cellular reservoirs that can replenish viremia if antiretroviral therapy (ART) is interrupted. Therefore, insight into the nature of those reservoirs may be revealed from the composition of recrudescing viremia following treatment cessation. Most attention has focused on the CD4+ T cell reservoir in patients on ART. We hypothesize that macrophages also serve as a viral reservoir under ART. To assess this, we examined the composition of rebound viremia in individuals undergoing an analytic treatment interruption (ATI). Specifically we examined whether post-ATI viremia harbored viral variants that exhibited a highly macrophage-adapted phenotype.
Methods: A total of 551HIV-1 full-length envelopes were isolated by single genome amplification from plasma of six individuals who underwent ATI. Isolated envsequences were used to construct recombinant, infectious HIV-1 molecular clones. The recombinant viruses were assessed for the ability to fuse and replicate within primary macrophages.To determine whether macrophages were a source for macrophage-adapted HIV-1 variants, immunoprecipitation of plasma-containing virions was performed using a macrophage-specific marker (CD14). To assess whether macrophage-tropic viruses identified in post-ATI viremia originated from macrophages prior to treatment interruption, we inferred time-scaled phylogenies, through Bayesian phyloanatomy framework using a robust estimate of intra-host evolutionary rate in the envgene (7.53 10-3 nt substitutions/site/year).
Results: Macrophage-tropic viruses were identified at low frequency in a library of recombinant viruses constructed with individual envelope genes that were obtained from plasma of six individuals undergoing analytic treatment interruption (ATI). Macrophage-tropic viruses could also be enriched from post-ATI plasma using macrophage-specific (CD14) but not CD4+ T cell-specific (CD3) antibodies, suggesting that macrophage-tropic viruses had a macrophage origin. Phylogenetic relationships indicatethat the establishment of macrophage-tropic HIV-1 variants predated ATI in 4 out of 6 study participants.
Conclusion: Collectively, these data suggest that macrophages are a viral reservoir in HIV-1-infected individuals on effective ART and contribute to viral recrudescence when treatment is interrupted. These findings have implications for the design of curative strategies for HIV-1.

324 THE ELUSIVE SOURCE OF HIV-1 REBOUND AFTER TREATMENT INTERRUPTION

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Background: Identifying the source of viral rebound during a monitored analytical treatment interruption (ATI) would reveal potential targets for cure strategies. Therefore, we examined the genetic composition of proviral DNA in different subsets from participants on antiretroviral therapy and compared this to rebounding virus after an ATI.
Methods: Eleven participants underwent a monitored ATI and were sampled from different anatomical sites prior to and after the ATI. From the peripheral blood, Naïve (TNA), central (TCM), transitional (TTM) and effector (TEM) memory CD4+ T cells were sorted as were CD45 cells from gut-associated lymphoid tissue (GALT). Using single-genome sequencing (SGS) the env region of HIV DNA and plasma-derived RNA was sequenced. In an ongoing study, Full-Length Individual Proviral Sequencing (FLIPS) and Integration Site Loop Amplification (ISLA) assays were performed on the T cell subsets from 2 participants.
Results: For participant STAR10, 87 integration sites (IS) and 113 proviral genomes were sequenced while only 3 unique intact proviruses (3%) were identified. A cluster of 17 identical defective proviruses were linked to an IS (9% of all IS) in STAT5B located in TCM, TNA, TEM and TTM. When comparing the FLIPS to SGS env sequences a 100% match was found between one defective provirus and one plasma HIV RNA sequence after rebound. For participant STAR11, 37 IS and 105 proviral genomes were sequenced yielding 14 intact proviruses (13%) with the highest proportion found predominantly in the TEM subset (n=13, 45%). Four different clusters of identical sequences could be identified of which 2 (n=3 and n=9) consisted of intact TEM sequences with the smaller cluster linked to an IS in ZNF274. A 99% match between 2 env from rebounding plasma RNA and this smaller cluster of intact proviral genomes was identified.
Conclusion: Comparing proviral sequences and their IS to plasma-derived RNA sequences after an ATI reveals additional information in terms of the source of viral rebound. However, this comparison is complicated by multiple factors. For example, we found a plasma-derived RNA sequence obtained during viral rebound matched a defective proviral sequence which highlights the problem of using one HIV RNA subgenomic region for identifying replication-competent virus. In addition, ongoing viral replication during rebound may prevent a 100% match with genetically intact proviral sequences making it challenging to determine the absolute source of rebound.

325 HIV POSTTREATMENT CONTROL DESPITE PLASMA VIRAL EVOLUTION AND DUAL INFECTION

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Background: HIV post-treatment controllers (PTCs) serve as models for sustained HIV remission. These individuals frequently have early HIV rebound before viral control and subsequent periods of intermittent low-level viremia. Little is known about the viral composition during these periods of viremia.
Methods: We extracted longitudinal plasma HIV RNA from PTCs and post-treatment non-controllers (NCs) from AIDS Clinical Trials Group (ACTG) analytic treatment interruption (ATI) trials. Single-genome sequences (SGSs) of HIV-1 pol were obtained at pre- and multiple post-ATI time points (median 90 wks at the late time point for the PTCs). Sequence analysis included calculations of viral genetic diversity by average pairwise distance (APD), root-to-tip distances, percent of HLA-escape mutations, and panmixia testing.
Results: Despite low plasma viremia, >1200 SGSs were obtained for 20 PTCs and 13 NCs. Early after ATI, chronic-treated NCs had the highest levels of plasma HIV diversity while viral diversity was limited for both early-treated PTCs and NCs. Over time, increasing viral diversity was detected in almost all PTCs, but rates of diversification were significantly slower in PTCs compared to NCs (median 0.05% vs 0.27% per year, p=0.007). PTCs were also able to maintain viral control despite evidence of viral evolution. This included increasing root-to-tip distances of HIV sequences by phylogenetic analysis over time for all PTCs, divergent population structures by the panmixia test in 73% of PTCs, and accumulation of HLA escape mutations in longitudinal sampling for 2 chronic-treated PTCs (Figure). The proportion of HLA-escape mutations were common in plasma HIV sequences from PTCs and not significantly different than NCs (47% vs 59%, p=0.16). Unexpectedly, the presence of dual HIV infections (populations of HIV variants with ≥5% sequence divergence) was detected in the plasma SGSs for 3 PTCs (1 early-treated, 2 chronic-treated) and for none of the NCs. In two participants, dual infection was detected at the early ATI time point with one variant becoming dominant over time. One individual was found to have an apparent superinfection with a late post-ATI viral rebound of a second HIV variant before subsequently regaining HIV control.
Conclusion: PTCs exhibit sustained HIV remission despite evidence of slow plasma viral diversification and evolution. The detection of dual HIV infection in a subset of PTCs suggests the presence of an antiviral response that can control a diverse viral population.

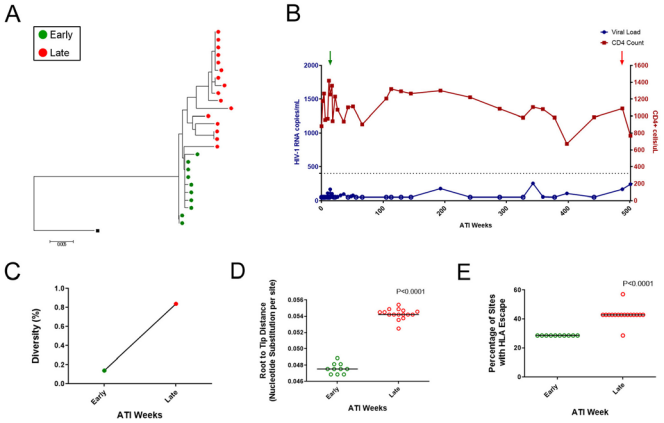


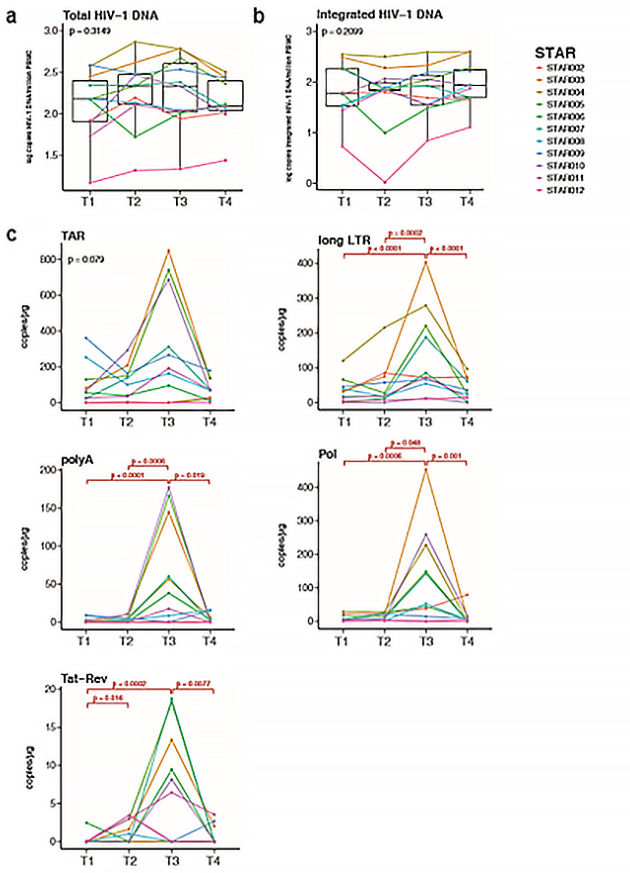
Figure. Example of HIV sequence evolution for one PTC. Neighbor-joining phylogenetic tree of the single-genome pro-rt sequences at early (14 week) and late (488 week) time points after analytic treatment interruption (ATI) (A). Graph of the post-ATI viral load and CD4+ cell count in (B) with upper arrows indicating samples used for plasma sequence analysis. Changes in viral diversity by average pairwise distance (C), root-to-tip distance (D),and proportion of sites with HLA escape mutations (E) at the early and late ATI time points.

326 EVALUATING BIOMARKERS FOR HIV REBOUND DURING TREATMENT INTERRUPTION

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Background: Validated biomarkers to evaluate HIV-1 cure strategies are currently lacking, therefore requiring analytical treatment interruption (ATI) in study participants, potentially impacting their health. Here we assessed these patients safety concerns by evaluating viral reservoir size in blood and inflammatory levels in the brain. Furthermore, restriction factor (RF) expression levels and cell-associated (CA) HIV-1 RNA transcripts were assessed as potential biomarkers for predicting viral rebound.
Methods: In the HIV-STAR study, we collected peripheral blood mononuclear cells (PBMC), plasma and cerebrospinal fluid (CSF) from 11 participants at 4 time-points on-and off-treatment to assess these safety concerns and screen potential biomarkers for predicting viral rebound. Total and integrated HIV-1 DNA, CA HIV-1 RNA transcripts and restriction factors (RF) expression were measured. Markers of neuro-inflammation and neuronal injury were measured in CSF and immune activation was assessed in plasma and CSF.
Results: Total HIV-1 DNA, integrated HIV-1 DNA and CA viral RNA transcripts did not differ pre- and post-ATI. Similarly, no significant NfL or YKL-40 increase in CSF was observed between baseline and viral rebound. Furthermore, markers of immune activation did not increase during ATI. Interestingly, RF SLFN11 and APOBEC3G increased after ATI before viral rebound was observed. Similarly, Tat-Rev transcripts were increased preceding viral rebound after interruption.
Conclusion: ATI did not increase viral reservoir size, nor did it reveal signs of increased neuronal injury or inflammation, suggesting that these well-monitored ATIs are safe. Elevation of Tat-Rev transcription and induced expression of RF SLFN11 and APOBEC3G after ATI prior to viral rebound indicates

that these markers could be used as potential biomarkers predicting viral rebound.



Viral reservoir size quantification at the four different time points during ATI. Boxplots demonstrating levels of total HIV-1 DNA (a) and integrated HIV-1 DNA (b) at T1, T2, T3 and T4. Levels for the different transcripts (TAR, long LTR, polyA, Pol and Tat-Rev) of cell-associated HIV-1 RNA (c) at T1, T2, T3 and T4. Friedman statistical analysis with posthoc Dunn test was performed. Significant p-values are indicated in red.

327 HIV DIRECTLY INFECTS RESTING MEMORY CD4 T CELLS

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Background: The establishment of the latent HIV reservoir in resting memory CD4 T cells occurs early in infection. Resting CD4 T cells are more difficult to infect than activated CD4 T cells. Therefore, the HIV reservoir is thought to form when HIV infects a few activated CD4 T cells that are resting down. Furthermore, HIV encodes four proteins: Vif, Vpr, Vpu, and Nef, which play an important role for the persistence of HIV. For example, Nef is known to downregulate MHC class I molecules (pMHCs) which prevents the recognition by CD8 T cells. However, the precise timing of expression of these four HIV proteins and the downregulation of their targeted host proteins in resting memory CD4 T cells is unknown.
Methods: We explored this question by direct infection and longitudinal analysis of primary resting CD4 T cells with a CCR5-tropic replication-competent reporter virus in which GFP reports the expression of Nef. We then measured pMHCs by flow cytometry and performed bulk and scRNAseq of sorted GFP+ cells to measure host and HIV mRNAs. We also performed scATACseq to identify the sites of HIV integration to determine their influence on the timing of Nef expression.
Results: We detected resting memory GFP+ cells 3 to 4 days after infection. These GFP+ cells showed low surface levels of pMHCs. By scRNAseq HIV mRNAs were identified in GFP+ cells and they encoded for Nef, Vpr, Vif or Vpu-Env, but never for Gag-Pol, Tat or Rev. The analysis of scATACseq and scRNAseq revealed this differential expression of HIV mRNAs was due to HIV integration into genes that are stochastically transcribed across resting CD4 T cells. Importantly, RNAseq analysis identified the expression of a cell-cycle independent form of ribonucleotide reductase, which converts ribonucleotides to deoxynucleotides. Also, the pathway for thymidine synthesis was not active in resting T cells. Thus, using a real-time qPCR assay that distinguishes proviruses with deoxyuracils or thymidines, we found the proviruses in resting T cells had deoxyuracils instead of thymidines. Lastly, we revealed Vpr protected proviruses from an UNG-dependent inactivation mechanism.
Conclusion: We conclude that HIV can directly infect primary resting memory CD4 T cells to establish the reservoir. HIV-infected resting CD4 T cells incorporate deoxyuracils, which is deleterious in the absence of Vpr inhibiting UNG. Finally, we believe the integrated HIV genome persists through transcription and alternatively splicing for mRNAs encoding Nef, Vif, Vpr, or Vpu-Env.

328 ESTABLISHMENT OF THE HIV-1 DNA RESERVOIR MIRRORS THE REPLICATION-COMPETENT RESERVOIR

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Background: All HIV-infected people on ART have a long-lived reservoir. We recently showed that the replication-competent portion of this reservoir originates from viruses circulating near the time of ART initiation, similar to a previous report that examined total viral DNA. Here we examine both the replication-competent reservoir and the viral DNA reservoir in the same set of participants.
Methods: Plasma was collected longitudinally from 16 women in the CAPRISA-002 cohort pre-ART, with PBMCs then collected after 4.8 years (average) of suppressive ART. MiSeq with Primer ID was used to sequence 5 genomic regions from RNA in the pre-ART plasma samples. Outgrowth virus was generated from quantitative viral outgrowth assays (QVOA) using resting CD4+ T cells collected post-ART. PCR was used to generate overlapping half genome amplicons from QVOA-derived viral RNA and from total cellular DNA from the post-ART PBMCs and sequenced using PacBio with barcodes. Phylogenetic trees were constructed using all pre-ART sequences and reservoir sequences. Reservoir entry time was estimated by the phylogenetic relationship between each reservoir sequence and the pre-ART sequences.
Results: A median of 10 (range: 4 to 54) reservoir sequences were generated for each participant. In all 5 women with both QVOA and DNA sequences, we did not detect a difference in the timing of establishment of the DNA compared to the replication-competent reservoir (Fisher's exact test, all $p > 0.05$). For the overall cohort (N=16; 4 DNA only, 7 QVOA only and 5 DNA and QVOA), a median of 71% of reservoir sequences were seeded in the year before ART initiation. In one individual where only late viruses had been detected using QVOA, deeper sampling of viral DNA identified a minority of early viruses, consistent with the potential for virus to enter the reservoir when active replication is ongoing.
Conclusion: Viral evolution prior to ART was used to date when both replication-competent viruses and proviral DNA were seeded into the long-lived reservoir. We observed no difference in when these reservoirs formed; both formed predominantly around the time of ART initiation. Our results suggest that the probability an infected cell contributes to the long-lived HIV-1 reservoir is largely determined by the biology of the infected T cell, not the provirus that it carries. In this interpretation a larger population of cells transition to a long-lived state around the time of ART initiation, with some of these cells being nonproductively infected.

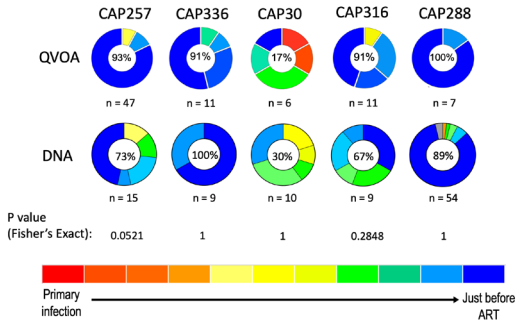


Figure 1. Estimating the timing of reservoir formation using QVOA-derived and DNA-derived sequences. Pie charts showing the entry of QVOA-derived (top) and DNA-derived (bottom) sequences into the reservoir. The percent shown in each pie chart represents the proportion of sequences that entered the reservoir in the year before ART. Fisher's exact test was used to compare the proportion of QVOA-derived sequences that entered the reservoir in the year before ART to the proportion of DNA-derived sequences that entered the reservoir in the year before ART.

329 CD127+ LYMPHOID MEMORY CD4+ T CELLS PREFERENTIALLY SUBJECT TO LATENT HIV INFECTION

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Background: Lymphoid tissues are a primary site of HIV replication and persistence. We recently demonstrated that tonsillar memory CD4+ T cells expressing CD127, efficiently fused to HIV but did not allow the fused virus to complete a round of productive infection. Mechanisms that prevent transcription off the viral LTR can prevent completion of the viral life cycle, and also promote HIV latency which is one of the main barriers to an HIV cure. In this study, we set out to better characterize the molecular basis for the block in HIV replication in tissue CD127+ memory CD4+ T cells by considering two main possibilities: post-entry restriction by SAMHD1, or latent infection of these cells by HIV.

Methods: Tonsil cells from uninfected donors were mock-treated or exposed to a CCR5-tropic HIV reporter virus for 3 days. Multiple populations of memory CD4+ T cells were compared for SAMHD1 expression and infection levels by FACS. These subsets were sorted and quantified for levels of integrated HIV-1 provirus using 2-step Alu-gag PCR with ddPCR. Global expression profiling of the sorted subsets was conducted.

Results: Lymphoid CD127+ mem CD4+ T cells do not exhibit early post-entry restriction by SAMHD1, but rather preferentially undergo latent infection as they harbor high levels of integrated HIV DNA in the absence of reporter gene expression. Relative to other memory CD4+ T cell subsets highly permissive for productive infection, the CD127+ cells preferentially expressed host transcripts associated with cellular quiescence explaining how these cells can preferentially silence the HIV LTR. Latently-infected CD127+ memory cells were reactivated by stimulation through the TCR.

Conclusion: We identify a population of tissue-specific memory CD4+ T cells expressing CD127 that upon exposure to HIV preferentially supports latent infection. Because these cells can undergo IL7-driven homeostatic proliferation and can be reactivated, they may serve as an important reservoir to target for HIV eradication efforts. They also serve as a useful in vitrotissue model of HIV latency that can be used to investigate multiple aspects of latency establishment and maintenance. Although CD127 has not been found to be preferentially expressed on latent cells in vivo, the data presented herein warrant investigation of this receptor as a potential biomarker of latently infected cells residing in tissues.

330 UNPRIMED CD8+ LYMPHOCYTES PROMOTE THE ESTABLISHMENT OF HIV LATENCY IN CD4+ T CELLS

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Background: The persistence of HIV infection under ART is due to a reservoir of latently infected cells that remain indefinitely despite suppression of virus replication.Defining the mechanisms responsible for the establishment and maintenance of the HIV reservoir under ART has been the focus of efforts aimed at HIV eradication. Several studies have demonstrated that CD8+ T cells inhibit virus replication during untreated HIV/SIV infection; however, the mechanisms responsible for this antiviral effect remain poorly understood.

Methods: We used our primary cell based in vitromodel of HIV latency to study the CD8+ T cell mediated suppression of HIV expression. To examine the impact of CD8+ T cells on the establishment of HIV latency, memory CD4+ T cells from HIV naïve donors were infected in vitroand then co-cultured with activated CD8+ T lymphocytes (1:1 or 1:5 target:effector ratios) in the presence of the anti-retroviral compound saquinavir. After three days, we assessed intracellular Gag expression on CD4+ T cells by flow cytometry, and quantified the frequency of integrated HIV DNA by qPCR. To assess the role of CD8+ T cells in latency reversal, latently infected CD4+ T cells generated in our in vitrolatency model were TCR stimulated in the presence or absence of activated CD8+ T lymphocytes (1:1 or 1:5 target:effector ratios). After three days of activation, we again assessed intracellular Gag expression on CD4+ T cells, and quantified the frequency of integrated HIV DNA.

Results: In the establishment of HIV latency, we found that HIV expression in CD4+ T cells was reduced when co-cultured with CD8+ T cells an average of 9-fold ($p<0.0001$) and 18-fold ($p<0.0001$) at 1:1 or 1:5 ratios respectively, without significantly reducing the frequency of HIV-infected cells (n=21). We also observed a significant suppression of HIV latency reversal, a 6-fold decrease at 1:1 target: effector ratio ($p= 0.0156$) and 14-fold decrease at 1:5 ratio ($p= 0.0156$).

Conclusion: Our studies demonstrated a CD8+ lymphocyte mediated suppression of HIV expression in CD4+ T cells that functions to induce the establishment as well as maintain latency in the presence of activation signaling. Understanding the mechanisms by which CD8+ lymphocytes suppress virus transcription and ultimately promote HIV latency in ART-treated HIV-infected individuals may provide critical insight to support the design HIV eradication approaches.

331 THE HIV ANTISENSE TRANSCRIPT AST INDUCES VIRAL LATENCY VIA SEVERAL SILENCING PATHWAYS

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Background: The HIV-1 antisense transcript (Ast) induces the establishment and maintenance of HIV-1 latency via recruitment of the Polycomb Repressor Complex 2 (PRC2) to the HIV-1 5'LTR, leading to trimethylation of lysine 27 on histone H3 (H3K27me3), nucleosome assembly and transcriptional silencing.

Methods: Ast mutants were tested after stable transduction in Jurkat E4 cells. To identify new binding partners, Ast was fused to a streptavidin-binding RNA aptamer, expressed in 293 cells, affinity-purified by streptavidin, and binding proteins identified by mass spectrometry (MS). For RNAseq, differential analysis was performed with edgeR with negative binomial distribution using FANTOM-CAT permissive set as reference transcriptome.

Results: We produced a panel of substitution and deletion mutants. A 376-nt segment at the 5' end of Ast (5AST, from the 3'LTR) mediates binding of Ast to the proviral 5'LTR via sequence homology. We divided the Ast sequence downstream of 5AST into four segments (A through D). Substitution of segment A or B reduces Ast function. Substitution of 70nt in segment B containing a putative PRC2-binding motif also reduces Ast activity decreasing H3K27me3 levels at Nuc-1. Concurrent substitution or deletion of segments C and D also impacted Ast activity, suggesting the recruitment of additional factors. We found that Ast interacts with several repressors such as NuRD, CTCF, YY1, TDP-43, forming a complex of ~2MDa. To assess off-target effects of Ast, we performed RNAseq in cells stably transduced with Ast compared to cells stably transduced with empty lentivirus and parental cells, and using three different cellular backgrounds. Only 7 and 16 host genes differentially expressed in Ast-expressing cells compared to parental cells and empty lentivirus cells, respectively. To gain insight into Ast transcriptional regulation, we measured Ast expression in response to a panel of LRAs and found that all agents induced antisense transcription to similar or greater extent than sense HIV-1 transcription.

Conclusion: We identified the LTR- and PRC2-binding regions of Ast, and new Ast-binding partners. We found that Ast does not affect host gene expression and is highly specific for HIV-1. These results identify Ast an ideal tool for the development of a functional cure. Induction of Ast to greater extent than sense HIV transcripts in response to LRA may explain their limited efficacy in HIV reactivation.

332 LUNG DOUBLE NEGATIVE T CELLS HARBOR HIV IN ACUTE INFECTION AND DURING LONG-TERM ART

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Background: The lungs are relatively unexplored reservoirs in the ART era. Double negative (DN) T-cells originate either from the thymus by escaping negative selection, or in the periphery following CD4 downregulation by HIV Nef/Vpu. As circulating DN T-cells have been described as cellular HIV reservoirs,

we undertook a thorough analysis of DN T-cells in the lungs vs blood of ART-treated HIV-infected individuals.
Methods: 17 long-term ART-suppressed adults (median 9 years) and 8 uninfected controls, both without active respiratory symptoms, were recruited. Bronchoscopies were performed to obtain bronchoalveolar lavage (BAL) fluid, and matched blood was collected. T-cell subsets and HIV p24 were characterized by flow cytometry and HIV-DNA levels were measured by ultrasensitive PCR. To examine DN T-cell dynamics in acute vs chronic infection lung, spleen and blood specimens from R5-HIV infected BLT humanized mice (hu-mice) were assessed.
Results: FACS-sorted DN T-cells from BAL harbored HIV-DNA in ART+ adults although HIV-DNA levels were lower in DN vs lung CD4 T-cells. Both HIV+ and HIV- adults had greater CD3+CD4-CD8α-CD8β- cell frequencies in BAL vs blood, while CD3+CD4-CD8-TCRαβ-TCRγδ- cells were only enriched in BAL from HIV+ individuals. In contrast to blood, pulmonary DN T-cells in both HIV+ and HIV- groups displayed mostly an effector memory phenotype (CD45RA-CD28+). However, HIV+ individuals had more activated (HLA-DR+) DN cells and fewer senescent (CD28-CD57+) and recent thymic migrant (CD31+) lung DN cells. No changes were noted in CXCR3+ (lung epithelium homing) DN T-cells within lungs vs blood. Similar to humans, CD3+CD4-CD8α-CD8β- DN T-cells were enriched in BAL vs blood of HIV+ and HIV- hu-mice. Importantly, p24+ DN T-cell frequencies within the lungs were consistently higher than in blood and spleen in both acute and chronic HIV infection of hu-mice. Like in humans, fewer lung DN T-cells in hu-mice had a recent thymic migrant phenotype, suggesting their local expansion within the lungs due to HIV infection.
Conclusion: Long-term ART-suppressed adults have higher frequencies of DN T-cells in lungs vs blood and exhibit HIV-DNA persistence within their lung DN T-cells. In hu-mice, HIV is seeded within the lung DN T-cells during acute infection. As in HIV infection lung DN T-cells are activated effector memory cells expressing reduced senescence and thymic migration phenotypes vs blood, viral reservoirs are likely to be more active in lungs despite long-term ART.

333 EFFECT OF TAMOXIFEN ON VORINOSTAT-INDUCED HIV RNA EXPRESSION IN WOMEN ON ART (A5366)

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[1]Johns Hopkins University, Baltimore, MD, USA, [2]Brigham and Women's Hospital, Boston, MA, USA, [3]Harvard T.H. Chan School of Public Health, Boston, MA, USA, [4]University of Rochester, Rochester, NY, USA, [5]The Ohio State University, Columbus, OH, USA, [6]Merck & Co, Inc, Upper Gwynedd, PA, USA, [7]University of California San Francisco, San Francisco, CA, USA, [8]University of Arizona, Tucson, AZ, USA, [9]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [10]Case Western Reserve University, Cleveland, OH, USA, [11]Massachusetts General Hospital, Boston, MA, USA

Background: HIV reservoirs differ between men and women but few women have been enrolled in HIV cure trials to date. In vitro and ex vivo data have identified a suppressive role for the estrogen receptor in HIV transcriptional control. ACTG A5366 investigated whether the selective estrogen receptor modulator tamoxifen enhances HIV transcription in vivo after vorinostat exposure.
Methods: Postmenopausal women with HIV suppression for >1 yr and continuous ART for >=2 yrs were randomized 2:1 to 5 wks of tamoxifen (ArmA) vs observation (ArmB); both groups then received 2 doses of 400mg of vorinostat separated by 72 hrs. Primary outcomes were safety in all treated women and change in HIV RNA expression from baseline to 5 hrs after second vorinostat dose in those receiving full study treatment (efficacy group). Total HIV DNA and unspliced cell-associated RNA(caRNA) were measured in $5x10^6$ CD4 T cells by qPCR, and spliced HIV envelope transcripts were measured in 106 resting memory CD4 cells by EDITS assay. Single copy assay(SCA) of plasma viremia and histone acetylation by ELISA were measured. Arms were compared by t-tests.
Results: 31 women enrolled in 3 months; median age 57, 58% African American, median CD4 count 688 cells/mm_3. No >=Grade 3 adverse events related to study drugs were seen. 27 women comprised the efficacy group (19 ArmA, 8 ArmB). There was no difference between the groups in the change in HIV expression by caRNA (mean fold change: ArmA 1.2, ArmB 1.5, p=0.6) or in EDITS (mean fold change ArmA 1.5, ArmB 4.3, p=0.12). Following vorinostat, 18 participants had increased histone acetylation; in these women, HIV expression by EDITS also increased (mean fold increase: Overall 2.8; ArmA 1.7; ArmB 7.4; Table 1). There were no changes in HIV DNA or SCA. Targeted plasma concentrations of tamoxifen and vorinostat were achieved.
Conclusion: In post-menopausal women receiving vorinostat, ESR1 antagonism with tamoxifen was not associated with a significant change in the magnitude of HIV RNA induction by qPCR or EDITS. Induction of HIV RNA after vorinostat by the EDITS assay was primarily seen in women with increases in histone acetylation which was only observed in 67% of trial participants; this may have limited the ability to detect an effect of tamoxifen. This clinical trial, the first to study HIV latency reversal exclusively in women, was rapidly enrolled and completed, supporting the feasibility of future efforts to investigate sex-specific features of the HIV reservoir.

Table 1. Changes in HIV expression stratified by change in histone acetylation

	Overall		Arm A (tamoxifen + vorinostat)		Arm B (vorinostat alone)	
Histone 3 acetylation	Decrease N=9	Increase N=18	Decrease N=7	Increase N=12	Decrease N=2	Increase N=6
EDITS log_{10} HIV+ cells/10^6 memory CD4 mean change [Q1,Q3]	0.02 [-0.40,0.16]	0.44 [-0.04,1.06]	0.05 [-0.40,0.16]	0.23 [-0.08,0.79]	-0.09 [-0.40,0.22]	0.87 [0.51, 1.24]
EDITS Fold Change	1.05	2.75	1.12	1.70	0.81	7.41

334 EFFECTS OF IMMUNE CHECKPOINT THERAPY ON LATENT HIV IN PEOPLE WITH HIV AND MALIGNANCY

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Background: Immune checkpoint blockade (ICB) is highly effective for the management of some malignancies and can potentially perturb HIV persistence in people living with HIV (PLWH) on antiretroviral therapy (ART) by enhancing HIV-specific CD8+ T cells and/or reversing HIV latency. We established a prospective cohort of PLWH on ART with malignancy who received any ICB and quantified immunological and virological changes in three participants.
Methods: Blood was collected prior to and following the first 4 cycles of ICB at day-1,+1 and +7. We quantified cell associated (CA) unspliced (US) RNA and HIV DNA from peripheral blood CD4+ T cells, frequency of cells with inducible multiply spliced (MS) HIV RNA by the Tat/rev Induced Limiting Dilution Assay (TILDA) and HIV RNA in plasma by single copy assay (SCA). Gag specific immune responses were measured by intracellular cytokine staining (ICS) for IFN-γ, TNF-α, and CD107a in T-cell subsets defined by expression of CD45RA and CCR7.
Results: Participant (P) 1 received avelumab (anti-PD-L1) 2 weekly for chest wall Merkel cell carcinoma. P2 and P3 received ipilimumab (anti-CTLA4) and nivolumab (anti-PD1) 3 weekly for metastatic melanoma. P1 demonstrated partial response to ICB, before relapse and progression of disease. P2 had disease progression on ICB and died before study completion. P3 responded to ICB and remains on maintenance anti-PD-1.
An increase in CA-US RNA following each infusion was noted in all 3 participants (Fig1 A,B). There was an increase in the mean fold change in CA-US RNA from cycle 1 to 4 of 1.3, 3.1, 6.8 and 8.6 respectively. No consistent changes in HIV DNA were noted in any participants. P3 had an increase in plasma viremia from a baseline of 4 c/mL to 16 and 8 c/ml following cycle 2 and 3 respectively, and a 33% reduction in inducible MS RNA as measured by TILDA. There were no changes in plasma viremia or inducible MS RNA in P1 or P2. With respect to gag-specific ICS, P2 demonstrated a striking increase in the frequency of central and effector memory CD8+ T cells producing IFN-γ, TNF-α, and CD107a (Fig1C-E), which were not demonstrated in P1 and P3.
Conclusion: Increases in HIV transcription were observed on ART in all three participants following each cycle of either anti-PD-L1 or anti-PD-1 + anti-CTLA-4, with variable effects on plasma viremia, TILDA and ICS. Our results highlight that ICB can perturb HIV latency and increase HIV-specific immune responses but with significant variation between individuals.

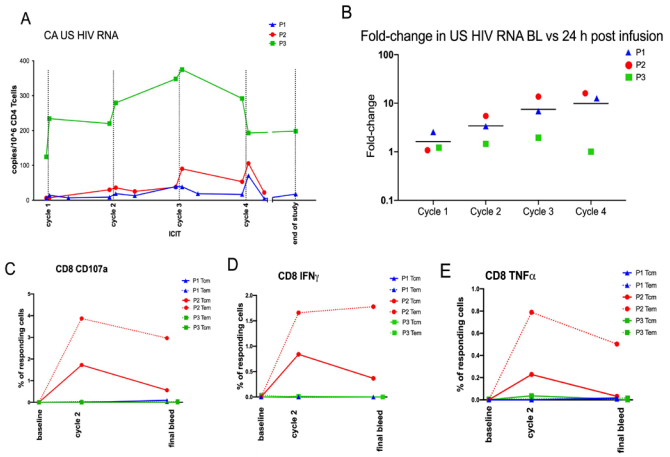


Figure 1: Longitudinal measures of HIV persistence and HIV-specific immune response during ICIT therapy in 3 participants (P1, P2, P3). CA-US RNA absolute values (A) and fold change post each infusion compared to baseline (B). Frequencies of CD8+ T cells developing cytokine responses (IL-2, CD107a, IFN-γ, TNF-α) to HIV gag peptides (C-E).

335 ABX464 DECREASES THE TOTAL HIV RESERVOIR AND HIV TRANSCRIPTION INITIATION IN VIVO

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Background: Antiretroviral treatment (ART) intensification and disruption of latent HIV infection (reversal or silencing) have been suggested as strategies to eradicate HIV. ABX464 (AbiVax) is a novel antiviral that binds to the cap binding complex, interfering with splicing and Rev-mediated export of newly transcribed HIV RNA. ABX464 has been shown to inhibit HIV RNA biogenesis in vitro and delayed viral rebound in a humanized mouse model. We investigated the effect of ABX464 on the HIV transcription profile and total and intact HIV DNA in circulating CD4+ T cells from ART-suppressed participants enrolled in the ABIVAX-005 clinical trial (NCT02990325).

Methods: Eleven participants on suppressive ART were treated daily with 150mg of ABX464 for 4 weeks. Peripheral CD4+ T cells from nine study participants were available for HIV transcription profile and reservoir size analysis. Total HIV DNA, intact HIV DNA (IPDA), and Read-through, total/initiated, 5'elongated, unspliced, polyadenylated and multiply-spliced HIV transcripts were quantified at weeks 0, 4 and 8 using ddPCR.

Results: We observed a significant decrease in the total HIV DNA (p=0.008, median fold-change=0.8) and a lower median level of intact HIV DNA (p=n.s., median fold-change=0.8) after ABX464 treatment (wk0 vs. wk4). However, intact HIV DNA increased significantly (p=0.008, fold-change=1.6) after ABX464 discontinuation (wk4 vs. wk8). After 4 weeks of ABX464 treatment, we observed a decrease in total initiated HIV RNA per million CD4+ T cells and per provirus (HIV RNA/HIV DNA) (p=0.05, median fold-change=0.7; p=0.004, median fold-change=0.5, respectively), a trend towards a decrease in the 5'elongated HIV RNA per provirus (p=0.07, median fold-change=0.5), and a lower median level of unspliced HIV RNA (p=n.s., median fold-change=0.6), but no decrease in polyadenylated or multiply-spliced HIV RNA. However, 5'elongated HIV RNA per million CD4+ T cells increased significantly (p=0.04, fold-change=1.4) after ABX464 discontinuation (wk4 vs. wk8).

Conclusion: In this substudy, ABX464 had a dual effect of decreasing total HIV DNA (and possibly intact proviruses) and decreasing the amount of HIV transcription per provirus, although these changes were reversed after drug discontinuation. Our data suggest that ABX464 acts as an ART intensifier in vivo. To further characterize its specific mechanism of inhibiting HIV transcription, long-term administration of ABX464 in a larger cohort should be studied.

336 ATTACKING LATENT HIV WITH CONVERTIBLE CAR-T CELLS, A MODULAR KILLING PLATFORM

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Background: Reducing the size of the latent HIV reservoir and controlling subsequent viral rebound by immune engineering could lead to a sustained viral remission in HIV-infected individuals in the absence of ART. CTLs could reduce the size of the reservoir by recognizing and killing reactivated reservoir cells. However, cellular exhaustion and the presence of CTL-resistant viruses may undermine their effectiveness. We have tested a new approach to reservoir reduction where convertibleCAR-T cells (cCAR-Ts) programmed with multiple HIV-specific broadly neutralizing antibodies (bNAbs) are deployed.

Methods: cCAR-Ts utilize a mutated, inert form of the NKG2D receptor. Orthogonal MIC ligands that bind to inert NKG2D but not wild-type NKG2D are fused to antibodies to generate bispecific MicAbodies for directing cCAR-T targeting and activation. cCAR-Ts can therefore be readily redirected by altering the antibody component of the MicAbody and furthermore, MicAbodies can be multiplexed. 4 bNAbs were engineered as MicAbodies and tested for their ability to kill tonsil, spleen, or blood cells infected with GFP-tagged R5 or X4-tropic or transmitted/founder viruses. Specificity of infected cell killing was monitored by loss of GFP+ vs GFP- cells. Reactivated CD4 T cells from HIV-infected individuals on ART were assayed for loss of cell-associated viral RNA in the presence cCAR-Ts either armed or not armed with bNAbs. The platform was checked in vivo, in NSG mice model of cancer, by measuring size reduction of cancer tumors.

Results: In the presence of bNAb-MicAbodies, CD8 cCAR-Ts effectively killed HIV-infected, but not uninfected, cells from tonsil, spleen and blood. Killing was strictly dependent on the presence of bNAb-MicAbodies targeting HIV Env. Multiplexing of four MicAbodies increased the breadth of killing. cCAR-T cells also reduced by more than half the inducible reservoir present in blood of HIV-infected individuals on ART. Administration of cCAR-Ts cells in a mice cancer model, demonstrated highly effective in vivo killing.

Conclusion: An attractive feature of cCAR-Ts is that it is a modular platform that not only allows for multiplexing of MicAbodies, but also targeted delivery of kill switches if needed or cytokines for cCAR-T rejuvenation. This platform could be an important tool for reducing and controlling the size of the latent HIV reservoir.

337 CAR-T CELLS AT 15 YEARS: PERSISTENCE OF CD4-ZETA TRANSGENE AND EFFECT ON RESERVOIR

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Background: Despite effective antiretroviral therapy, cellular reservoirs of HIV persist. CD4ζ is a chimeric T cell receptor with the intracellular and transmembrane domain of CD4 linked to the zeta signaling chain of the CD3 T cell receptor. The long term persistence of this CAR-T cell therapy was previously estimated.

Methods: Fifteen individuals were randomized to 3 groups (cells, IL-2, cells + IL-2) to receive a single infusion of 5-9 x 109 autologous CD4ζ gene modified T cells ± subcutaneous IL-2 at 1.2 million IU/m^2 for 56 days. Inclusion criteria included CD4≥200, viral load<50, stable HAART for ≥8 weeks. Pheresis and rectal biopsy were performed at baseline and at 13-15 years follow up. Real-time PCR was used to detect and measure the CD4ζ transgene and the HIV-1 gag gene in PBMCs and rectal tissues. RNAscope using HIV-1 Clade B probe was performed on formalin fixed rectal tissue at long term follow-up. Total and integrated HIV DNA were measured in PBMCs using a highly sensitive nested PCR assay. Mixed models and ANCOVA were used to assess the effects of treatment arms on CD4, CD4%, CD4:CD8, total and integrated HIV DNA over time.

Results: Fifteen persons enrolled (mean age 38.4 ± 7.9 years) and thirteen individuals,11 males and 2 females, completed the long term follow up (LTFU). Race/ethnicity of the participants included one Asian, four Blacks, two Hispanics and six Caucasians. The median CD4 count on enrollment was 821 (IL-2), 712 (cells) and 822 (cells + IL-2), p=0.468. At LTFU median CD4 counts were 779, 720 and 1047 respectively, p=0.376. HIV viral loads were suppressed except in one nonadherent subject at LTFU. No differences by race or sex were seen. There was

persistence of CD4ζ CAR-T cells 13-15 years post infusion in both PBMC and rectal tissues in all recipients. Rare HIV-RNA+ cells can be identified in the majority of rectal biopsies. Total PBMC HIV DNA at long-term follow up, and the change in total and integrated HIV DNA from pre- and post-treatment compared among the treatment arms was not statistically different.
Conclusion: The CD4ζ transgene persisted for 13-15 years in CAR-T cell treated subjects. With the caveat of a trial with a small number of subjects, coupled with intersubject variability, our analysis suggests that there was no statistical difference in baseline to LTFU between arms and that HIV remains present in PBMC and rectal tissue. Furthermore, this is the most mature data set to date to indicate that CAR-T cells are safe for at least 15 years.

338 PHASE I STUDY OF GENE-MODIFIED CD4+ CELLS AND CD34+ CELLS W/ WO BUSULFAN IN HIV+ ADULT

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Background: HIV gene therapy could reduce viral load, preserve immunity and mitigate ART toxicities. Safety and feasibility of an anti-HIV-1 dual-gene construct LVsh5/C46 (Cal-1) in modified, autologous CD4+ T-cells (Ttn) and HSC (HSCtn) was assessed.
Methods: PLWH with CD4+ count > 500/mm$_3$ and voluntary ART suspension (drug toxicities, treatment fatigue or other reasons) underwent aphereses for CD4+ T-cells and CD34+ HSC following mobilization, then gene-modified cell infusion. Busulfan pre-conditioning was: none (Cohort 1), 4 mg/kg on Day -2 (Cohort 2) and 3mg/kg (Day -2) to a total AUC exposure of 8,000 µmolar/min at Day -4 (Cohort 3). Subjects were followed for 48 weeks with ART reinitiation if CD4+ count or viral RNA reached safety thresholds, or participant decision. BM aspirates and GALT biopsies were taken at 24 and 48 weeks.
Results: 12 participants (4 per cohort) were treated. At 48 weeks, 4 remained off and 8 resumed ART. Only 1 unrelated SAE was reported. Procedure-related AEs included neutropenia, thrombocytopenia, fatigue, nausea, and back pain. One pt in Cohort 1 had Cal-1 marking in PB >1% at Wk 4 which was not sustained. All Cohort 2 pts had >1% marking at early time points which was not sustained. Cohort 3 had highest levels of Cal-1 marking at peak and longest persistence. While no association was seen between Cal-1 marking and Ttn dose, there was a correlation between HSCtn dose in Cohort 3. For all Cohorts, marking at wk 24 and 48 was not substantive in GALT and very low in BM. Higher busulfan AUC correlated with higher peak Cal-1 marking in PB. There was no effect on plasma HIV RNA. Absolute CD4+ counts were reduced following apheresis.
Conclusion: Delivery of HSCtn and Ttn was feasible and well-tolerated. Low to moderatedose busulfan was safely administered in an all-outpatient settingThe impact of HSCtn and Ttn on control of HIV replication could not be fully assessed because of low level of marking in PB. Busulfan exposure correlated with higher levels of marking. Potential reasons for the lack of long-term survival of Cal-1 transduced cells include persistent HIV viremia and inflammation. Future research should focus on administering gene-modified stem cells in fully-suppressed individuals

339 HIV-SPECIFIC T-CELL RESPONSES IN AN HIV-POSITIVE COHORT POST ALLO-HSCT

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only medical intervention which has led to HIV cure. While the size of the HIV reservoir sharply decreases after allo-HSCT, the dynamics of the T-cell reconstitution has not been comprehensively described.
Methods: We analyzed the activation and differentiation of CD4+ and CD8+ T-cells, and the breadth and quality of HIV- and CMV-specific CD8+ T-cell responses in 16 HIV-infected patients who underwent allo-HSCT (including 4 individuals who received cells from CCR5D32/D32 donors) to treat their underlying hematological malignancy and remained under antiretroviral therapy (ART).
Results: We found that reconstitution of the CD4+ and CD8+ T-cell compartment was slow and heterogeneous with an initial expansion of activated CD4+ T-cells that preceded the expansion of CD8+ T-cells. Transplanted patients did not achieve full immune reconstitution after allo-HSCT. While HIV-specific CD8+ T-cells disappeared immediately after allo-HSCT, weak ex vivo HIV-specific CD8+ T-cell responses were detectable several weeks after allo-HSCT, and could still be detected at the time of full T-cell chimerism, indicating that de novo priming, and hence antigen exposure, occurred during the time of T-cell expansion. These HIV-specific T-cells had limited functionality compared to CMV-specific CD8+ T-cells, and persisted years after allo-HSCT.
Conclusion: In conclusion, immune reconstitution was slow, heterogeneous and incomplete and coincided with de novo detection of weak HIV-specific T-cell responses. The initial short phase of high T-cell activation, in which HIV antigens were present, may constitute a window of vulnerability for the reseeding of viral reservoirs, emphasizing the importance of maintaining ART directly after allo-HSCT.

340 MYCOPHENOLATE MOFETIL FOR DEPLETION OF THE HIV RESERVOIR

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Background: Recent data suggests that proliferation of latently infected memory CD4+ T cells is essential to the maintenance of the HIV reservoir in individuals who are taking suppressive antiretroviral therapy (ART). Mathematical model projections suggest that curtailing lymphocyte proliferation may accelerate the rate of reservoir clearance. We conducted a clinical trial to test this hypothesis.
Methods: We performed a small (n=4), open-label, non-randomized Phase II clinical trial (NCT03262441) to assess the safety and tolerability of 22 months of low-dose mycophenolate mofetil (MMF) in chronically HIV-infected men on suppressive ART. The in vivo anti-proliferative effect of MMF was assessed using a "total antiproliferation test" (TAPT) assay, in which anti-CD3/CD28-stimulated participant T cells are exposed to serum from participants after MMF dosing. The TAPT is reported as percent reduction in proliferation compared to serum/cells taken before the start of the trial. We escalated the MMF dose in those individuals with <80% anti-proliferative effect at peak drug levels (one-hour after dosing). We measured the effect of MMF on levels of total ("total") and potentially intact ("intact") HIV proviral DNA at 3-month intervals. HIV proviral DNA was measured with a multiplexed digital droplet PCR assay simultaneously targeting HIV-1gag, env and pol genes.
Results: All participants maintained stable CD4 T cell counts and subset composition, remained suppressed on ART and tolerated MMF. One participant required dose escalation from MMF 500 to 750 mg twice daily to achieve >80% anti-proliferative effect at drug peak. Proliferation inhibition at drug trough pre-dosing was highly variable. No participant met the pre-specified criteria for study continuation at 12 months (0.25 log reduction in total HIV DNA) and MMF was therefore stopped for all participants. Intact HIV DNA levels were undetectable in one participant and remained stable in the remaining participants over one year of MMF (Table).
Conclusion: One year of low-dose MMF was safe and well-tolerated in ART suppressed men but did not lower total or intact HIV proviral DNA levels. The anti-proliferative effect waned during the dosing interval, suggesting that higher doses, or more frequent or extended-release dosing may be necessary to lower the HIV reservoir.

Table 1. Clinical trial participant clinical data and outcomes.

Age (years)	CD4/mm^3 (baseline)	CD4/mm^3 (12 months)	MMF dose (mg. twice daily)	TAPT peak (%)	TAPT trough (%)	Total HIV DNA / 10^6 T cells (baseline)	Total HIV DNA / 10^6 T cells (12 months)	Intact HIV DNA / 10^6 T cells (baseline)	Intact HIV DNA / 10^6 T cells (12 months)
54	492	382	500	83.9	9.3	2286	2045	188	125
60	573	460	500	97.0	32.2	1860	2074	22	61
26	606	468	750	98.4	88.2	273	217	0	0
62	799	793	500	92.8	ND	885	846	18	25

341 VIRAL RESERVOIR DISRUPTION WITH PANOBINOSTAT AND IFN-A: FIRST RESULTS

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Background: Reactivation of viral transcription can sensitize viral reservoir cells to immune-mediated killing which may reduce long-term persistence of virally-infected CD4+ T cells in ART-treated individuals. The ACTIVATE study is an ongoing, prospective, randomized, dose-escalation clinical trial in which the histone deacetylase inhibitor (HDACi) panobinostat is administered as a latency-reversing agent in combination with pegylated IFN-α2a as an innate immune modulator.
Methods:ART-treated participants were randomized to receive three consecutive doses of 5mg (phase I) or 10mg (phase II) of panobinostat alone (Arm A, n=2 participants in stages I and II each), or in combination with one dose of pegylated IFN-α2a (Arm B, n=6 participants in stages I and II each). Before and at multiple timepoints after study drug administration, cell-associated HIV-1 RNA from the CD4+ T cells were quantified using ddPCR; moreover, innate and adaptive immune responses and acetylated H3 expression were analyzed by flow cytometry. HIV-1 DNA was evaluated using the IPDA.
Results: Relative to baseline, the expression of acetylated histone H3 increased 1.5 times (p=0.025) on day 4 after 3 doses of panobinostat, an effect that was most visible in naïve, stem cell memory and central-memory CD4+ T cells. In parallel, a significant increase of HIV-1 gene expression relative to baseline levels was seen for TAR transcripts (p=0.0234) and long-LTR transcripts (p=0.0156) in stage II, but not in stage I. The frequency of activated CD38+ NK cells and NKp30+ NK cells increased significantly at day 4 and day 10 from participants receiving IFN-α2a in stages I and II, which was mostly seen in the cytokine producing (CD16- CD56+), cytotoxic (CD16+ CD56+) and immature (CD16+ CD56-) NK cell subsets. Moreover, the proportion of IL-2-producing HIV-1-specific CD4+ T cells increased during treatment with IFN-α2a, while IFN-g secreting CD4+ T cells were reduced. There were no changes in HIV-1 DNA levels among timepoints and between medication arms in both phases. No unexpected or severe clinical adverse events occurred so far.
Conclusion: First results indicate that the medication induces HIV-1 transcription and augments innate and adaptive immune cells. Phase III with 15mg panobinostat administered is ongoing.

342 IAP ANTAGONISM PROMOTES PD-1 BLOCKADE-MEDIATED ELIMINATION OF HIV IN HUMANIZED MICE

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Background: The immune checkpoint programmed cell death protein 1 (PD-1) plays a major role in T cell exhaustion in cancer and chronic HIV infection. Inhibitor of apoptosis protein antagonists (IAPa) reverse HIV latency and costimulate T-cells through modulation of NF-kB signaling in vitro.
Methods: We asked in this study whether a new IAPa would stimulate the potency of an anti-human PD-1 monoclonal antibody (mAb) to reduce HIV loads in humanized mice.
Results: Four weeks of Anti-PD-1 mAb treatment decreased the PD-1+ CD8+ cell population among CD45+ in blood by 22% compared to vehicle, while IAPa co-treatment reduced it by 50%. Anti-PD-1 mAb administration reduced HIV load in blood by 94% with detectable levels in 8 of 8 mice, and addition of the IAPa further enhanced this reduction from 94 to 97% with undetectable levels in 5 of 8 mice. 2 weeks after drug treatment interruption, Anti-PD-1 mAb administration had reduced HIV loads in CD4+ cells also in all tissues analyzed compared to vehicle, including spleen (5.6 to 2 log in viral RNA copies), lymph nodes (5.6 to 1.1 log in viral RNA copies), liver (5.4 to 1.6 log in viral RNA copies), lung (5.6 to 2 log in viral RNA copies) and thymic organoid (5.5 to 1.2 log in viral RNA copies). IAPa further enhanced the anti-PD-1-mediated reduction of HIV tissue loads achieving a >5 log reduction in all tissues analyzed, notably with undetectable levels in some individual organs; spleen (5.6 to 0.2 log in viral RNA copies), lymph nodes (5.6 to 0.2 log in viral RNA copies), liver (5.4 to 0.3 log in viral RNA copies), lung (5.6 to 0.2 log in viral RNA copies) and thymic organoid (5.5 to 0.1 log in viral RNA copies). Following the 4 weeks of in vivo treatments, ex vivo anti-CD3/CD28 stimulation increased the ability to activate CD8+ T cells in infected mice having received in vivo anti-PD-1 treatment by 7.9-fold (5 to 39.6%), and an additional increase by 1.7-fold in mice having received IAPa co-treatment (39.6 to 67.3%).
Conclusion: These findings demonstrate for the first time that an IAPa greatly enhances the effects of an immune checkpoint inhibitor on antiviral immunity resulting in undetectable HIV titers in blood and organs of humanized mice. This suggests that the combination of two distinct classes of immunomodulatory agents constitutes a promising immunotherapeutic approach to cure HIV.

343 IMPACT OF GS-986, PGT121 AND N6-LS ON CNS IMMUNE ACTIVATION IN SHIV-INFECTED MACAQUES

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Background: Kick and kill strategies using TLR-7 agonist and broadly neutralizing antibodies (bNab) have shown promise in non-human primates, but effects on the central nervous system (CNS) have not been evaluated.
Methods: Rhesus macaques (n=16) were intrarectally inoculated with SHIV-1157ipd3N4 at wk0 and initiated on ART (PMPA, FTC, DTG) on Day14. Active group (n=8) received GS-986 every 2 weeks from wk14 and intravenous N6-LS and PGT121 every 2 weeks from wk24. The development of anti-drug antibodies limited number of bNAb administrations. Active group animals received at least 7, 2 and 2 doses of GS-986, PGT121 and N6-LS, respectively. ART was ceased 2 weeks after plasma levels of bNAbs <0.25ug/mL. Control animals (n=8) received intravenous saline and ART was ceased at wk40. Plasma and cerebral spinal fluid (CSF) SHIV RNA levels were measured by PCR and soluble markers of immune activation by multiplex assay using Luminex.
Results: Median wk2 (pre-ART) plasma and CSF SHIV RNA was 5.7 (range 4.1-6.8) and 3.1 (range 2.2-4.2) log_{10}copies/mL respectively. After ART initiation on Day14, plasma SHIV RNA was undetectable in all animals by wk8 and remained undetectable until ART interruption. CSF SHIV RNA was also undetectable in all animals during GS-986 dosing (wk24). Median time to viral rebound was 6 weeks in active arm and 3 weeks in control arm (p=0.024). At 12 weeks post rebound, median plasma SHIV RNA was 1.2 (range 1.0-2.2) and 2.1 (range 1.0-2.8) log_{10}copies/mL in the active and control arm respectively. CSF SHIV RNA was only detectable at low levels in 1 active and 1 control arm animal. Longitudinal CSF samples from the active group showed significant increases in IL-15 (p=0.008), MCP-1 (p=0.008), IL-8 (p=0.008), IL-1RA (p=0.016), IL-2 (p=0.031), and G-CSF (p=0.008) at wk2 when compared to pre-infection, that decreased after ART initiation to pre-infection levels. Importantly, levels remained similar post GS-986 administration at wk24 and post bNabs prior to ART interruption. At 12 weeks post rebound, CSF IL-2 (p=0.031), and G-CSF (p=0.008) were increased relative to pre-infection levels.
Conclusion: Administration of GS-986, PGT121 and N6-LS did not increase SHIV RNA or markers of immune activation in CSF, suggesting that this strategy may be pursued in humans without impacting CNS activation.

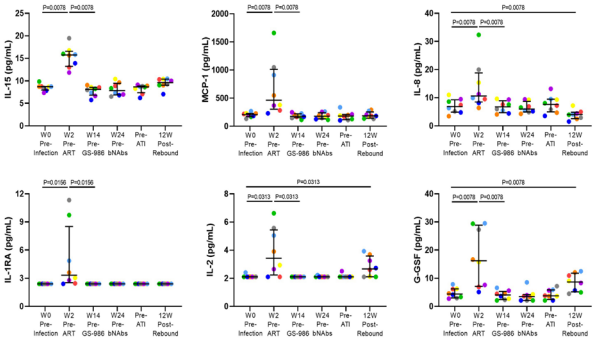
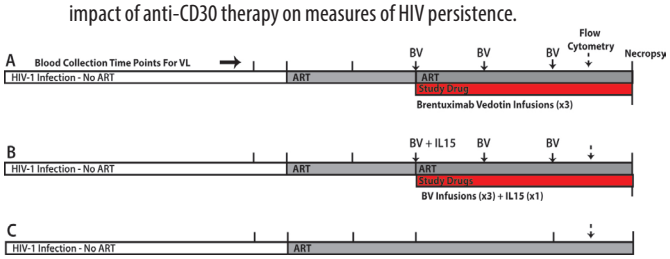


Figure 1: Markers of selected soluble markers of immune activation measure in CSF of active arm (n=8). Lines represent median and interquartile range. Each color represent data from an individual animal.

344 BRENTUXIMAB VEDOTIN REDUCES CD30 EXPRESSION AND GUT HIV DNA LEVELS IN HUMANIZED MICE

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Background: CD30 is preferentially expressed in HIV-infected and viral transcriptionally active CD4 T cells from viremic and ART suppressed individuals. We observed treatment with anti-CD30 antibody drug conjugate, brentuximab vedotin (BV), leads to reduced cell-associated HIV DNA in vitro and transient decreases in cell-associated HIV RNA in vivo. The impact of anti-CD30 therapy on tissue measures of HIV burden is unknown.
Methods: Humanized BLT mice were initiated on daily TDF, FTC, and DTG by oral gavage approximately 3 weeks following intraperitoneal infection with HIV-1 JR-CSF. After mice achieved viral suppression they were divided into three treatment cohorts: [1] ART alone control (N=16); [2] ART and 3 intraperitoneal (IP) weekly infusions of 20 mg/kg BV (N=18); [3] ART, BV and a single 2.5/10 µg IP injection of IL15/IL15RaFC given with the first dose of BV (N=18). Three weeks after the last BV infusion, mice were sacrificed and HIV DNA and RNA were isolated from blood, ileocecal junction, spleen, lymph nodes, and liver.
Results: Although the frequency of CD30 expression on human CD4 T cells was low in all cohorts, BV with and without IL15/IL15RaFC led to significant reduction in the frequency of human CD45+CD4+ T cells expressing CD30 (0.09% in ART controls, 0.05% in both treatment cohorts; P=0.03) and HLA-DR (4.0%, 0.6%, 0.6%, respectively; all P<0.01). BV with and without IL15/IL15RaFC also led to the reduced frequency of effector memory CD4 T cells (14% to 8% and 6%, respectively) and increased frequency of naive CD4+ T cells in peripheral blood (68% to 71% and 75%, respectively). Overall, there were no significant changes in blood, spleen, lymph node, and liver levels of cell-associated HIV RNA or DNA, but BV treated mice had significantly lower HIV DNA measured in gut tissue compared with ART-only controls at the time of necropsy (HIV DNA 164 c/10^6 vs 21,788 c/10^6 cells; P=0.04). Gut HIV DNA levels were similar to controls in mice that received concomitant BV and IL15/IL15RaFC.
Conclusion: BV treatment in BLT mice decreased the frequency of CD4 T cells expressing CD30, markers of T cell activation, and effector memory phenotype. BV alone, but not in combination with IL15/IL15RaFC, led to decreased gut HIV DNA levels. However, the high percentage of circulating naive lymphocytes and overall low CD30 expression in the BLT mouse model may have dampened the impact of anti-CD30 therapy on measures of HIV persistence.



345LB PGT121 AND VESATOLIMOD IN CHRONICALLY TREATED SHIV-INFECTED RHESUS MONKEYS

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Background: We have previously reported that administration of the broadly neutralizing antibody PGT121 with the TLR7 agonist vesatolimod (VES) delayed or prevented viral rebound in SHIV-infected rhesus monkeys following ART discontinuation in animals that initiated ART early during acute infection. However, the efficacy of bNAbs has not previously been evaluated in the more clinically relevant model of animals that initiated ART during chronic infection with extended ART suppression.
Methods: 24 rhesus monkeys were infected with SHIV-SF162P3 and initiated daily ART (TDF/FTC/DTG) after 12 months of chronic infection. Following 30 months of continuous daily suppressive ART, animals received 10 infusions of 10 mg/kg PGT121 and 0.15 mg/kg VES (N=8), an Fc-modified version of this antibody GS-9721 and VES (N=9), or sham control (N=7) every 2 weeks. At week 42 following initial antibody dosing, which was 24 weeks after the final antibody and VES doses, ART was discontinued and viral rebound was monitored for 140 days.
Results: PGT121 and GS-9721 infusion resulted in 24 weeks of therapeutic antibody levels without the development of ADA, followed by a decline to undetectable levels prior to ART discontinuation. VES administration led to activation of multiple cellular immune subsets including CD4+ T lymphocytes and increased levels of serum cytokines. Following ART discontinuation, 100% (7 of 7) of sham controls exhibited rapid viral rebound with a median rebound time of 21 [IQR 14-21] days. In contrast, only 50% (4 of 8) of PGT121 + VES treated animals and 66% (6 of 9) of GS-9721 + VES treated animals rebounded by day 140 after ART discontinuation (P=0.05, Fisher's exact test compared with sham controls) and showed a delay in the median rebound time of 28 [IQR 21-140+] days.
Conclusion: In SHIV-infected rhesus monkeys that initiated ART after 1 year of chronic infection and that were virologically suppressed with ART for 2.5 years, administration of PGT121 or GS-9721 with VES prevented viral rebound in 41% (7 of 17) of animals following ART discontinuation. These data suggest therapeutic efficacy of broadly neutralizing antibodies with TLR7 stimulation in targeting the viral reservoir in the rarely used but clinically more relevant model of chronic SHIV infection in rhesus monkeys.

346LB SUSTAINED HIV REMISSION IN THE LONDON PATIENT: THE CASE FOR HIV CURE

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Background: The London Patient underwent allogeneic stem cell transplantation with d32 homozygous tissue and remission was reported at 18 months. Here we present longer term data including tissue sampling.
Methods: Ultra sensitive plasma, semen and CSF viral load assays were used to detect HIV-1 RNA. The method for HIV DNA quantification in gut biopsies and lymph nodes was as follows: tissue samples from each site were mixed with ceramic beads and Qiagen RLT Plus buffer. The tube contents were then homogenised using a MagNA Lyser (Roche) set at 6000rpm for 45 seconds. Genomic DNA was then extracted using a Qiagen AllPrep DNA/RNA Mini Kit. Cell-copy number and total HIV DNA levels were quantified both in triplicate using droplet digital PCR.
Results: HIV-1 viral load in plasma and proviral HIV DNA in CD4 cells have remained below detection up to 30 months. The most recent CD4 count was 370 cells/Ul (20.3%) and CD4/CD8 ratio 0.65. Plasma HIV antibodies have remained undetectable by western blot except low level Env reactivity. Semen viral load was below limit of detection in both plasma (LLD in seminal plasma is <12 copies/ml) and cells (LLD 10 copies/million cells).CSF protein and glucose were normal with no cells detected. HIV-1 viral load in CSF was below detection limit (LLD 1 copy/ml). HIV DNA by ddPCR was negative in Rectum, Caecum, sigmoid and T.Ileum. Lymph node tissue from the axilla was positive for LTR and Env at around 30 copies/million cells, but negative for packaging signal and integrase. The intact proviral DNA assay (IPDA) was negative.
Conclusion: The London patient has been in HIV remission for 2.5 years with no detectable replication competent virus in blood, CSF, intestinal tissue or lymphoid tissue. Donor chimerism has been maintained at 99% in T cells. We conclude that this represents HIV-1 cure with evidence of low level defective HIV genomes in lymphoid tissue.

Tissue site	Sample day*	PCR Target				
		LTR	Gag	Pol	Env	Psi
Lymphoid tissue						
Lymph node	1295	34 c/million cells	5 c/million cells	negative	26 c/million cells	negative
GI Tract						
Terminal ileum	1210	Negative	ND	Negative	ND	ND
Caecum	1210	Negative	ND	Negative	ND	ND
Sigmoid	1210	Negative	ND	Negative	ND	ND
Colon	1210	Negative	ND	Negative	ND	ND
CNS						
CSF plasma (HIV RNA)	1309	Negative	ND	ND	ND	ND
CSF cells	1309	Negative	ND	ND	ND	ND
Genital tract						
Seminal plasma (HIV RNA)	1152	Negative	ND	ND	ND	ND
Seminal cells	1152	Negative	ND	ND	ND	ND

Table: HIV reservoir measurements across tissue sites. HIV DNA was measured unless indicated otherwise. Quantification is expressed in copies HIV-1 DNA per million cells. ND: not done. * post allogeneic stem cell transplant

347LB SUSTAINED REMISSION IN A 4-YEAR-OLD HIV-INFECTED CHILD TREATED IN FIRST YEAR OF LIFE

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Background: Very rarely children with vertically acquired HIV and given antiretroviral therapy (ART) soon after birth, then stop ART, have extended periods without detectable HIV in peripheral blood by routine testing. We report a child with intrauterine-acquired HIV, who started on combined antiretroviral therapy at 33 hours of life and remains undetectable over 3 years after discontinuing ART.

Methods: In addition to routine clinical assays, HIV DNA was assayed using droplet digital PCR (ddPCR) for gag and pol using DNA extracted from available CD4 lymphocytes purified by negative selection.

Results: A healthy newborn was born to a mother with no prenatal care and a 6-year history of diagnosed, but untreated HIV infection, with 14,400 HIV RNA copies/ml and 27% CD4 at delivery. The child was started on ART at 33 hours of life. A blood sample submitted for HIV DNA on day of life (DOL) 1 and another for HIV RNA on DOL 2 failed due to technical issues. A DOL 14 sample tested positive for HIV DNA. Because of this finding dried blood spots from DOL 1 from routine newborn screening were tested for HIV DNA with a positive result (CDC). The mother discontinued the child's ART after 1 year. From birth through 4 years old the child remained clinically well with undetectable HIV RNA (<20) by routine laboratory testing, and HIV specific antibodies becoming and remaining negative from 15 months. Testing by HIV ddPCR-DNA was performed at intervals beginning at DOL 114 and were intermittently detected with the most recent one showing <1 copy of gag and pol DNA/ million CD4 cells.

Conclusion: We present a child with intrauterine- acquired HIV infection, initiation of ART at 33 hour of life who was maintained on ART for 1 year and has remained clinically well through 4 years of age including 3 years without ART. Whether viral control was affected by ART, characteristics of the child or virus are being investigated.

	Day of Life										
Outcome	1	14	36	54	114	184	389	402	1017	1210	1274
HIV DNA Qualitative	Pos	Pos	ND	Neg	ND	Neg	Neg	ND			
HIV ddPCR-DNA (*gag/pol*)	ND				<5/<5*	ND	3/2*	ND	1/1*	42/31*	<1/<1*
HIV RNA	ND	<- <20 ->									
CD4 Abs,%	ND			2170, 33%	ND						1390, 34%
Serology	ND						POS	<- Neg ->			

ND: not done,*HIV *gag/pol* DNA by ddPCR (copies/106 CD4 cells)

348LB CCR5Δ32 SCT-INDUCED HIV REMISSION: TRACES OF HIV DNA BUT FADING IMMUNE REACTIVITY

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Background: To date only 3 patients have achieved long-term HIV-remission after analytic therapy interruption (ATI). Here we provide an update of the Duesseldorf patient (IciStem#19). This HIV-infected male patient (50y, heterozygous CCR5Δ32 allele) received unmodified stem-cell transplantation (SCT) from a 10/10 matched CCR5Δ32/Δ32 donor in Feb/13 for acute myeloid leukemia. At time of SCT complete western blot pattern was detected, proviral load was 1.45 log_{10}cop/Mio PBMCs with R5-coreceptor-tropism. In Jun/13 complete remission was achieved by 5-Azacytidine and donor lymphocyte infusions (DLI) after a 2nd relapse. PBMC were negative for HIV-DNA by qPCR/ddPCR during relapse and thereafter. However, in T-cell subsets few positive signals were observed. qVOA/mVOA were negative. Biopsies: CSF Jul/14, rectum Apr/15+Mar/16, ileum Mar/16 and bone marrow Aug/15, and lymph nodes (LN) May/17 were HIV-DNA negative by PCR. In situ hybridization assays (RNAscope, DNAscope) detected few positive signals in LN. Moderate acute and mild chronic GvHD occurred after DLI but Tacrolimus could be finally stopped in Oct/17. He remained on ART with undetectable plasma VL until analytic therapy interruption (ATI) in Nov/18.

Methods: PBMC/tissues analysed by ddPCR/qPCR and in situ hybridization. T-cell responses with peptide stimulation assays. qVOA analysed on CD4+T-cells. Drug level assessment by liquid chromatography mass spectrometry.

Results: After ATI no antiretrovirals could be detected in multiple plasma samples. In Jul/19 no HIV DNA was detected in CD45+ cells extracted from biopsies (duodenum/ileum/rectum). Neutrophils and IFN-1 responses in the GI tract were very low. CD4 T cells were abundant within GI tract follicular aggregates, RNAscope was negative, DNAscope showed few positive signals, but not clearly above the false detection rate. In Nov/19, 12 mo after ATI, HIV DNA was negative in naive, central memory, transitional memory, and effector/effector memory CD4 T-cells. qVOA in total CD4 T cells was also negative. Peptide stimulation assays showed CCR5-negative HIV-specific CTL with loss of recognition of RTYV9-specific and decrease of Gag-specific CTL after stopping immunosuppression. The absence of HIV-antigen is confirmed by fading humoral reactivity.

Conclusion: No viral rebound was observed for 14 months following ATI, 83 months after allogeneic CCR5Δ32 SCT. In depth analyses of the viral reservoir still showed traces of HIV DNA in LN and GI tract, not clearly representing infectious virus though, since all functional assays were negative. These results are compatible with sustained remission of HIV.

349LB EDITING OF SIV IN NONHUMAN PRIMATES BY CRISPR-CAS9 IN VIRAL RESERVOIRS

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Background: Antiretroviral therapy (ART) suppresses but does not eliminate replication competent HIV proviral DNA from latently infected cells, thus resulting in viral reactivation upon ART cessation. Therefore, removal of HIV proviral DNA from infected individuals is needed. We have assessed a CRISPR-Cas9 based gene editing strategy for the elimination of the SIV proviral DNA in the rhesus macaque model.

Methods: An all-in-one AAV9 gene therapy vector was constructed to deliver CRISPR-Cas9 plus two gRNAs targeting sequences within the 5' and 3' viral LTRs and the Gag gene to excise the intervening proviral DNA fragment. Ten adult Indian rhesus macaques were i.v. infected with SIVmac239 then treated daily with a drug regimen of tenofovir, emtricitabine and dolutegravir (5.1/50/2.5mg/kg daily s.q.). Animals were randomized into groups to receive low versus high dose of AAV9-CRISPR-Cas9 in a single i.v. infusion (low dose: $1.4x10^{12}$GC/kg n=4; high dose: $1.4x10^{13}$GC/kg n=3) as well as control SIV infected animals (n=3). Longitudinal blood samples and lymph node biopsies were collected, and animals were necropsied at 3 (n=8) or 6 months (n=2) after CRISPR treatment.

Results: SIV-infected animals treated with AAV9-CRISPR-Cas9 at both high and low doses showed vivo excision of viral DNA from serial blood and lymph node samples. Results from Sanger sequencing confirmed the precise breakpoint of the viral DNA in samples in which excision was detected. Biodistribution of the AAV9-CRISPR-Cas9 vector was assessed by PCR to detect the presence of the Cas9 gene sequence. DNA and RNA scope were performed on lymph nodes in parallel to detect the AAV9-CRISPR-Cas9 viral vector and expression of the Cas9 gene. Broad excision of SIV proviral DNA was observed in lymph nodes and other tissues known to be viral reservoirs including spleen, gut, and brain. A dose response between low and high doses, as well as temporal distribution between 3 and 6 months, was observed for AAV9-CRISPR-Cas9 viral DNA in the blood.

Conclusion: Here we demonstrate broad SIV DNA excision in viral reservoirs leading to permanent inactivation of SIV proviral DNA in a one shot CRISPR molecule. We observed biodistribution of AAV9-CRISPR-Cas9 in the blood in a dose and time dependent manner for the elimination of SIV DNA. These findings support the utilization of AAV9-CRISPR-Cas9 as a potential therapeutic strategy for in vivo gene editing of HIV proviral DNA from latent tissue reservoirs.

350LB EFFICIENT DELETION OF CCR5 PROVIDES COMPLETE PROTECTION AGAINST HIV IN XENOGRAFT MICE

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Background: Hematopoietic stem cell transplant (HSCT) with CCR5d32/d32 defective stem cells has resulted in long-term remission of HIV infection in three patients ("Berlin", "Dusseldorf", and "Oxford") that received allogeneic HSCT for co-occurring malignancies. However, the scarcity of HLA-matched, CCR5d32 homozygous stem cell donors represents a significant hurdle to more widespread adoption of HSCT for treatment of HIV infection. The ability to effectively delete CCR5 in autologous, mobilized, CD34+ hematopoietic stem progenitor cells (mobHSPCs) would overcome this hurdle and provide a path toward an autologous HSCT cure for HIV infection.

Methods: Guides were screened for editing efficiency by CRISPR/Cas9 ribonucleoprotein (RNP) nucleofection of primary human CD4+ T cells. Edited CD4+ T cells were then stimulated and challenged with R5-tropic HIV. A dual guide approach engendered the highest level of CCR5 editing and complete protection from high titer HIV challenge in vitro and was selected for HSCPC editing and transplant.

Results: Dual guides achieved a 92% CCR5 editing frequency in mobHSPCs from an anonymous HIV-negative donor (guide 1: 70%; guide 2: 58%; total: 92%). After transplant into NSG mice, CCR5edit HSPCs displayed slightly delayed but otherwise normal hematopoiesis resulting in human immune cell reconstitution with frequencies of human monocytes, B cells, and T cells comparable to the control sham (GFP guide) edited mice. High frequency CCR5 editing was detected in descendant monocytes, B cells, and T cells (median 89%), and the frequency of circulating T cells expressing CCR5 on the cell surface was <0.25% compared to 57% in the sham edited controls. Importantly, CCR5edit mice were completely refractory to challenge with an ID100 of a CCR5-tropic HIV (0/5 CCR5edit mice infected) that infected 8/8 control mice. CCR5edit mice further resisted a challenge dose of 50x ID100. In contrast, subsequent intraperitoneal challenge of a CCR5edit mouse with a CXCR4-tropic HIV strain resulted in robust infection and plasma viremia confirming CCR5-specific protection.

Conclusion: These data demonstrate that high frequency CRISPR/Cas9-mediated editing of CCR5 in human HSPCs is achievable and is sufficient to prevent infection during multiple, high dose exposures to a highly pathogenic strain of HIV. These experiments provide the basis to explore the prevention of systemic HIV rebound in an autologous transplant setting to help guide future clinical approaches to achieve a functional cure.

351 ANTAGONISM OF PPARG FOR TH17 MUCOSAL IMMUNITY RESTORATION AND HIV-RESERVOIR PURGING

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Background: The Th17-polarized CCR6+RORγt+CD4+T-cells are key players in mucosal homeostasis. These cells are preferential targets for HIV/SIV infection at mucosal sites and their depletion/functional alteration persist despite viral-suppressive antiretroviral therapy (ART) in people living with HIV (PLWH). Moreover, Th17 cells carrying replication-competent HIV persist during long-term ART. Therefore, novel Th17-targeted HIV remission/cure strategies are needed. Considering that PPARγ represses RORγt, Th17-specific master regulator and HIV transcription, we hypothesized that PPARγ pharmacological inhibition will enhance Th17-effector functions and facilitate HIV reactivation from latency.

Methods: PBMC from ART-treated PLWH (n=14; CD4 counts >300 cells/µl, plasma viral load <40 HIV-RNA copies/ml) and HIV- (n=8) were used to isolate total/CCR6+/CCR6- memory CD4+T-cells by magnetic and flow cytometry sorting. Cells from HIV- were stimulated via CD3/CD28 for 3 days, exposed to transmitted founder HIVTHRO and cultured in the presence/absence of the PPARγ antagonist T0070907 for 12 days. Short/long-term viral outgrowth assays (VOA) were performed with cells from ART-treated PLWH in the presence/absence of T0070907 and/or antiretroviral drugs. Cell-associated (CA)/free HIV RNA/DNA and HIV-p24 levels were quantified by real-time PCR, ELISA, and flow cytometry. Transcriptional profiling was performed using the Illumina RNA Sequencing technology. Results were validated by flow cytometry, ELISA and miR29 antagomir.

Results: While PPARγ antagonist increased IL-17A and CA HIV RNA levels in cells of ART-treated PLWH, viral outgrowth was unexpectedly inhibited. To define the mechanism of action, RNA-sequencing/functional validations were performed. PPARγ inhibition in CCR6+CD4+T-cells up-regulated transcripts linked to Th17 polarization (RORγt, STAT3, BCL6 IL-17A/F, IL-21), HIV transcription (CDK9, HTATIP2) and restriction (Caveolin-1, TRIM22, TRIM5α, BST2, miR29), and down-regulated transcripts encoding key HIV-dependency factors (CCR5, furin). Moreover, T0070907 increased the antiviral IL-21/miR29 axis. MiR29 antagomir increased HIV replication in the absence but not in presence of T0070907, pointing to miR29-independent antiviral mechanisms.

Conclusion: These results provide the rationale for considering PPARγ antagonism as a novel strategy towards Th17-mediated mucosal immunity restoration and HIV-reservoir purging.

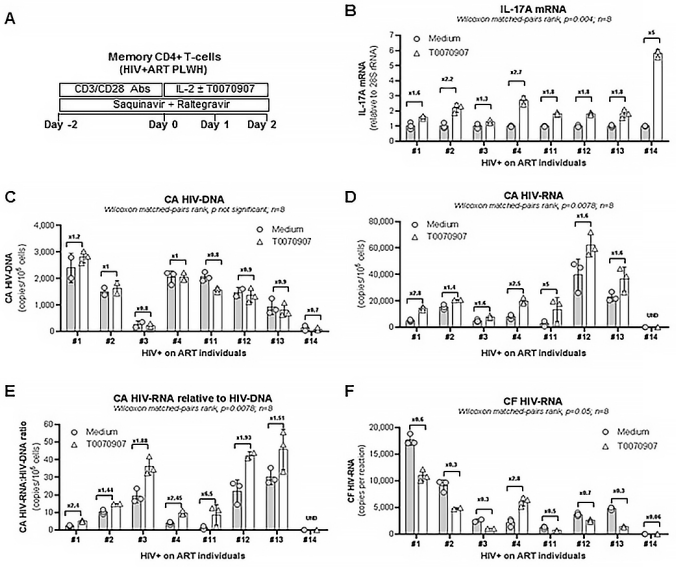


Figure 1: The PPARγ antagonist T0070907 increases HIV and IL-17A transcription but inhibits viral production in memory CD4⁺ T-cells of ART-treated PLWH.

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352 A JAK1 INHIBITOR SUPPRESSES HIV-1-DRIVEN ABERRANT HOST GENE TRANSCRIPTION

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Background: More than 50% of the latent reservoir are maintained through clonal expansion. While ART effectively blocks new rounds of infection, HIV-1 promoter remains intact, drives HIV-1 expression and aberrant cancer-related gene expression, and contributes to HIV-1 integration site-related clonal expansion. New therapeutic approaches targeting the clonal expansion of HIV-1-infected cells is required to reduce the size of the latent reservoir. We hypothesize that suppressing HIV-1 transcription can disrupt HIV-1-driven clonal expansion of the infected cells.

Methods: We first developed a dual-reporter cell line model and screened a library of 1,430 FDA-approved small molecule compounds to identify HIV-1-suppressing agents. Second, we examined the effect of candidate HIV-1-suppressing agents on HIV-1 transcription and HIV-1-driven aberrant host gene

transcription at the integration site. Third, we examined cellular transcriptional landscape of cells treated with candidate HIV-1-suppressin agents to understand how these agents affect host cell environment. Fourth, to understand whether candidate HIV-1-suppressing agents can disrupt the proliferation dynamics of HIV-1-infected cells, we examined the frequency of HIV-1-infected cells from HIV-1-infected individuals upon ex vivo T cell activation with and without ex vivo treatment of candidate HIV-1-suppressing agents.

Results: We identified four FDA-approved drugs – JAK1 inhibitor filgotinib, JAK1/2 inhibitor ruxolitinib, spironolactone and guanine synthesis inhibitor mycophenolic acid – which reduce HIV-1-GFP reporter expression in cell line models and HIV-1 RNA transcription in CD4+ T cells from HIV-1-infected individuals. Among them, filgotinib, spironolactone and mycophenolic acid suppress HIV-1-driven aberrant host gene transcription and aberrant oncogenic protein production in a HIV-1-reporter cell line model. Filgotinib alters host transcriptional landscape by changing host RNA processing involving intron retention and RNA splicing. During CD3/CD28 induced T cell activation and proliferation, filgotinib reduces the frequency of cells harboring inducible HIV-1 ex vivo.

Conclusion: Filgotinib preferentially reduce the proliferation of HIV-1-infected cells upon T cell activation. HIV-1 suppressing agents serve as a new therapeutic approach to target the clonally expanding HIV-1-infected cells.

353 DEVELOPMENT OF A PSEUDOVIRUS DELIVERY SYSTEM FOR HIV-1 ELIMINATION

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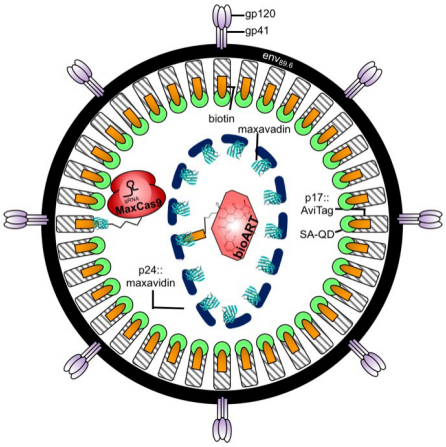
Background: A key challenge in developing successful HIV-1 cure strategies rest in eliminating the integrated provirus from the genomes of infected CD4+ T lymphocytes and monocyte-macrophages. In a first step towards this end, we recently demonstrated success by the sequential use of long acting slow effective release (LASER) ART and CRISPR-Cas9 in achieving viral sterilization from a subset of infected humanized mice. We sought to improve upon the transduction and known immunogenicity of the adeno-associated virus 9 (AAV9; 1012 genome copies/mouse) by generating an HIV-1 pseudovirus enabling both CD4 and CCR5 receptor targeting. We hypothesize that virus-like particles, bearing antigenic resemblance to HIV but lacking infectivity, will utilize viral glycoprotein-120 (gp120) to specifically deliver curative agents to CD4+ cells.

Methods: Viral matrix (HIV-1p17) and capsid (HIV-1p24) were genetically fused to biotinylated peptide (AviTag) and monomeric streptavidin (maxavidin) encoding sequences, respectively, to facilitate encapsulation of bioconjugated payloads. We generated VLPs (figure 1) by pseudotyping modified lentiviral structural proteins with dual-tropic HIV-189.6 envelope by co-transfection of plasmids in HEK293FT cells. A duplex LTR and gag splicing CRISPR-Cas9 system was inserted via plasmid. Non-gene payloads including streptavidin quantum dots, biotinylated fluorophore and a cabotegravir (CAB) prodrug were independently loaded in the VLPs.

Results: VLPs retained the same 150nm size, spherical morphology, and targeting epitope (gp120) expression as native infectious HIV-1 but were replication incompetent. Using our bioconjugation system, streptavidin quantum dots and biotinylated fluorophore were detected in the VLPs at 1.4 and 3.6-fold above baseline measurements. In human PBMC, 57% of monocytes and 9.5% of CD4+ T cells co-localized with fluorescently labeled VLPs. VLPs bearing CRISPR-Cas9 showed gp120-mediated entry and robust excision of proviral DNA from HIV-1 infected CD4+ T cells.

Conclusion: HIV-1 VLPs, engineered for loading with bioconjugated theranostic agents, direct payloads to CD4+ cell targets. VLPs specifically delivered proviral DNA excision therapy to HIV-infected T cells supporting the need for their development in HIV-1 cure strategies.

Figure 1: HIV-1 VLP Schematic



354 ROMIDEPSIN COMBINED WITH PRO-APOPTOTIC DRUGS REDUCE INTEGRATED HIV DNA

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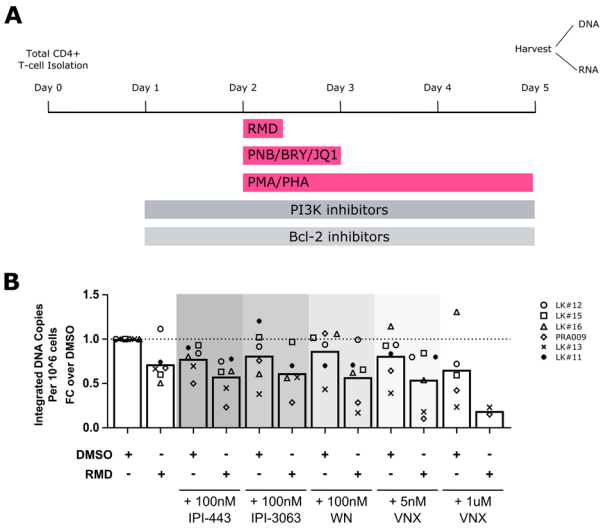
Background: Effective elimination of latently infected cells in people living with HIV (PLWH) on antiretroviral therapy (ART) through activation of HIV transcription will also require the induction of death of the infected cell. Given that HIV proteins, such as envelope and vpr, expressed late in the productive replication cycle, can induce apoptosis of CD4+ T-cells, we hypothesised that using latency reversing agents (LRAs) to induce expression of pro-apoptotic viral proteins combined with pro-apoptotic drugs will enhance the reduction of latently infected cells.

Methods: Total CD4+ T-cells were isolated from peripheral blood collected by leukapheresis from PLWH on ART. CD4+ T-cells were treated with pro-apoptotic drugs (the phoshoinositide-3 kinase (PI3K) inhibitors, IPI-443, IPI-3063 and wortmannin or an inhibitor of B-cell lymphoma (Bcl)-2, venetoclax) for 24 hours, followed by treatment with five different latency reversing agents (LRAs; panobinostat, romidepsin, bryostatin, JQ1 or PMA/PHA) for 4 or 24 hours and then the pro-apoptotic drugs alone for a further 48 hours. We measured integrated HIV DNA and cell-associated unspliced (CA-US) HIV RNA by RT-qPCR.

Results

The combined treatment of romidepsin with each of the four pro-apoptotic drugs led to a greater decline in integrated HIV DNA versus either romidepsin or pro-apoptotic drug alone. Romidepsin together with 5nM venetoclax showed the greatest decline in integrated HIV DNA. Romidepsin or venetoclax alone resulted in a mean fold change (MFC) in HIV integrated DNA of 0.72 and 0.18, respectively while the combined treatment resulted in an MFC of 0.54. Panobinostat and JQ1 combined with 1μM venetoclax also led to a reduction in HIV integrated DNA (PNB+1μM VNX MFC=0.47; JQ1+1μM VNX MFC=0.60), compared to the decline resulting from each drug alone (PNB MFC=0.71; JQ1 MFC=0.88; 1μM VNX MFC=0.76). We observed increases in CA-US HIV RNA and the ratio of CA-US HIV RNA to integrated DNA following treatment of CD4+ T-cells with all four LRAs as well as each of the pro-apoptotic drugs alone or combined.

Conclusion: Using CD4+ T-cells from PLWH on ART ex vivo, reduction of integrated HIV DNA could be significantly enhanced using the combination of romidepsin with either a PI3K or Bcl-2 inhibitor. The addition of a pro-apoptotic drug could potentially provide the ''kill'' needed for effective ''shock and kill''.



355 NOD2 AND TLR8 AGONISTS ENHANCE IL-15-MEDIATED ACTIVATION OF HIV EXPRESSION

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Background: The latent HIV reservoir is a barrier to achieving an HIV cure. Individual reservoir-targeting agents have shown potential activity in exploratory clinical trials, but it is likely that activation of HIV expression would enhance and/or accelerate the depletion of the latent reservoir. We previously identified clinically advanced agents that modestly activate HIV expression in cells isolated from ART-suppressed people living with HIV (PLWHIV), including IL-15 and agonists of multiple pattern recognition receptors (PRRs), such as toll-like receptor (TLR) and Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) agonists. Here we identify combinations of agents that have greater activity than either agent alone.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from ART-suppressed PLWHIV then treated with various PRR agonists individually or in combination with IL-15. Cytokine production and surface markers of T cell activation were assessed 24 hours after treatment initiation. HIV RNA in culture supernatants and T cell proliferation were quantified following a 4-day treatment with PRR agonists. Wilcoxon matched pair signed rank test and Bliss independence model were used for statistical and synergy analysis, respectively.

Results: In PBMCs from 7 ART-suppressed PLWHIV, IL-15 alone induced a 3.9-fold increase in HIV expression relative to control, while NOD2 and TLR8 agonists induced 3.0- and 3.2-fold increases, respectively (geometric means, $p < 0.05$ for each). In combination with IL-15, NOD2 and TLR8 agonists had the greatest effect, increasing HIV expression 14- and 11-fold, respectively ($p < 0.05$ for both compared to IL-15 alone). This was not significantly different from that induced by PMA and ionomycin (18-fold). The combination of NOD2 and IL-15 showed the clearest synergy. Correspondingly, both NOD2 and TLR8 agonists increased the levels of cytokines and activation markers produced in response to IL-15 stimulation, but had minimal additional effect on CD4 T cell proliferation.

Conclusion: Combining either NOD2 or TLR8 agonist with IL-15 significantly increased HIV expression and, in cells from several donors, approached that observed with the mitogenic activation control. This identifies clinically tested agents capable of robustly inducing HIV. It is important to consider that these combinations can also activate broader immunity and potentially augment immune-mediated reservoir clearance.

356 HIV-1 GENE EXPRESSION DURING REVERSAL OF LATENCY USING RNA-Seq WITH PROBE ENRICHMENT

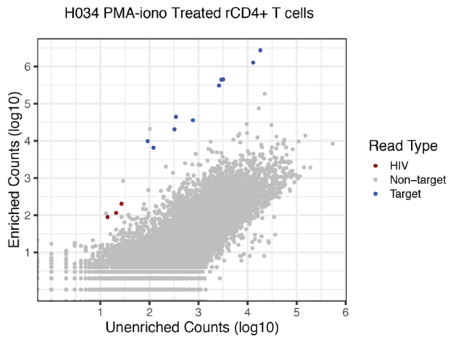
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Background: Transcriptomic analysis of the human and HIV-1 expression profile that is essential for successful reactivation of latently infected cells promises to help inform the next generation of latency reversal agents. However, because of the rarity of latently infected cells, the HIV-1 genome is poorly covered by bulk RNAseq. To address this limitation, we developed an RNAseq method with probe-based enrichment of HIV-1 reads.

Methods: Resting, non-naïve CD4 T cells were isolated from leukapheresis samples from four HIV-1 Eradication and Latency Study (HEAL) participants. 15 million cells were treated for 24 hours with: 1) unstimulated 2) PMA-ionomycin (iono) 3) romidepsin (rmd) 4) bryostatin (bryo) 5) IL-15 6) rmd/bryo. Total RNA was extracted using Trizol. RNA was poly-A selected and libraries were generated following an adapted TruSeq library generation protocol. A custom set of tiling probes was used to enrich HIV-1 and control gene PCR constructs. The unenriched and enriched libraries were sequenced on NextSeq, 40x40 paired-end reads. The reads were aligned to the human transcriptome and HIV-1 genome. A custom script was used to count reads per gene and per region of the HIV-1 genome.

Results: For both host control genes and HIV-1, we observed an average ~50-fold enrichment after probe capture (see Figure 1). HIV-1 reads aligned across all regions of the genome. PMA-iono and combination rmd/bryo had the greatest increase in HIV-1 transcription. To test the reproducibility of the probe-enrichment, we performed linear regression on normalized RNAseq reads from cells treated with PMA-iono. We observed a Pearson's R2 of 0.95 for total RNAseq between two participants and 0.97 for enriched RNAseq between the same participants. We also found evidence of hypermutated HIV-1 RNAseq reads in the enriched samples.

Conclusion: Our approach to analyzing host and HIV transcriptomes leverages next-generation sequencing to investigate latency reactivation. Probe-based enrichment allowed RNAseq quantification of HIV-1 reads from resting memory CD4+ T cells without the need for sorting of HIV-infected cell populations. We were able to measure HIV-1 transcription after reactivation from latency using a variety of latency reversal agents and compare HIV-1 gene expression across conditions. Analysis of differential host gene expression will yield insight into host factors necessary for HIV-1 reactivation in latently infected resting memory CD4+ T cells in persons with HIV.



357 SURFACE ENGINEERING OF EXTRACELLULAR VESICLES TO TARGET HIV PERSISTENCE

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Background: Current limitations of antiretroviral therapy are driving interest in novel HIV eradication strategies. Extracellular vesicles (EVs) are nano-sized membrane vesicles involved in cell signaling which have shown promise as engineerable therapeutic agents. We used surface display technology to engineer HIV-targeting EVs (HTEVs) that block HIV infection and target infected cells.

Methods: EVs were isolated from healthy donor plasma using polymer-based precipitation and column purification. EVs were decorated with single-chain variable fragment (scFv)-C1C2 fusion proteins targeting the HIV envelope protein. Surface-engineered EVs and HIV particles were fluorescently labeled and incubation reactions were visualized in dual-color channel and single-particle tracking analysis using a Nanoimager (ONI). Decorated EVs were incubated for two hours with a GFP-reporter HIV strain at 1:1, 2:1, and 4:1 ratios. Jurkat E6.1 cells and primary human CD4+ T cells were infected via spinoculation. Reporter virus was incubated with no EVs, undecorated EVs, or anti-PD-1 scFv-decorated EVs as negative controls. Jurkat 2D10 cells were induced with PMA/TSA to reactivate latent HIVNL4-3-Dgag/pol-GFP reporter

virus and then were treated with Texas red-labeled control or anti-HIV-C1C2 fusion proteins decorated EVs. After 24h, cells were analyzed by flow cytometry. TZM-bl cells were in vitro infected with HIVNL4-3P2A-Nef and two days later were treated with labeled EVs, decorated with C1C2 (control) or anti-HIV-C1C2 proteins. Internalization of decorated EVs was assessed after 18h incubation using fluorescence microscopy.
Results: Tracking data revealed that HTEVs clustered and moved in tandem with HIV virions, in contrast to negative controls which did not form clusters and tracked independently of virions. HTEVs significantly inhibited HIV infection in Jurkat E6.1 cells (n=3) and CD4+ T cells (n=5 donors) with respect to negative controls ($p<0.05$, paired t-test). HTEVs efficiently directed EVs into latently-infected, reactivated T lymphoid cells and in vitro HIV-1-infected TZM-bl cells.
Conclusion: HTEVs suppress HIV infection and selectively target infected cells ex vivo following latency reversal. HTEVs may facilitate the clearance of the latent HIV reservoir by delivering cytotoxic cargo specifically to infected cells.

358 IN VITRO MODEL FOR STUDYING T-CELL PROLIFERATION/SURVIVAL DRIVEN BY HIV INTEGRATION

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Background: The latent HIV reservoir is maintained through clonal expansion of T cells containing latent proviruses. Several clusters of HIV integration sites have been identified in a fraction of highly expanded T cell clones from patients on long-term ART. These clusters are characterized by proviruses in few introns in the same orientation as the host target gene. Similar patterns are hallmarks of insertional mutagenesis by oncogenic retroviruses; in these cases the integrated provirus causes aberrant gene expression, leading to cancer if the target gene is a proto-oncogene. The HIV provirus clusters in expanded cell clones likely reflect the alteration of host gene expression to promote growth/survival of the host cell, contributing to the persistence of the latent reservoir during ART, and possibly promoting tumor development in infected cells.
Methods: Primary human CD4+ T cells were infected with an HIV vector and reactivated every other week for 3 months to allow the T cells to proliferate and rest repeatedly. Each donor sample was divided into three independent replicates. Integration site analysis on randomly fragmented genomic DNA after each reactivation event was used to monitor provirus dynamics: clonal expansion of an infected cell was determined by the observation of multiple DNA fragments with different breakpoints and identical HIV-host junction sites from the Illumina sequencing library.
Results: We observed expansion of clones containing specific HIV provirus insertions, supporting our model of T cell expansion during HIV infection. We did not observe expansion of cell with proviruses in the known gene, but we identified large provirus clusters in one small intron of the STAT3 gene associated with extensive clonal expansion. Interestingly, there was a recently reported case of an AIDS-related B cell lymphoma with an HIV integration in the same region and orientation of STAT3.
Conclusion: Although in our pilot experiment we did not observe clonal expansion of cells with proviruses in the genes identified in vivo, we did observe significant expansion of cells that contained a provirus in a small region in the STAT3 gene in each of six replicates from two donors. This in vitro system will be an important tool for identifying new genes that HIV may disrupt to promote proliferation of the host cell to play a direct role in HIV-related cancer.

359LB AMINOBISPHOSPHONATES REVERSE LATENCY IN HIV-SEROPOSITIVE INDIVIDUALS

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Background: We hypothesized that aminobisphosphonates (N-BPs), such as pamidronate (PAM), zoledronate (Zol) and alendronate (ALN), that inhibit the formation of farnesyl pyrophosphate groups, used for protein prenylation disrupting cell signaling, may induce reversal of HIV latency. Therefore, here we explore their potential as novel latency reversing agents.
Methods: Latency reactivation capacity of N-BPs was analyzed ex vivo in nine HIV-seropositive individuals on suppressive antiretroviral therapy (ART). Resting CD4 T cells were isolated and left untreated or treated with PHA, PAM or Zol, and then cell-associated HIV RNA (caRNA) levels and replication-competent HIV were measured. RNA-seq was used to explore the N-BPs' mechanism of action, and flow cytometry was used to analyze the ex vivo effect of N-BPs on immune cell activation and proliferation. Longitudinal PBMC (baseline and weeks 2, 24, 48 post intervention) were obtained from the ACTG A5163. This trial examined the effects of weekly dosing of ALN or placebo (PLB) on low bone density associated with HIV and ART. We measured caRNA levels and total HIV DNA levels. A Wilcoxon matched-pairs signed-rank test was used to analyze patient-specific replicate data across treatment types, and a Mann-Kendall test was used to test for time trend (in either direction) in HIV DNA levels.
Results: N-BPs induced reactivation of latent HIV ex vivo (Figure 1A) without causing non-specific activation or other significant alterations on peripheral immune cell populations. RNA-seq analysis showed a correlation between pathways altered by N-BP treatment and those altered following HIV infection ($R=0.44$, $p<0.001$). In vivo administration of ALN induced perturbations of the latent reservoir in 8 of 9 participants analyzed who took ALN, that were not detected in participants who took PLB (N=5). Most importantly, treatment with N-BP ALN resulted in a 2.9 to 49.1-fold decrease in total HIV DNA levels in three of eight participants (Figure 1B), while no changes were detected in the PLB arm.
Conclusion: We present the first demonstration that N-BPs can reactivate latent HIV in primary CD4 T cells and show that, in vivo, N-BPs can function as latency reversing agents and significantly reduce total DNA levels. These findings, together with the known safety profile of N-BPs, support the need for further clinical testing of N-BPs to reduce persistent HIV infection in vivo.

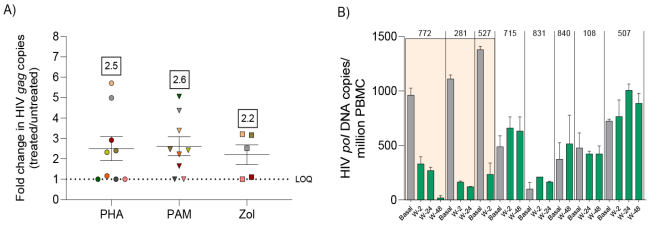


Figure 1: **Effect of Aminobisphosphonates (N-BPs) on HIV reactivation. A)** N-BPs, pamidronate (PAM) and zoledronate (Zol) exhibit a similar *ex vivo* capacity to induce caRNA HIV that is comparable to PHA (mean fold change in HIV copies of 2.6 for PAM, 2.2 for Zol and 2.5 for PHA, shown in the graph). Each symbol represents one individual for whom 6-15 replicates of $1x10^6$ cells were assayed, and the mean ± SEM is represented. **B)** Total HIV DNA levels in participants pre (gray bars) and 2, 24 or 48 weeks post (green bars) *in vivo* treatment with the N-BP alendronate. Orange shade identifies the three participants in which N-BP treatment results in a sustained decrease in total HIV DNA levels (two-sided, Mann-Kendall test for monotonic trend was used to compute permutation p-values (10,000 permutations).

360 PARALLEL HIV RNA, INTEGRATION SITE, AND PROVIRAL SEQUENCING IN SINGLE RESERVOIR CELLS

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Background: Highly durable latent reservoirs constitute the major barrier to HIV cure. The ability of viral reservoir cells to persist long-term may depend on the proviral sequence, corresponding integration site and HIV gene expression, but technical limitations have hindered efforts to obtain all three features from single reservoir cells. Here, we describe a novel technology that accomplishes this goal.
Methods: PBMC from 2 HIV-infected patients, collected during pre-ART viremia and during suppressive ART, were subjected to a novel assay termed Parallel RNA, Integration Site and Proviral Sequencing (PRIP-Seq). Briefly, PBMC were diluted to single viral reservoir cells, subjected to parallel extraction of cellular DNA and RNA, and exposed to whole-genome (WGA) and whole-transcriptome amplification (WTA). Subsequently, near-full-length proviral sequences, integration sites and the expression of immature and mature HIV RNA transcripts were determined using WGA and WTA products.
Results: Paired HIV RNA expression profiles and proviral sequences were determined for 219 total proviruses. HIV transcription was observed in 35% and 31% of cells containing genome-intact and defective proviruses, respectively. Integration sites were simultaneously obtained for 99 of these sequences. Among proviruses with defined integration sites as well as detectable and intact viral promoter regions (n=34), transcriptionally-silent proviruses were 2.8-fold more frequently located in non-genic/pseudogenic regions and were positioned 2.9-fold further away from proximal host transcriptional start sites

relative to transcriptionally-active proviruses. Longitudinal analysis in one patient indicated an enrichment of non-genic/pseudogenic integrations after suppressive ART (21%) as compared to pre-ART levels (0%). This trend was paralleled by a 59-fold reduction in the number of transcriptionally-active intact proviruses, and a 7-fold reduction in the number of transcriptionally-silent intact proviruses per million PBMC after suppressive ART. In comparison, transcriptionally-active and -silent defective reservoirs declined 6-fold and 4-fold, respectively.
Conclusion: Parallel analysis of proviral sequences, integration sites and viral gene expression from single reservoir cells suggests progressive enrichment of transcriptionally-silent proviruses integrated into non-permissive genomic regions during prolonged ART. Future use of PRIP-Seq will allow profiling of the evolutionary dynamics of viral reservoir cells in great detail.

361 SINGLE-CELL ATLAS AND CLONAL EXPANSION DYNAMICS OF CD4+ T CELLS DURING HIV INFECTION

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Background: Despite effective antiretroviral therapy (ART), HIV-1 persists in CD4+ T cells as a major barrier to cure. More than 50% of the HIV-1 latent reservoir is maintained by clonal expansion. HIV-1-infected cells undergo clonal expansion through antigen-driven proliferation, homeostatic proliferation and integration site-driven proliferation. Targeting clonally expanding HIV-1-infected cells without damaging uninfected cells is required to eliminate the latent reservoir. We constructed a single-cell multiomic atlas of CD4+ T cells from HIV-1-infected individuals during acute HIV-1 infection and after viral suppression at its native status without ex vivo stimulation.
Methods: We obtained paired CD4+ T cells from three HIV-1-infected individuals from the MERLIN cohort during acute infection (within one month of the estimated day of infection) and after suppressive ART (11 months of ART with viral suppression [plasma viral load <200 copies/ml] within the past 6 months). CD4+ T cells from three uninfected individuals were obtained as negative controls. Using ECCITEseq (Expanded CRISPR-compatible Cellular Indexing of Transcriptomes and Epitopes by sequencing), we captured 1) surface protein expression, including memory phenotypes, activation status and exhaustion markers, 2) transcriptome, 3) HIV-1 RNA and 4) T cell clonality by T cell receptor sequences in the same single cells. We analyzed T cell clonal abundance, repertoire dynamics and clone tracking.
Results: We captured an average of 7,950 single cells, 1,504 genes mapped to human genome and 6,110 T cell clones per sample. Among them, we identified a total of 67 HIV-1-infected cells and 25 expanded CD4+ T cell clones harboring HIV-1-infected cells. We mapped the single-cell atlas of CD4+ T cells from HIV-1-infected individuals which is distinct from that of uninfected individuals. We found upregulation of interferon-stimulated genes and T cell activation, reflecting T cell responses to acute HIV-1 infection. We also identified CD4+ T cell clones that persist despite suppressive ART. Even within the same CD4+ T cell clone, CD4+ T cells exhibit heterogeneous transcriptional profiles.
Conclusion: We captured the cellular environment of HIV-1-infected cells from HIV-1-infected individuals at the native status without ex vivo stimulation. Transcriptional signatures of HIV-1-infected cells may serve as therapeutic targets for HIV-1 cure strategies.

362 TCR SEQUENCING REVEALS CLONAL EXPANSIONS OF INDUCIBLE RESERVOIRS IN SPECIFIC SUBSETS

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Background: Clonal expansions occur in the persistent HIV reservoir as demonstrated by the duplication of HIV genes and/or integration sites reported in several studies. However, these approaches do not permit to phenotypically analyze these expanded clones of infected cells nor the inducibility of the proviruses. We took advantage of the uniqueness of the T-cell receptor (TCR) expressed by a given T-cell clone to unravel the phenotype and dynamics of the inducible HIV reservoir.
Methods: Blood samples from 8 individuals on suppressive ART for at least 2 years were collected longitudinally. Clonotype characterization of HIV-infected cells was determined by combining index single-cell sorting of HIV-infected cells by HIV-Flow (which allows recording the memory phenotype of individual p24+ cells, according to their differentiation status: central, transitional, effector memory cells) with multiplex PCR of the V-J junction of the TCRbeta chain (including the CDR3 region) followed by sequencing. A representative subset of p24- cells was analyzed to determine TCR diversity in the CD4+ T-cell compartment.
Results: We obtained the TCR sequences from 538 p24+ and 346 p24- single-sorted cells. There was no bias in the selection of V and J segments in p24+ cells when compared to p24- cells. Expanded TCR clonotypes were present in 7/8 individuals and accounted for the majority of reservoir cells (median 89%, range 77-100). These expanded clonotypes were maintained over time on ART in 5 individuals and persisted for up to 6 years. The dynamic of the HIV reservoir on ART greatly varied between individuals, with some participants showing a stable repertoire, whereas others displayed emergence of new clonotypes over time. Expanded infected clones were systematically overrepresented in the most differentiated cells (i.e. transitional and effector memory). Nonetheless, these expanded clones were also identified within the central memory compartment from the majority of the participants, albeit at lower frequencies. Importantly, the memory phenotype of these expanded reservoir cells was maintained over time on ART.
Conclusion: Through the repertoire analysis of infected cells, we show that antigen-driven clonal expansion highly contributes to the persistence of the translation-competent HIV reservoir during ART. Our results suggest that infected T cell clonotypes displaying a differentiated phenotype are the progeny of infected central memory cells undergoing clonal expansion during ART

363 ONLY A FEW HIV-1 INTEGRATION SITES CONFER GROWTH ADVANTAGE TO INFECTED CELLS IN VIVO

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Background: HIV persists during antiretroviral therapy (ART) as proviruses in latently-infected cells that are descendants of a tiny fraction of the CD4+T cells infected prior to ART initiation. We and others previously reported in vivo selection of cell clones with proviruses integrated in several specific genes, based on analyzing small numbers of integration sites.
Methods: We compared about 380,000 integration sites in PBMC infected ex vivo to sites combined from 32 individuals on suppressive ART for >1 year. The on-ART dataset comprised about 52,000 sites, of which about 31,000 were unique. The two datasets were compared to look for evidence of selection in vivo, and to infer its mechanism.
Results: The overall distribution of unique integration sites was nearly identical between the two datasets. As expected, there was preferential integration in highly-expressed genes (84% of sites) in the ex vivo infected PBMC dataset, and the proviruses were randomly oriented relative to the host gene. By contrast, in the on ART dataset, there was a modest (55%), but significant (P~10-50), bias for integration in the reverse orientation, which was the result of a weak selection acting on a large number of genes, rather than of strong selection acting on a few genes. Proviruses integrated in three genes (MKL2, BACH2, STAT5B), known to be drivers of cell growth or survival, were enriched in vivo (Table 1) and were preferentially integrated in one or two introns in the same orientation as the gene. We detected three more genes (MKL1, IL2RB, MYB) in which the data also suggest proviral effects on cell growth or survival (Table 1). Taken together, the proviruses in the 6 genes comprised only 2.3% of unique integration sites. Outside of these genes there was no evidence of clustering, orientation bias, or local enrichment of clonally amplified proviruses.
Conclusion: The primary determinant of the distribution of integration sites in persons on ART is their initial distribution, which is subsequently modified only modestly by selection against proviruses in the sense orientation. Proviruses integrated in the sense integration in any one of 6 genes can enhance cell expansion and/or survival; however, these few selected cells are unlikely to be of major importance to HIV-1 persistence. Other mechanisms driving clonal expansion, for example immune signaling, are more important.

Table 1. Genes in Which Proviruses Can Contribute to Growth and Persistence of Clones

Gene Name	Unique IS in Genes on Therapy	IS in Stimulated PBMC	Ratio PBMC/on Therapy	Enrichment Probability	Provirus Orientation: with gene/ against	Orientation Probability (binomial)	Introns with selected IS	Selected IS upstream or in coding
Unique IS in Genes on Therapy	23,200	323,917	13.97		10426/12774	3X10e-50*		
STAT5B	268	562	2.10	<1X10e-50	197/71	2.2X10e-15	1	Upstream
BACH2	91	132	1.45	1.2X10e-43	71/20	2.6X10e-8	5	Upstream
MKL2	46	69	1.50	7.9X10e-16	40/6	1.3X10e-7	4-6	In
MKL1	83	331	3.99	1X10e-20	53/30	3.6X10e-3	4	In
IL2RB	26	68	2.62	7.9X10e-7	17/9	4.7X10e-2	1	Upstream
MYB	10	31	3.10	0.075	10/0	9.8X10e-4	14	In

364 HIV DYNAMICS AND REPOPULATION OF RESERVOIRS IN THE HUMAN BODY

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Background: Characterizing HIV persistence and dynamics across the human body is important to develop ways to clear reservoirs. This goal has been hampered by technical difficulties and obtaining fresh tissues.

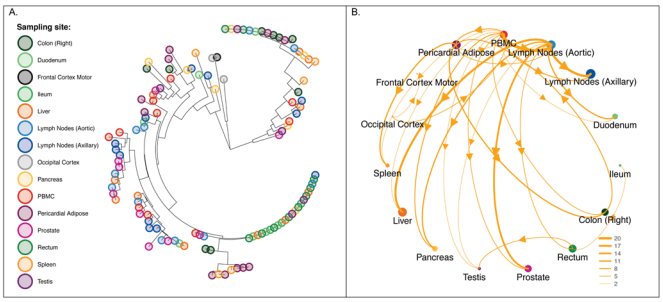
Methods: Samples were obtained from 6 Last Gift participants, who provided blood ante-mortem and their whole bodies for rapid autopsy within 6 hours of death. Two voluntarily stopped their antiretroviral therapy (ART) before death and 4 remained on ART. HIV reservoirs were characterized by digital droplet PCR and single genome amplification and sequencing of full-length (FL) envelope HIV. Phylogeographic methods reconstructed HIV spread and generalized linear models (GLM) tested for associations between HIV diversity, divergence, predicted tropism, DNA level, and viral dispersal.

Results: Across participants, HIV DNA levels ranged from ~0 copies/10^6 cells in the occipital lobe (interquartile range: [IQR] 0-4.6) to 659 cp/10^6 cells in lymph nodes (IQR 580-753), mean=98 cp/10^6 cells (IQR:23-132) across all tissues. We recovered 603 intact FL env sequences in antemortem blood cells and across 28 anatomical sites (mean of 7 viruses/site, IQR: 5-10), including the central nervous system (CNS). Among the 2 participants stopping ART, viral diversity was lower ($p<0.01$) in blood plasma than in most tissue-derived HIV DNA. Most of the rebounding intact HIV RNA populations in blood (65% and 80% of variants) were clonal (>99% identical). There was also evidence of clonal expansion within tissues (Fig.), especially gut and genital tract (e.g. 30 identical proviruses observed across 8 tissues in 1 participant). While the main sources of viral dispersal were blood, gut and lymph nodes, our models also revealed viral exchanges within the CNS (Fig.) and from blood toward the CNS. The GLM models revealed that low HIV genetic divergence between sites and high HIV diversity in the recipient sites but not HIV DNA levels were associated with viral exchange.

Conclusion: This study found: 1) The emergence of large, clonal, intact HIV RNA populations after stopping ART, which repopulated tissues throughout the body; 2) Multiple sites can act as hubs for dissemination of HIV within the host; 3) Viral exchanges occur within the CNS areas and between the CNS and blood; 4) viral dynamics are associated with low HIV divergence between sites and high HIV divesity at the recipient site.

***FIGURE. Maximum Likelihood Phylogeny and* Lineage Dispersal Events between Compartments for One Participant.**

A. Phylogenies were estimated from the full length HIV intact *env* sequences obtained from tissues and PBMC collected during rapid autopsy. B Circle size is proportional to the number of sequences recovered in each compartment. The thickness of the arrows corresponds to the average number of inferred migration events between compartments.



365 LONGITUDINAL CHARACTERIZATION OF HIV PROVIRUSES IN PEOPLE ON SUPPRESSIVE ART

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Background: Clonal proliferation of CD4+ T cells harboring HIV proviruses is a major contributor to HIV persistence despite antiretroviral therapy (ART). Most proviruses are defective, and it is unknown whether cells harboring intact and defective proviruses or those with escape epitopes experience differential rates of clonal expansion and persistence during ART.

Methods: To determine whether HIV-specific cytotoxic T lymphocyte (CTL) pressure or differential rates of clonal proliferation shape the HIV provirus landscape during long-term ART, we sequenced 661 near-full length proviruses from two samples, average 7 years apart, from 8 individuals with suppressed viral loads on ART. 3 of these were elite controllers on ART. The best-defined CTL epitopes based on HLA type were identified in HIV Gag, Pol, and Nef, and each epitope in each provirus was categorized as recognized or not based on its sequence and published data.

Results: We found that the provirus landscape of intact and defective proviruses does not change dramatically over time on suppressive ART, although there was a trend towards fewer intact proviruses over time when analyzed by dual primer-probe ddPCR. There was no evidence for longitudinal selection effects in HIV epitopes in Gag, Pol, and Nef. Intact proviruses appear in large clones at least as often as defective proviruses, and proviruses found in large clones are not enriched in escape/ unrecognized epitopes. Elite controllers on ART have a similar distribution of defective proviruses and similar proportions of escape and unrecognized epitopes as other individuals on ART. The proportion of proviruses present in large clones increased over time on ART in all participants. Albeit with small sample sizes, modeling of this data suggests that over time on ART a smaller number of very large infected CD4 clones come to dominate the observed provirus landscape.

Conclusion: We demonstrate that the mechanisms of clonal proliferation in vivo do not activate HIV expression often enough to discern dramatic differences in the types of proviruses found in large clones due to viral cytotoxicity or CTL recognition. Our work suggests that CTL targeting of activated CD4+ T cells expressing HIV genes during long-term suppressive ART shapes the provirus landscape only subtly if at all. Our findings in elite controllers on ART indicate that the drivers of HIV persistence are similar in this population despite stronger, polyfunctional HIV-specific CTLs.

366 IDENTICAL HIV PROVIRUSES ARISE FROM CELL EXPANSION AND INFECTION BY COMMON ANCESTOR

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Background: Understanding the mechanisms of HIV-1 persistence during ART is crucial for developing curative strategies. Identical proviral sequences that are observed during ART can result from the proliferation of single infected cells or from genetic bottlenecks leading to viral clones that can spread prior to ART initiation. To investigate the origins of identical proviruses in individuals on ART, we sequenced near full-length proviruses and determined their sites of integration.

Methods: PBMC was obtained from 5 donors on ART and analyzed by Multiple-Displacement Amplification (MDA) Single-Genome Sequencing in which DNA is diluted to a proviral endpoint, subjected to whole genome amplification, and used for both integration site analysis and full-length proviral sequencing. 15 sets of identical sub-genomic sequences (12 in P6-PR-RT, 3 in env) were examined to determine if i) identical proviruses also had identical integration sites (cell clones), ii) identical proviruses had different integration sites (viral

clones), or iii) identical proviruses resulted from some with identical integration sites and some with different sites (both cell and viral clones).

Results: Of the 12 sets of identical P6-PR-RT sequences, 3 contained only identical integration sites (4, 2, and 2 MDA wells), 7 contained integration sites observed only once (2-5 MDA wells per set), and 2 contained a combination of identical (19 and 13 MDA wells) and singly-observed integration sites (4 and 2 MDA wells). From the 3 sets of identical env populations, one had integration sites observed only once (7 different sites) and 2 contained a combination of identical (3 and 28 MDA wells) and singly-observed integration sites (1 and 3 MDA wells). Two of the cell clones contained replication-competent proviruses, confirmed by VOA. Within the populations of defective proviruses, near-full length sequence analyses showed that sequences identical in sub-genomic regions were often identical throughout the genome, except for non-overlapping deletions, making it possible to reconstruct the sequence of the shared viral ancestor.

Conclusion: The finding that identical proviruses can have different integration sites demonstrates that sub-genomic SGS is not sufficient to identify clones of infected cells and suggests that multiple infected cell clones can be established from the same viral ancestor. Such viral clones can arise from the transmission bottleneck, escape from immune pressure, or selection for drug resistant virus.

Table 1.

Category	Sets of Identical P6-PR-RT Sequences (Number of Integration Sites Observed in Each Cluster)	Sets of Identical *env* Sequences (Number of Integration Sites Observed in Each Cluster)
i) All integration sites observed were identical	3 (2-4 observations in each cluster)	0
ii) All integration sites observed were different	7 (2-5 observations in each cluster)	1 (7 observations)
iii) Combination of identical and different integration sites were observed	2 (19 and 30 identical, 2 and 4 seen only once)	2 (3 and 28 identical, 1 and 3 seen only once)

367 HIGH-THROUGHPUT SEQUENCING OF INTEGRATED HIV-1 REVEALS NOVEL PROVIRAL STRUCTURES

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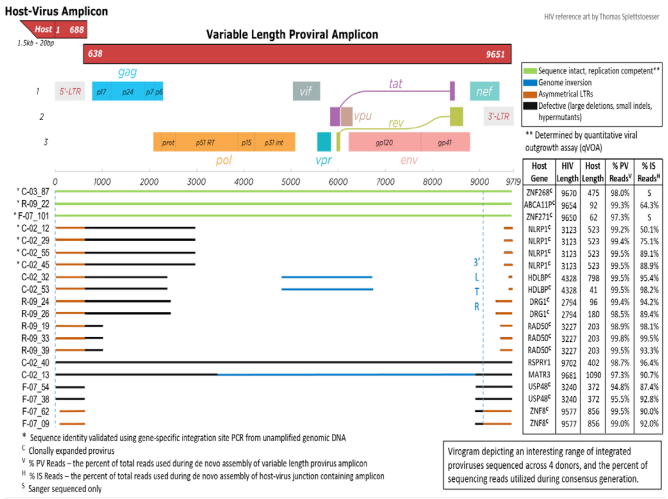
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Background: Efforts to cure HIV-1 infection will require a better understanding of the HIV-1 reservoir but characterizing individual integrated proviruses has remained difficult because of technical challenges related to the rarity of proviruses in CD4+ T-cells. Current approaches for sequencing integration sites using NGS are inefficient (most reads are off-target reads) and restricted read lengths can make it difficult to definitively identify both integration sites and proviral sequences.

Methods: We have developed a new automated approach that sequences single HIV proviruses and their 5' host integration sites by: i) amplifying the whole cellular genome at a proviral end point through multiple displacement amplification; ii) performing long-range PCR that amplifies variable and near-full length proviruses; and iii) performing nullomer-mediated PCR using a linker consisting of nullomer motifs absent in target genomes that markedly enhances specificity for integrated proviral targets. Amplicons can be sequenced by dideoxy (e.g., Sanger) and/or NGS methods.

Results: Amplicons sequenced by NGS utilized >90% of reads on average during consensus generation for both proviral and integration site amplicons. The workflow sequences all but 69 bp of the 3' LTR of the provirus. Across 5 donors, an average of 78% of HIV-positive MDA reactions yielded the 5'-host-virus junction containing 400 + 297 bp of flanking host sequence (compared to about 5 nucleotides by standard integrations site analyses) and 13.4% of proviruses were near-full length (determined by sequencing, N=33 out of 247 total proviruses). To date, the assay has been used to characterize a broad range of intact and defective integrated proviruses in blood mononuclear cells from donors on suppressive ART including replication-competent proviruses in cell clones (proven by viral outgrowth) and novel proviral structures such as asymmetrical LTR deletions (revealed by sequencing both LTRs) and genome inversions. The accuracy of the method has been confirmed by sequence identity with full-length and deleted proviruses amplified directly from blood mononuclear cells using host sequences flanking the integrated provirus.

Conclusion: This novel integrated proviral sequencing assay provides an efficient and high-throughput means of characterizing HIV-1 reservoirs that need to be targeted to achieve a cure of HIV-1 infection.



368 CELL PROLIFERATION CONTRIBUTES TO THE INCREASE OF GENETICALLY INTACT HIV OVER TIME

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Background: Effective HIV eradication strategies require an understanding of the mechanisms maintaining persistent HIV during therapy. We examined the role of memory cell proliferation in maintaining genetically-intact proviruses over 4 years of effective therapy.

Methods: Naïve (N), central (CM), transitional (TM) and effector (EM) memory CD4+ T-cells were sorted from the peripheral blood of two participants on long-term ART. Additional sequences from naïve, CM HLA-DR+/DR-, TM HLA-DR+/DR- and EM HLA-DR+/DR- T cells were obtained 4 years later. Full-length individual proviral sequencing was used to characterise proviruses as intact or defective. Clusters of ≥2 100% genetically identical proviral sequences - indicative of host cell proliferation – were identified.

Results: A total of 287 and 448 sequences were isolated from the first and second time-points, and 34 (12%) and 90 (20%) were considered intact. At both times the frequency of intact genomes differed between cell subsets, EM>TM>CM/N. In each subset, HLA-DR+ cells contained more intact provirus than HLA-DR- cells. The proportion of identical sequences was significantly higher in intact proviruses compared to defective at the second time-point (85% vs 41%, p=0.03), but not the first. There was a significant correlation at the second time-point between the proportion of identical sequences overall and the proportion of intact proviruses (R2=0.58-67, p=0.02-0.04). The majority (44/51, 86%) of sequences observed at both time-points were found in cells of the same memory phenotype. The number and size of identical sequence clusters differed depending on activation status. A greater number of identical sequence clusters were derived from HLA-DR+ cells. However, the size of clusters derived from cells of mixed activation status was larger, with 60% of all identical sequences derived from a cluster of both HLA-DR+ and HLA-DR- cells.

Conclusion: Genetically intact proviruses were found most frequently in the more differentiated EM cells. However, the frequency of intact proviruses was increased in each memory cell subset when the cell expressed HLA-DR, highlighting the role of cellular activation in maintaining the reservoir. Moreover, the correlation between cellular proliferation and intact provirus highlights the importance of host cell proliferation in maintaining HIV over time. These findings demonstrate the importance of limiting cellular activation, differentiation and proliferation in strategies aimed at reducing the reservoir.

369 WITHDRAWN

370LB ANTIGEN RESPONSIVE CLONES OF CD4+ T CELLS CONTRIBUTE TO THE INTACT LATENT RESERVOIR

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Background: Antiretroviral therapy suppresses but does not cure HIV-1 infection due to the existence of a long-lived reservoir of latently infected cells. The long half-life appears to partially result from expansion and contraction of infected CD4+ T cell clones over time. However, the mechanisms that govern this process in vivo are poorly understood.

Methods: To test the hypothesis that expanded clones harboring latent proviruses respond to foreign antigens, we exposed CD4+ T cells from ART suppressed individuals to overlapping peptide pools from either a negative control protein, HIV-gag or CMV-pp65. Following overnight culture, activated CD4+ T cells from 8 donors were purified by cell sorting based on expression of two or more activation induced markers (AIM+: CD69, PD-L1, and 4-1BB). Total, live CD4+ T cells were sorted from the negative control. Integrated proviruses harbored by control and antigen responsive cells were enumerated and further characterized as intact or defective by combining quantitative PCR and next-gen sequencing.

Results: The overall frequency of intact and defective proviruses contained within antigen responsive (AIM+) cells varied among individuals. We analyzed all HIV-1 sequences across all groups and identified clones of viral sequences in all participants. Seven of 8 donors harbored intact or defective clones of proviral sequences in antigen responsive cells. The clonal distribution of HIV-1 sequences found in AIM+ cells was significantly different from the negative control in 4 of 6 individuals for whom we obtained sufficient data. Intact sequences from AIM+ cells were identical to replication competent viruses sequenced during outgrowth in 2 of 5 donors assayed.

Conclusion: We show that both intact and defective HIV-1 proviruses can persist in clones of CD4+ T cells that respond to CMV and HIV antigens. The data suggests that infected clones of CD4+ T cells may respond to diverse pathogens in HIV-1 infected individuals. Their intermittent exposure to these and other antigens found in the virome and microbiome may account for the reported waxing and waning of individual clones of latently infected cells and their persistence over time.

371 SINGLE-CELL ANALYSIS OF IN VIVO HIV RESERVOIR UNCOVERS NOVEL MARKERS OF LATENT CELLS

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Background: Direct phenotypic analysis of the in vivo latent HIV reservoir is complicated by the need to reactivate these cells ex vivo to identify them, which changes the phenotypes of the latent cells. We used CyTOF to quantitate the levels of 43 different proteins on reactivated cells from ART-suppressed, HIV-infected individuals, and implemented a bioinformatics approach to trace each reactivated cell to its original latent state.

Methods: PBMCs (n=7), rectosigmoid biopsies (n=7), and lymph node aspirates (n=2) from treated individuals were phenotyped by CyTOF immediately after cell isolation, or stimulated with PMA/ionomycin or LRAs and then phenotyped. Reactivated cells were traced back to their original pre-stimulation state using the bioinformatics approach PP-SLIDE (Cavrois et al, Cell Reports 2017). Markers identified as preferentially expressed on latent cells were validated by sorting the cells and then conducting viral outgrowth assays and proviral sequencing.

Results: Latent cells were non-randomly distributed amongst memory CD4+ T cells. Markers preferentially expressed on latent cells included those that were shared between donors (PD1, CCR5, CD2, CD49d, 0x40) and donor-specific ones (CXCR5, TIGIT, CCR6, CD28, CD7). Markers differentially expressed between latent cells in blood vs. tissues, and between latent cells reactivatable by different stimulation methods, were identified. Analysis of longitudinal samples suggested the phenotype of latent cells is stable over time. Multiparameter sorting revealed that donor-shared surface markers identified by CyTOF markedly enriched for latent cells with replication-competent HIV: Tfh, already highly enriched for replication-competent HIV, was further enriched by 3 orders of magnitude using such markers. Viral sequencing analysis revealed the enriched cells to be largely clonally expanded.

Conclusion: We have validated CyTOF phenotyping of reactivated latent cells paired with bioinformatics analysis by PP-SLIDE as an effective way to chart the in vivo blood and tissue HIV latent reservoir. Our results demonstrate that 1) latent cells are not randomly distributed amongst memory CD4+ T cells, 2) the phenotypes of latent cells are stable over time, 3) LRAs can target different latent cells than PMA/ionomycin, 4) there are shared as well as donor-specific surface markers of latent cells, and 5) sorting of cells based on surface markers identified by CyTOF markedly enriches for clonally-expanded latent cells with replication-competent HIV.

372 INTACT HIV GENOMES ARE ENRICHED IN MEMORY T CELLS WITH SHORT HALF-LIVES

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Background: Future HIV curative therapies require a thorough understanding of the distribution of genetically intact HIV within T cell subsets during short-term antiretroviral therapy (ART) and the cellular mechanisms which maintain this reservoir. Therefore, we genetically characterized HIV genomes within T cell subsets from participants on <4 years of therapy.

Methods: Seven participants were treated for <4 years either within 5 months (early, n=4) or after 7 months (late, n=3) of HIV infection. Near full-length proviral sequences were obtained from naïve (NV), stem-cell memory (SCM), central memory (CM), transitional memory (TM), effector memory (EM), and terminally differentiated (TD) CD4+T cells. Clusters of ≥2 proviral sequences which were 100% genetically identical and indicative of host cell proliferation were identified. Cellular half-lives were measured by in vivo incorporation of deuterium into genomic DNA within these cell subsets.

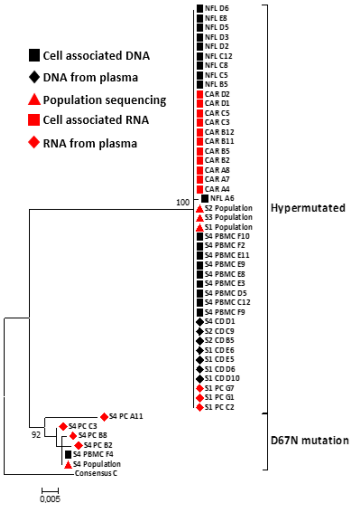
Results: A total of 893 sequences were isolated; 585 and 308 from the early and late ART participants respectively. From these 893 sequences, 57 were considered intact (6.4%); 13 and 44 respectively from the early and late ART groups. The proportion of intact sequences across the T cell subsets was different (p=0.03). In the late ART group, the intact sequences were concentrated in cells with shorter half-lives such as TM (6/10^6 TM cells; median half-life: 95 days) and EM cells (25/10^6 EM cells; median half-life: 82 days) compared to other subsets with longer half-lives (median half-lives: 162-1107 days for NV, SCM, CM, and TD cells). For the early and late ART groups, a correlation was found where cells with shorter half-lives contained more intact proviruses (p=0.03). For the early ART participants, the clusters of identical sequences were less frequent when compared to the late ART participants (p=0.006). However, the levels of identical sequences contributing to a cluster were highest within EM and TD in all participants (p<0.001).

Conclusion: The distribution of HIV genomes across T cell subsets during short-term therapy after both early and late ART suggests that a short cellular half-life could be a predictor of a higher frequency of intact proviruses. Both TD and EM cell subsets were marked by clusters of identical HIV genomes reflecting cellular proliferation. This indicates that specific cellular mechanisms such as a short half-life and greater proliferative potential, characteristics of EM T cells, contribute to the maintenance of intact HIV.

373 "FALSE ART FAILURE" FROM IDENTICAL HYPERMUTATED HIV NUCLEIC ACID IN PLASMA

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Background: Plasma HIV-1 RNA above the limit of detection of commercial assays on ART arise from i)complete cycles of viral replication as a consequence of inadequate drug exposure and/or drug resistance; or from ii)virions produced from proviruses in clonally-expanded cells without complete cycles of replication. Most proviruses that persist on ART are defective, including those hypermutated by APOBEC. Although hypermutated proviruses can be transcribed into mRNA and even spliced, their packaging into virions is expected to be very inefficient. Here we report the first instance of false virologic failure on ART arising from cells with hypermutated proviruses.
Methods: A 46 year old female presented with detectable HIV on ART ranging from 439 to 4230 copies/mL. Single genome sequencing (SGS) analysis (p6-Pro-RT) of 4 longitudinal plasma samples obtained over 13 months was performed. To characterize the source of viremia, fractions of plasma after low- (2700 g) and high-speed centrifugation (17 200 g) and total nucleic acid from PBMC were analyzed by SGS including cell-associated HIV mRNA and near-full length (NFL) sequencing of proviral DNA.
Results: SGS (p6-Pro-RT) revealed multiple, identical hypermutated sequences in all low-and one high-speed plasma pellet(s), and in PBMC HIV DNA (p6-Pro-RT and NFL) and cell-associated HIV mRNA (Figure). The only non-hypermutated sequences were from the high-speed plasma pellet (4 of 4) and PBMC HIV DNA (1 of 10) at the 13 month time point. Sequencing of gag revealed a stop codon at amino acid 211 which would prevent capsid (p24) formation.
Conclusion: This is the first report of false virologic failure of ART resulting from release of defective HIV nucleic acid into plasma. The source appears to be a large population of cells with identical hypermutated proviruses, i.e. an infected CD4+ T-cell clone that is undergoing cytolysis and release of cellular nucleic acid including HIV DNA and mRNA into plasma. Production of viral proteins and packaging of viral genomes is a highly unlikely source given the hypermutated genome with at least one stop codon in gag-p24. Release of cellular nucleic acids into plasma may be an underappreciated cause of false virologic failure.



374 ART-TREATED SUBJECTS WITH LOW VIRAL RESERVOIR SHOW UNUSUAL HIV LATENCY DISTRIBUTION

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Background: Small-size viral reservoirs are predominantly found in HIV-1 controllers and individuals treated during acute/early HIV-1 infection. However, other HIV+ subjects could naturally also harbor low viral reservoirs. We have established a cohort of "Low Viral Reservoir Treated" subjects" (LoViReT) to further explore the mechanisms associated with low reservoir levels.
Methods:
42 HIV+ subjects on ART and <50 HIV-DNA copies/10^6 PBMCs constitute the LoViReT cohort; at least 66% of whom initiated ART during the chronic phase of HIV (>6 months since acquisition). In 12 LoViReTs, total HIV-DNA was longitudinally measured in cryopreserved CD4+ T cells by ddPCR, including a pre-ART time point. 14 LoViReTs underwent a leukapheresis to measure the replication-competent virus by qVOA (37x10^6 CD4+ T cells), and total HIV-DNA in sorted CD4+ T cell subsets. In 9 LoViReTs with <0.1 infectious units per million (IUPM), total HIV-DNA was measured in rectal and/or lymph node biopsies (LN). Clinically matched individuals with HIV-DNA >50 HIV-DNA copies/10^6 PBMCs were recruited as controls.
Results: LoViReT harbored significantly lower total HIV-DNA in CD4+ T cells before ART initiation compared to controls (1,051 and 5,995 HIV-DNA copies/10^6 CD4+ T cells respectively, p=0.002) despite comparable pre-ART viral load. These differences became higher after 5 years on ART (16 vs 5-folds decay respectively, p<0.001). 10/14 LoViReTs had undetectable replication-competent virus (IUPM<0.0185) >10 years after ART. Among them, we detected low levels of HIV-DNA in rectum in 6/8 subjects with a median of 57 HIV-DNA copies/10^6 CD45+ T cells [IQR:37-114]. In LN, only 3/8 subjects had detectable reservoir (263[36-2,112] HIV-DNA copies/10^6 CD45RA- T cells). Unexpected HIV reservoir distribution was observed in LoViReTs, being the short-live transitional memory (TTM) and effector memory (TEM) T cells the major contributors to the total reservoir (47% and 29% respectively). TCM presented limited contribution to the HIV reservoir (24%).
Conclusion: LoViReT individuals have abnormally low HIV reservoirs before ART initiation. 71% of LoViReTs did not have replication-competent virus and harbored limited provirus in tissue sanctuaries after a median of 15 years on ART. A cause of this exceptional low reservoir could be the high contribution of the short-live TTM and TEM cells in the total HIV reservoir. This unique group of individuals are of great interest as trial participants in eradication studies.

375 A NEW LONG-READ NGS METHOD TO SEQUENCE HIV1 INSERTION SITES AND ASSOCIATED PROVIRUSES

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Background: The HIV-1 reservoir represents a major obstacle to HIV cure, making its exploration a priority, however, this task is complicated by its elusiveness, with only ~0.1% of CD4 T cells carrying integrated HIV-1 DNA. Substantial effort has been expended to determine the patterns of proviral integration in this latent reservoir and simultaneously identify the sequence of the associated HIV-1 proviruses. Recent approaches based on short-read high throughput sequencing allow the sequence of individual proviruses to be linked to the integration site, however, these methods rely on whole genome amplification of isolated HIV-1 genomes, with separate reactions to identify the integration site and sequence the provirus, limiting the number of proviruses one can reasonably interrogate.
Methods: To exploit the potential of long reads we developed Pooled CRISPR Inverse PCR sequencing (PCIP-seq), a method that leverages selective cleavage of circularized DNA fragments carrying HIV-1 proviral DNA with a pool of CRISPR guide RNAs, followed by inverse long-range PCR and multiplexed sequencing on the Oxford Nanopore MinION platform.
Results: We first tested PCIP-seq on 0.1 and 0.01% dilutions of the HIV-1 cell line U1 and demonstrated its utility to examine low proviral loads. We then applied PCIP-seq to CD4 T cells of two HIV-1 patients on long term cART, generating the sequence from hundreds of HIV-1 proviruses and linked this sequence to specific integration sites. We identified proviruses with single nucleotide variants and large deletions as well as intact proviruses. Among these, we found proviruses present in clonally expanded cells mapping to segmentally duplicated regions and satellite repeats of the centromeres of chr13, 14, 21 and 22. Both patients had four integration sites in intron 1 of STAT5B, all in the same transcriptional orientation as the host gene. In addition to HIV-1 we also successfully applied the technique to oncogenic retroviruses HTLV-1 and BLV.
Conclusion: Using long reads, we can simultaneously identify the integration site and track clone abundance while also sequencing the HIV-1 provirus inserted at that position. Methods currently used are labor intensive, costly, and only examine a handful of patients. Using PCIP-seq it is feasible to sequence thousands of bases from hundreds of proviruses in a single experiment, opening

the landscape of proviral variation and evolution within, and between large numbers of hosts.

376 COMBINED ASSAYS SHED NEW LIGHT ON HIV-1 PROVIRAL SEQUENCE AND LINKED INTEGRATION SITE

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Background: HIV-1 infection remains incurable due to the establishment of a persistent viral reservoir, capable of rebounding upon treatment interruption. Evidence has shown that only a small proportion of this reservoir contains intact proviruses, and these are maintained, at least in part, by clonal expansion. We have generated integration site (IS) data down to single cell level on patients on cART using different approaches, comparing strengths/weaknesses and complementarity of the methods.

Methods: Two patients (PT1, PT2) underwent leukapheresis and CD4+ T-cells were isolated. DNA was extracted and IS were sequenced using Integration Site Loop Amplification (ISLA). DNA from the same extract was analyzed using Pooled CRISPR Inverse PCR sequencing (PCIP-seq), a new long-read NGS method, to generate both IS and adjacent proviral genomes. CD4+ T-cells were stimulated, stained for two epitopes of p24, and double positive cells were single-cell sorted. After DNA amplification, near full-length (NFL) proviral genomes and corresponding IS were sequenced. Subsequently, all data were subjected to an in-depth comparison.

Results: Using ISLA, we recovered 144 IS for PT1, and 201 IS for PT2. The former displays a limited degree of clonality (7%, 4 clones) while the latter is highly clonal (75%, 13 clones). PCIP yielded 80 IS for PT1 and 161 IS for PT2. Comparison showed that most clonal IS were detected by both ISLA and PCIP, validating the results of PCIP. Moreover, NFL genomes from 4 clones were identified by PCIP in PT2. One of them contained a 115 bp deletion, disrupting the packaging signal. The second one is located in the MLLT3 gene, which protein product has been shown to interact with HIV-1 Tat. Importantly, both of these clones were detected using the p24 stimulation assay while the other two, integrated within centromeric regions, were not detected with the assay.

Conclusion: Comparing PCIP to ISLA, we show that PCIP is a potent method to retrieve both IS and linked proviral genome. Next to that, we show that while the stimulation assay biases towards proviruses that are translationally competent, it does not bias towards replication competent ones. The fact that the stimulation assay does not reveal intact proviruses in centromeric regions hints to deep latency and the inability of the assay to reactivate these. We conclude that the PCIP yields the most comprehensive overview of proviruses and their associated IS, while the stimulation assay adds functional data on translational competency.

377 ULTRADEEP ANALYSIS OF PRETHERAPY HIV PREDICTS GENETICALLY COMPLEX RESERVOIRS

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Background: Measuring the genetic characteristics of HIV populations is essential to understanding the formation of HIV reservoirs that persist during antiretroviral therapy (ART). Analysis of plasma HIV using new next generation sequencing (NGS) approaches using primer ID [ultrasensitive single genome sequencing (uSGS)] and advanced bioinformatic analyses (Boltz et al 2016), yields large HIV sequence datasets with the same, low PCR error and recombination rate as standard SGS. We used uSGS to determine population parameters (replicating population size, in vivo recombination rate). We also extended the uSGS approach to characterize cell associated (CA) HIV RNA and DNA derived from peripheral blood lymphocytes (PBLs).

Methods: Plasma samples were obtained from chronically infected ART naïve individuals (N=6) enrolled in HIV studies at the NIH in 2000-2002. uSGS of HIV RT [HXB2nt 2704-2943 and 3046-3253] using primer-ID in the Illumina NGS yielded 400-nt sequences. Replicating population sizes were estimated as previously described (Maldarelli et al 2013) and linkage disequilibrium was calculated using DNASP; recombination rate was calculated directly by measuring the rate at which linked alleles become unlinked. To obtain uSGS sequences from PBL, DNA was sheared (avg 10 kb), and subjected to a linear PCR step to add primer-IDs before the uSGS procedure.

Results: Longitudinal plasma samples were obtained from chronically infected ART naïve individuals (median CD4=498 c/ul, viral RNA=4.3 $\log_{10}$ cps/ml). uSGS from plasma derived HIV resulted in total of 17,172 (median 1,252/patient, range 54-3165) sequences from 6 subjects from 2 time points. Maximum replicating population sizes exceeded 10^7/person. Viral populations were highly polymorphic, but nearly all polymorphisms were in linkage equilibrium. With a single exception, all linked loci (3-12/patient) became unlinked over short periods (30-413 generations). The measured recombination rate (range 0.004-0.07) is similar to previous estimates (Batorsky et al 2011) indicating that virtually all sequences were the product of recent recombination events. Analysis of CA HIV from PBL of one patient revealed HIV was readily recovered with 742 DNA sequences, and 946 RNA sequences.

Conclusion:
Prior to ART, HIV populations are large (>10^6-10^7/person) and compose of variants that undergo frequent recombination. uSGS predicts that viruses rebounding from reservoirs are diverse and likely to have evidence of prior recombination events.

378 HIV CONTROLLERS HAVE LOW FREQUENCIES OF INTACT PROVIRAL DNA

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Background: Elite controllers or suppressors (ES) are subjects who control viral replication without antiretroviral therapy. Studies using standard DNA PCR assays or the quantitative viral outgrowth assay (QVOA) have shown that these subjects have smaller viral reservoirs than chronic progressors (CP) on antiretroviral therapy (ART). However, standard DNA PCR assays measure both defective and replication-competent virus and the QVOA measures only a fraction of the replication-competent reservoir. The objective of this study was to better approximate the size of the latent reservoir in ES by measuring the frequency of CD4+ T cells that contained intact proviral DNA.

Methods: Total and intact proviral DNA was measured in unfractionated CD4+ T cells from 9 CPs, 8 treatment naïve ES and 2 viremic controllers (VCs, VL < 1000 copies pre-treatment) on ART with the recently described intact proviral DNA assay (IPDA). CD4+ T cells from 5 ES and the 2 VCs on ART were also cultured in the standard QVOA.

Results: The median frequency of total provirus was 24.7 per million CD4+ T cells in the ES, 220.1 per million CD4+ T cells in the 2 VCs on ART and 574.6 per million CD4+ T cells in the CPs on ART. The median frequency of intact provirus was 1.2 per million CD4+ T cells in the ES, 2.83 per million CD4+ T cells in the 2 VCs on ART and 36.2 per million CD4+ T cells in the CPs on ART. While the absolute frequencies of total and intact provirus per million CD4+ T cells were significantly lower in ES than in CP, there was no significant difference in the fraction of total proviral DNA that was found to be intact between these 2 subject groups. There was a positive correlation between the frequency of intact proviral DNA and the frequency of latently infected cells as measured by QVOA in the ES and VCs on ART.

Conclusion: We show that ES have a median frequency of both intact proviral DNA and total proviral DNA that are more than 1 log lower than the frequencies seen in CPs. These findings suggest that while the absolute frequency of persistent HIV is lower in ES as compared to CP, the relative composition of that pool of persistent proviruses may not differ significantly. Furthermore, this data has implications for HIV cure strategies as it demonstrates that while this small reservoir size may contribute to the control, it is not an absolute requirement as one ES had a higher frequency of intact proviral DNA than all of the CPs in our study.

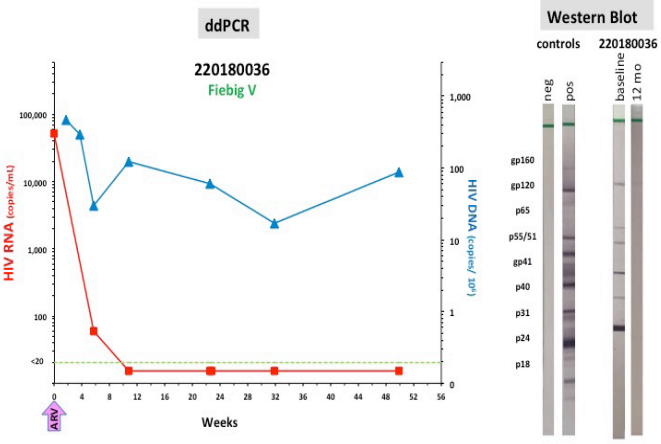
379 EARLY THERAPY OF YOUTH WITH ACUTE/RECENT HIV: EFFECT ON HIV DNA & ANTIBODY (ATN 147)

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Background: Recent studies in adults indicate early potent antiretrovirals (ARV) in acute HIV infection may reduce viral reservoir size, and potentially result in better long- term viral control. There is limited data, however, on the large population of HIV-infected high-risk youth. We hypothesize that the decay of HIV reservoirs and accompanying immune responses are different in youth who have an active thymus and are treated early with potent ARV. As part of a clinical trial, ATN 147, which identified acutely or recently HIV- infected youth (12-24 years), we assessed HIV viral load by HIV RNA PCR, viral reservoirs by DNA ddPCR and HIV antibody at baseline and sequentially for 12-24 months.
Methods: ATN CARES enrolled 75 high risk youth in Los Angeles and New Orleans with newly diagnosed HIV infection; i.e., Fiebig 1-V, acute (34 %);, VI, recent (66%). Samples were collected at baseline, 1 & 2 weeks, 1, 2, 4, 8, 12, 18 and 24 months for plasma HIV RNA <20cp/ml (UD), HIV DNA measured by ddPCR on PBMC with primers SR1/661/ZXF. HIV antibody by Western blot (BioRad) was done at baseline for Fiebig staging and 12, and 24 mos. post treatment. Youth were considered complete responders (CR) if plasma HIV RNA became undetectable and sustained at <20cp/ml (UD), partial responders (PR) if HIV RNA became UD with minor blips and non-responder (NR) if HIV RNA never reached UD.
Results: 14 male MSM (mean age 21) reached > 12 mos. of follow-up to date. Eight were CR, 5 PR and 1 NR. Median HIV DNA ddPCR at baseline (N=14) was 457 (SD 852) and decreased to 186 (SD 304) copies/10e6 at 52 weeks (p=0.02). HIV DNA levels remained constant or increased in 3/14; 11 had a decrease and 1 of these had very low levels <4 cp/10e6 at 52 wks. HIV AB measured by Western blot showed a significant decrease in HIV bands resulting in a negative or indeterminate results in 6/14 (43%) at 12 months post ARV Two of these participants were Fiebig stage 5 at entry. The median time to UD plasma HIV RNA was 14 wks. (range 3-34) in 13/14 participants. An example of biomarkers in a CR is shown in the figure.
Conclusion: Identification, recruitment, treatment and follow up of high risk U.S. youth with acute/recent HIV is feasible. Early ARV can reduce HIV DNA levels and HIV antibodies in a subset with persistent virus suppression. Youth with lower levels of HIV viral reservoirs are a key target for future evaluation of CURE/ remission strategies including therapeutic vaccination.

Fig 1: Antiviral response (HIV RNA, DNA) to early ARV in acute infection



380 WIDE ANATOMIC DISTRIBUTION OF HIV-INFECTED CELLS IN INDIVIDUALS WITH COMORBID CANCER

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Background: HIV persistence during combination antiretroviral therapy (ART) is the principal challenge preventing viral eradication. We and others reported that HIV infected cells undergo clonal expansion during ART, and we reported that clones of infected cells are present in tissues and in a neoplasm. The tissue distribution of infected cells and their roles in HIV persistence are not well understood. To determine the distribution of clones of infected cells during ART, we analyzed tissues obtained from individuals who underwent autopsy after expiring with comorbid neoplasms.
Methods: Participants (N=2) underwent autopsy after therapy for primary effusion lymphoma (PEL) or metastatic adenocarcinoma; both were on effective ART with HIV RNA < 50 c/ml. Tissue samples (lung, mediastinal lymph node, spleen, testes, liver, and neoplastic tissue, including individual metastases) were obtained during autopsy; nucleic acid was extracted and levels of HIV and total cellular DNA were quantified by qPCR as previously described. HIV integration sites were determined for one individual with PEL [for whom single genome sequencing (SGS) have been reported]. For the individual with adenocarcinoma, HIV pro-pol SGS were obtained.
Results: Levels of HIV DNA were diverse (range 30-700 copies/10^6 cells), highest in lymphoid tissue. In the individual with PEL, 391 integration sites were obtained from lymph node, lung, spleen, and testes; 72 sites (18.4%) were from cell clones. Clones were detected within individual tissues, but were also present across tissues, in both local (lung and draining lymph node), and distant tissues (lung, spleen, testes); infected cells were present in the effusion. HIV was integrated in many host genes, including STAT5B, which has been associated with clonal expansion and persistence of infected cells. In the individual with adenocarcinoma, 183 SGS were recovered; HIV was genetically highly diverse, but identical sequences were present, these were possible cell clones. Identical sequences were present within and across tissues. Individual metastases all contained HIV infected cells.
Conclusion: Populations of clonally expanded HIV infected cells are widely, but not uniformly, distributed in individuals with neoplasms, showing that cells from some of the largest infected clones are widely distributed in different tissues. Tumors contain infected cells and analyzing neoplasms contributes to understanding their role in the immune response during ART.

381 LOW FREQUENCY OF CTL ESCAPE MUTATIONS IN INTACT PROVIRUSES FROM ELITE CONTROLLERS

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Background: Elite controlles (ECs), maintain undetectable plasma virus levels in the absence of antiretroviral therapy, and serve as a model for cure of HIV-1 infection. Cytotoxic T lymphocytes (CTL) are widely recognized as the immune correlate most closely associated with an elite controller phenotype, but the frequency of CTL-driven mutations in intact proviral sequences from such individuals is unknown.
Methods: Single-genome near full-length proviral sequencing was used to analyze the proviral reservoir in 49 untreated ECs with undetectable viral loads for 1-20 years and in 28 HIV-1 patients treated with ART for 2-19 years. Optimal epitopes and escape mutations associated each person's HLA-A, -B, and -C alleles were obtained from the Los Alamos HIV Immunology Database. Integration sites of intact proviruses were analyzed by Matched Integration Site and Proviral Sequencing (MIP-Seq) assays.
Results: We obtained 199 and 89 near full-length intact proviral genomes from ECs and ART-treated individuals. A median of 47 optimal epitopes corresponding to expressed HLA Class I alleles were analyzed in ECs, compared to 49 in ART-treated individuals. Frequencies of CTL epitopes matching the clade B consensus sequence were higher in ECs relative to ART-treated patients (47.4% vs 37.9%, p=0.0005). Moreover, the proportion of CTL epitopes displaying known escape mutations was lower in ECs than in ART-treated individuals but did not reach statistical significance (5.67% vs 7.32%, p=0.2818). Among individuals carrying the protective HLA-B*27 and B*57 alleles, optimal epitopes from EC were more likely to show wild-type sequences (43.5% vs 30.4%, p=0.0013), and less likely to encompass previously defined CTL escape mutations (5.84% vs 17.4%, p=0.0043). Notably, among ECs, intact proviral sequences integrated in centromeric satellite DNA and non-genic DNA tended to exhibit lower frequencies of defined CTL escape mutations, compared to the intact proviral sequences integrated in non-centromeric DNA (p=0.0245) or genic regions (p=0.0254).
Conclusion: EC exhibit low frequencies of CTL escape-associated mutations in intact proviruses, despite the absence of antiretroviral therapy, suggesting either lack of viral replication or effective targeting of mutationally intolerant epitopes. The low proportion of CTL escape mutations in intact proviruses

integrated in non-genic/centromeric DNA suggests that these sequences were seeded during early disease stages and are among the most ancestral proviruses in a given patient.

382 TH2 CYTOKINES ARE ASSOCIATED WITH HIGHER LEVELS OF INTACT PROVIRUSES ON ART

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Background: Th2 cytokines, such as interleukin (IL)-4 and IL-13, regulate humoral immunity, promote production of neutralizing antibodies, and can suppress Th1 and Th17 responses by upregulating repressors of interferon (IFN)-γ and IL-17 transcription. Th2 cytokines could affect the persistence of HIV-1 on ART, but their effects on the HIV-1 reservoir have not been defined.

Methods: Participants in AIDS Clinical Trials Group study A5321 who initiated ART during chronic HIV-1 infection with sustained virologic suppression had measurements of plasma HIV-1 RNA by single copy assay (SCA), total HIV-1 DNA and cell-associated RNA (CA-RNA) from PBMC, intact proviral DNA (IPDA) from CD4+ T cells, and plasma levels of IL-1RA, IL-4, IL-10, IL-11, IL-13, CCL-22, and TGFβ. Exploratory cross-sectional analyses assessed the relationship between these cytokines and measures of HIV-1 persistence.

Results: 98 participants (21 females) were evaluated with a median (IQR) age of 46 years (37, 53) and 6.7 (4, 8) years on suppressive ART. Plasma levels of IL-4 were associated with the levels of intact proviral DNA (r=0.37, p=0.009), and the other main Th2 cytokine, IL-13, showed a trend towards a positive association with intact proviral DNA (r=0.26, p=0.07) (Table 1). There was also a trend towards an association of IL-4 levels with SCA HIV-1 RNA (r=0.2, p=0.06) but not total HIV-1 DNA (r=0.14, p=0.18) or CA-RNA (r=0.16, p=0.14). IL-1RA, IL-10, IL-11, IL-13, CCL-22, and TGFβ were not significantly associated with plasma SCA (N=95), total HIV-1 DNA (N=95), CA-RNA (N=90), or IPDA (N=48).

Conclusion: The levels of Th2 cytokines IL-4 and IL-13 are associated with higher frequencies of cells containing intact proviral HIV-1 DNA but not total HIV-1 DNA, whereas other cytokines including IL-10 were not associated with intact or total HIV-1 DNA. There was a weaker association of IL-4 with residual viremia, which likely arises from cells with intact proviruses. This work demonstrates the value of measuring intact proviral HIV-1 DNA when evaluating the relationship between immune responses and the HIV-1 reservoir. While the mechanistic link between IL-4 and IL-13 levels and cells carrying intact proviruses is undefined, these findings suggest that the dampening effect of Th2 cytokines on Th1 and Th17 responses could promote persistence of the HIV-1 reservoir.

Associations between measures of HIV-1 persistence and Th2 or anti-inflammatory cytokines

	Total HIV-1 DNA n = 95		CA-RNA n = 90		Plasma SCA n = 95		IPDA n = 48	
	r	p	r	p	r	p	r	p
IL-4	0.14	0.18	0.16	0.14	**0.2**	**0.06**	**0.37**	**0.009**
IL-10	0.04	0.69	0.07	0.49	-0.01	0.93	-0.02	0.91
IL-11	0.14	0.17	0.15	0.16	0.04	0.73	0.04	0.8
IL-13	0.05	0.65	0.14	0.18	0.16	0.13	**0.26**	**0.07**
IL-1RA	0.09	0.39	0.05	0.62	0.07	0.52	0.09	0.55
CCL-22	0.04	0.7	0.02	0.89	-0.13	0.19	0.04	0.78
TGF-β	0.14	0.18	0.11	0.29	-0.08	0.41	-0.06	0.67

Table 1 shows Spearman associations (r) of total HIV-1 DNA, cell-associated HIV-1 RNA, plasma HIV-1 RNA by single copy assay, and intact proviral DNA with plasma cytokine levels (pg/mL).

383 HIV-1 ENVELOPES FROM PERSISTENT VIREMIA ON ART SHOW REDUCED ANTIBODY SENSITIVITY

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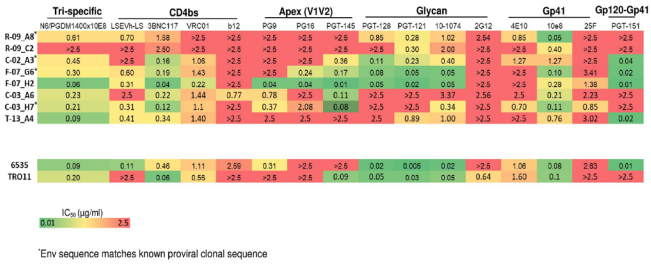
Background: Despite adherence to ART, clinically detectible viremia (HIV RNA >20 copies/ml) persists in some individuals and arises from large, infected cell clones. The mechanisms by which these clones escape immune responses is not defined but envelope (Env) resistance to antibodies (Abs) could contribute. To test this, we assessed the Ab neutralization sensitivity of HIV-1 Envs from 5 individuals on ART with non-suppressed viremia despite therapeutic drug levels and no evidence of drug resistance to the current ART regimen.

Methods: Single, full-length Env genes were amplified from plasma by RT-PCR. Amplicons were sequenced, ligated into a mammalian expression vector, and expressed as a pseudovirus (PSV) from HEK293T cells. A luciferase-based assay was used to measure the neutralization sensitivity of the plasma sequence-derived PSVs against a panel of 16 monoclonal antibodies (mAbs) directed to the CD4 binding site (CD4bs; VRC01, 3BNC117, b12, LSEVh-ls), V1V2 apex (PG9, PG16, PGT145), glycan (2G12), V3-glycan (PGT-121, 10-1074, PGT-128), gp120-gp41 interface (PGT-151), the membrane-proximal external region (MPER) of gp41 (10e8, 4e10, and 2F5), and a tri-specific antibody (N6/PGDM1400x10E8) directed to the CD4bs, V1V2 apex, and MPER binding sites.

Results: 40 unique Envs from 5 donors (R-09, C-03, C-02, T-13, F-07) were assessed. In general, the Envs tested were more resistant to Ab neutralization than a tier 1 (6535) or a tier 2 (TRO11) subtype B PSV (Table 1). Specifically, the Envs were more resistant to CD4bs, Gp41, and Apex mAbs but more sensitive to V3-glycan mAbs. Donor R-09 had the most neutralization resistant Env sequences: both R-09 PSVs (R-09_A8 and R-09_C2) showed resistance to the 3 Apex mAbs (PG9, PG16 and PGT145) and CD4bs mAb VRC01. Additionally, R-09_C2 was the only PSV that was resistant to neutralization by N6/PGDM1400x10E8. Of the 16 mAbs tested, only 3BNC117 and 10e8 potently neutralized all the PSVs.

Conclusion:
Plasma-derived Envs from individuals with persistent viremia on ART exhibit reduced sensitivity to mAbs targeting CD4bs, Gp41, and Apex, compared to tier 1 and 2 Envs. 3BNC117 and 10e8, however, neutralized all PSVs assayed, indicating therapeutic potential for clearing persistent viremia in the individuals studied.

Table 1. Neutralization sensitivity of plasma-derived HIV-1 envelopes from donors with residual viremia on ART



*Env sequence matches known proviral clonal sequence

384 MODELING HIV RESERVOIR DECLINE AFTER ART INITIATION AS A FUNCTION OF NK CELL FEATURES

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Background: A major challenge in the development of HIV curative strategies is the formation of viral reservoirs that are not eradicated with antiretroviral therapy (ART). Understanding mechanisms that determine HIV reservoir size may inform development of effective cure approaches. As natural killer (NK) cells may contribute to control of HIV infection, we hypothesized that NK cells may affect reservoir size.

Methods: To evaluate the association between NK cells and HIV reservoir, we used mass cytometry to profile NK cells from 50 people with HIV on suppressive ART in AIDS Clinical Trials Group study A5321. NK cell repertoire was assessed at time of study entry (median of 7.1 years after ART initiation) and 24 and 48 weeks later. Prior to ART initiation, one year following ART initiation, and at study entry, we assessed inflammatory markers and markers of HIV persistence (cell-associated DNA (CA-DNA), cell-associated RNA and HIV RNA by single copy assay). T cell responses to peptide pools were assessed at study entry.

Results: In participants on chronic ART, the NK cell repertoire was stable as assessed by expression patterns of NK cell activation and differentiation markers at study entry, week 24, and week 48. At study entry, there was no significant correlation between on-ART NK cell diversity and any of the on-ART HIV reservoir measures. We next evaluated whether NK cell features, inflammatory markers, or T cell responses can explain the reduction in $\log_{10}$-transformed HIV

DNA levels between the pre-ART time point and one year post ART initiation (CA-DNA reduction). We performed a supervised multivariate regression using the least absolute shrinkage and selection operator (LASSO). This approach selected the expression of perforin, CD38, 2B4, TIGIT, and CD96 on NK cells and the T cell response to "nef, tat, rev" peptide pools as the best explanatory variables for the prediction of CA-DNA reduction (see Table).
Conclusion: Here we show that specific NK cell marker expression levels and T cell responses can be used as explanatory variables in the regression analysis of the decline in HIV DNA levels following ART initiation. These observations suggest that specific NK cell features may drive an enhanced response to infected cells in the context of treatment initiation. Harnessing this potential may lead to the development of novel therapeutic strategies aimed at a functional cure for HIV.

Table: Features predictive of decline in reservoir following treatment initiation.
(positive coefficient corresponds to features predictive of greater reservoir decline, negative coefficient to those associated with a smaller reservoir decline)

Predictive Variable	Lasso coefficients in a model aimed at regression of the CA-DNA reduction following ART initiation	Pearson correlation coefficients with CA-DNA reduction following ART initiation
Perforin	2.6	0.35
CD38	-1.2	-0.31
2B4	0.95	0.33
TIGIT	0.81	0.29
CD96	0.75	0.36
Nef,tat,rev response	0.70	0.43

385 HIV-1 RESERVOIR SIZE CORRELATES TO PD-1 EXPRESSION IN MEN, BUT NOT WOMEN, IN UGANDA

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Background: There is evidence to suggest that HIV-1 latency varies by sex; women have been reported to have fewer CD4 T cells containing HIV-1 provirus, lower levels of residual viral activity in resting CD4 T cells (rCD4), and lower T cell activation. Immunologic characteristics that correlate with latent reservoir size have been used to inform cure strategies, but these studies have been performed in predominantly male cohorts. We sought to determine if immune correlates of reservoir size differed by biological sex.
Methods: Blood samples were collected from HIV-1+, ART-suppressed (<40 copies/ml for >1 year) adults living in Rakai, Uganda (n=42 females, n=20 males). The frequency of rCD4 containing replication competent provirus was estimated by quantitative viral outgrowth assay (QVOA). 14 soluble immune biomarkers were measured in plasma using custom multiplexed immunosorbent assays (MesoScale Discovery) and T cell memory subsets, activation and exhaustion markers, and effector T cell function were quantified by flow cytometry. Regression analysis was used to identify immune characteristics associated with reservoir size according to biological sex.
Results: Women and men were similar in terms of age, HIV-1 subtype distribution (A, D and recombinants), nadir CD4, pre-ART viral load and duration of viral suppression on ART. Compared to men, women had significantly higher serum concentration of D-dimer (272.8 vs. 130.1 ng/ml, $p<0.01$) and there was a trend ($p<0.1$) towards a lower proportion of IL2+ CD8 T cells (1.85 vs. 4.31%) and effector memory CD4 T cells (1.88 vs. 3.44%). Consistent with prior reports, among men reservoir size correlated positively with PD-1 expression on CD4 T cells ($r = 0.04$, $p<0.05$). However, this association was not observed in women. Among women, reservoir size correlated positively with CD8 and CD4 T cell effector function (IL2 and TNFa production, all $p<0.05$).
Conclusion: These data identify distinct immunologic correlates of the replication competent HIV-1 reservoir in men and women. Whether these measures are biomarkers or imply differential immune control/response to the reservoir is unknown. This is important to consider as interventions target immune checkpoint molecules, such as PD-1, for latency reversal and immune stimulation. Globally, females make up more than half of all individuals infected with HIV-1, and cure studies must be adequately powered to examine efficacy in both sexes.

386 EFFECT OF TIM-3 BLOCKADE ON T CD8+ AND NK CELLS IN ART-TREATED HIV-INFECTED PATIENTS

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Background:TIM-3 is a large transmembrane inhibitory receptor that is expressed in multiple cells of the immune system, including T-CD8+ cells and NK cells. Galectin-9 that has been described as a potent mediator of HIV transcription and reactivation constitutes one of the most important ligands of TIM-3.The purpose of this study was to analyze the effect of TIM-3 blockade on the specific HIV-1 CTL response of T-CD8+ cells and NK cells from HIV-infected-patients.
Methods: We included 10 ART-treated, HIV-1 infected donors from whom we obtained 200 mL of peripheral blood for the isolation of T-CD4+, T-CD8+ and NK cells. We cocultured the isolated T-CD4+ cells with T-CD8+ cells and NK cells in a 1:1 ratio. To evaluate the impact of TIM-3 blockade on the HIV-suppressive capacity of T-CD8+ cells we used a specific antibody against TIM-3. The impact of TIM-3 blockade was determined by measuring p24 levels in the supernatants of the cocultures at day 7 and day 10. To analyze the effect of Galectin-9 (natural ligand of TIM-3), p24 levels were compared in cocultures with or without the addition of exogenous Galectin-9
Results: The 10 patients had plasma HIV RNA <50 copies/mL with a mean T-CD4+ 661 cells/mm_3 and mean T-CD8+ 920 cells/mm_3. We observed a poor HIV suppressive capacity of T-CD8+ cells with a mean p24 decrease of 0.9 log. However it was significantly improved after TIM-3 blockade (mean 2.4log), mean difference 1.5log (IQR, [0.4–2.20], p=0.007). No differences were observed with the presence of NK cells in the coculture (mean difference with and without blockade, 1.15log [0.49-1.69], p=0.011). The addition of Galectin-9 did not change the effect of TIM-3 blockade (mean difference, 1.25log [0.77-1.42], p=0.012).
Conclusion: We demonstrated that the blockade of TIM-3 improves the CTL response of the T-CD8+ cells of ART-treated HIV-infected patients. No negative effects were observed with the same blockage in NK cells. Galectin-9 addition does not have impact on the response. A combination of Galectin-9/TIM-3 could be evaluated as an effective shock and kill strategy in HIV-eradication.

Table: Features predictive of decline in reservoir following treatment initiation.
(positive coefficient corresponds to features predictive of greater reservoir decline, negative coefficient to those associated with a smaller reservoir decline)

Predictive Variable	Lasso coefficients in a model aimed at regression of the CA-DNA reduction following ART initiation	Pearson correlation coefficients with CA-DNA reduction following ART initiation
Perforin	2.6	0.35
CD38	-1.2	-0.31
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TIGIT	0.81	0.29
CD96	0.75	0.36
Nef,tat,rev response	0.70	0.43

387 REDUCED MEMORY, FUNCTIONAL CONNECTIVITY IN 41- TO 70-YEAR-OLD HIV+ APOE E4 CARRIERS

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Background: ApoE ε4 is the strongest genetic risk factor for late onset Alzheimer's disease. In people with HIV (PWH), the potential impact of ApoE ε4 on brain structure and function remains to be determined. Older PWH ApoE ε4 carriers may experience additional impairment in brain structure and function compared to age-matched PWH non-carriers; however, results are unclear for middle-aged PWH. Moreover, the interactions between ApoE ε4 status and HIV disease severity are largely unknown.
Methods: Ninety-nine PWH participated in a cross-sectional study (56.2±6.5yrs, range 41-70yrs, 27 females). A comprehensive 7-domain neuropsychological (NP) test battery was administered and HIV-Associated Neurocognitive Disorders (HAND) diagnoses were assigned according to Frascati criteria. Structural MRI and resting-state functional MRI (functional connectiveity, FC) were collected. All statistical analyses were performed after controlling for demographics, and additional MRI-specific confounding factors were accounted for in the MRI data analysis.

Results: Between ApoE ε4 carriers (n=26) and non-carriers (n=73), there were no significant differences in age, education, sex, race, HIV disease, HAND diagnosis, and most individual NP test scores, except for memory performance measured by the Hopkins Verbal Learning Test–Revised (HVLT-R). Carriers had significantly lower delayed recall and retention score than non-carriers ($p<0.05$), but there was no interaction between age and ApoE ε4 status. For MRI, there was no difference in gray matter volume or cortical thickness between carriers and non-carriers. In contrast, the FC between the right caudate and right hippocampus was significantly lower in carriers ($p=0.0002$) and correlated with HVLT-R retention ($p=0.015$), along with a significant interaction between ApoE ε4 genotype and CD4 nadir ($p=0.026$). A similar marginal, but non-significant, effect was found in the FC between the left caudate and left hippocampus.

Conclusion: In this sample of PWH (41-70 years old), ApoE ε4 was associated with reduced verbal memory performance and disrupted FC between the caudate and the hippocampus, suggesting that ApoE ε4 may be a genetic risk factor for memory impairment in PWH. In addition, the interaction between ApoE ε4 allele and CD4 nadir on FC suggests that the severity of HIV disease may exacerbate the effect of ApoE ε4 on brain health, resulting in an increased risk of dementia and Alzheimer's disease later in life.

388 NEUROCOGNITIVE AND VOLUMETRIC CHANGES AFTER 24 WEEKS OF DTG/3TC/ABC DISCONTINUATION

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Background: Dolutegravir/lamivudine/abacavir (DTG/3TC/ABC) fixed dose combination (FDC) discontinuation is associated with improvement of neuropsychiatric (NP) symptoms. However, limited data exist on the effect of DTG/3TC/ABC discontinuation on neurocognitive (NC) function and brain structure. We assessed NC function and neuroimaging in participants enrolled in the DREAM study, a multicenter clinical trial designed to evaluate the reversibility of NP symptoms in virologically suppressed patients on DTG/3TC/ABC switching to Cobicistat-boosted elvitegravir/emtricitabine/tenofovir alafenamide FDC (E/C/F/TAF). Clinical results from this trial have demonstrated significant improvements in NP symptoms when switching from DTG/3TC/ABC to E/C/F/TAF.

Methods: All participants performed a comprehensive NC assessment (7-domain) following Frascati criteria and a 3-Tesla brain MRI on day 1 and 24 weeks after switching therapy. Global NC performance was assessed using the global deficit score (GDS). Changes in NC function and brain volumes were determined using neuromorphometrics atlas and analyzed using t-test. Multiple comparisons testing was corrected using the false discovery rate (FDR) adjustment.

Results: 38 participants, mostly Caucasian male of middle age with good immunological status, normal NC function that received DTG/ABC/3TC for a mean time of 1.45 years, were included. At week 24 after switching to E/CF/TAF, we observed significant improvements in the global NC function (mean±SD GDS change: 0.12±0.32; $p=0.029$) and in the speed of processing (-0.26±0.86; $p<0.001$), delayed recall (-0.33±0.8; $p=0.019$) and motor (-0.51±0.85; $p=0.001$) domains. Significant changes in several brain volumes were observed (table). After FDR adjustment, only the changes in the right frontal pole, a cerebral region involved in information processing, emotion and motivated behaviors, remained significant ($p<0.03$). We also observed a significant correlation between GDS changes and volume changes in the right superior occipital gyrus ($r=0.53$)

Conclusion: Our study suggests that switching from DTG/3TC/ABC to E/C/F/TAF was associated with an improvement in NC functioning, especially in speed of processing, delayed recall and motor domains. Brain volumes changes observed in our study could be useful to delve into the pathological mechanisms of DTG/3TC/ABC-related NP toxicity.

Table: Significant crude changes in brain volumes (mm^3) after switching ABC/3TC/DTG to E/C/F/TAF

Left Brain	Volume at day 1 *mean±SD*	Volume at week 24 *mean±SD*	P value	Right Brain	Volume at day 1 *mean±SD*	Volume at week 24 *mean±SD*	P value
Cuneus	3.81±0.48	3.9±0.5	p=0.004	**Cuneus**	4.3±0.52	4.37±0.55	p=0.02
Calcarine	3.38±0.54	3.52±0.66	p=0.01	**Calcarine**	3.5±0.51	3.64±0.59	p=0.004
Inferior occipital gyrus	5.66±0.59	5.74±0.59	P=0.02	**Inferior occipital gyrus**	5.95±0.68	6.02±0.64	p=0.02
Cerebellar vermal lobules I-V	1.72±0.19	1.8±0.19	p=0.004	**Cerebellar vermal lobules I-V**	1.53±0.16	1.6±0.17	p=0.003
Basal cerebrum and forebrain	0.7±0.09	0.72±0.08	p=0.03	**Inferior frontal angular gyrus**	3±0.43	2.96±0.42	p=0.004
Lingual gyrus	7.4±0.89	7.54±0.83	P=0.03	**Frontal pole**	3.17±0.42	3.09±0.4	P<0.001
Accumbens	0.43±0.07	0.44±0.06	p=0.006	**Caudate**	2.94±0.46	2.96±0.46	p=0.008
Central operculum	4.01±0.61	4.04±0.56	P=0.04	**CSF**	0.15±0.04	0.13±0.04	p=0.006

389 HIV IS INDEPENDENTLY ASSOCIATED WITH BRAIN MRI WHITE MATTER HYPERINTENSITIES

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Background: Brain white matter hyperintensities (WMH) are nonspecific in etiology but occur commonly in the setting of HIV infection. Their relevance to disease remains uncertain as previous studies have used various methods of estimation in heterogenous groups of people with HIV (PWH). We evaluated the frequency, severity and clinical correlations of WMH in the setting of well controlled HIV infection, using the Fazekas visual rating scale.

Methods: Research protocol images from brain 3D fluid attenuated inversion recovery (FLAIR) on a 3T MRI were reviewed to determine the Fazekas score (total score of 0-6, 0-3 for periventricular hyperintensity and 0-3 for deep WMH) in people with HIV (PWH) with well controlled infection (antiretroviral therapy for at least one year and plasma viral load <200 copies/ml) and in controls. Simple linear regression was used for covariate selection, and forward stepwise regression was performed to evaluate the effect of HIV on Fazekas scores.

Results: Fazekas scores were determined in 203 PWH and 58 controls. The PWH group had a higher mean total Fazekas score compared to controls (2.2±1 vs. 1.8±1.3, $p=0.008$). Age, history of cocaine abuse, prior smoking history, acetylsalicylic acid use, hepatitis C virus antibodies, higher hemoglobin A1C level (A1C), and lower estimated glomerular filtration rate were all associated with a higher Fazekas score in PWH and/or control group. The final forward stepwise regression model included age and history of cocaine abuse (n=200, $R2=0.24$), or age and A1C (n=242, $R2=0.27$). In both models, the adjusted mean total Fazekas score remained higher in the PWH group compared to the control group [2.3 (95%CI 2.1-2.5) vs. 2.0 (95%CI 1.7-2.3) with $p=0.046$ adjusted for age and cocaine abuse, 2.2 (95%CI 2.0-2.3) vs. 1.8 (95%CI 1.5-2.0) with $p=0.0039$ adjusted for age and A1C]. No specific cognitive measure correlated with the Fazekas score. In the PWH group, CD4 nadir <200 cells/ml was associated with a higher Fazekas score [age-adjusted mean 2.4 (95%CI 2.2-2.6) vs. 2.0 (95%CI 1.9-2.2), $p=0.01$].

Conclusion: HIV infection contributes to the extent of brain WMH, even in the setting of well controlled infection. Prior immunosuppression evidenced by lower nadir CD4 partially explains this association. The cohort is undergoing serial MRI scans and neuropsychological testing to evaluate the long-term clinical effects of WMH.

390 BRAIN AGE BASED ON SLEEP ENCEPHALOGRAPHY IS ELEVATED IN HIV+ ADULTS ON ART

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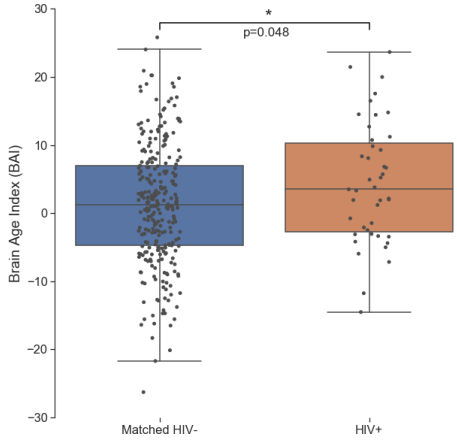
Background: Co-morbidities and increased inflammation associated with HIV have raised concern for excess brain aging, yet diagnostic biomarkers for brain aging are lacking. Our lab developed a machine learning model that estimates age from sleep EEG (brain age, BA), which reliably predicts chronological age

(CA) in healthy adults. The difference between BA and CA, termed the brain age index (BAI), independently predicts mortality, and is increased by cardiovascular comorbidities and dementia. Here, we assessed BAI in HIV+ compared to matched HIV- adults.

Methods: Sleep EEGs from 43 HIV+ adults on ART were gathered and matched to controls (HIV-, n=284) by age, gender, race, alcoholism, smoking and substance use history. We compared BAI between groups and used additional causal interference methods to ensure robustness. Individual EEG features that underlie BA prediction were also compared. Finally, we performed a sub-analysis of BAI between HIV+ with or without a history of AIDS.

Results: After matching, mean CA of HIV+ vs HIV- adults were 49 and 48 years, respectively (n.s.). The mean HIV+ BAI was 3.04 years higher than HIV- (4.4 vs 1.4 yr; p=0.048). We found consistent and significant results with alternative causal inference methods. Several EEG features predictive of BA were different in the HIV+ and HIV- cohorts. Most notably, non-REM stage 2 sleep (N2) delta power (1-4Hz) was decreased in HIV+ vs. HIV- adults, while theta (4-8Hz) and alpha (8-12Hz) power were increased. Those with AIDS (n=19, BAI=4.40) did not have significantly different BAI than HIV+ without AIDS (n=23, BAI=5.22). HIV+ subjects had higher rates of insomnia (56% vs 29%, p<0.001), obstructive apnea (47% vs 30%, p=0.03), depression (49% vs 23%, p<0.001), and bipolar disorder (19% vs 4%, p<0.001).

Conclusion: HIV+ individuals on ART have excess brain age compared to matched controls using a sleep EEG-based model of brain aging. This excess brain age is partially due to the relative reduction in delta power during N2, suggesting decreased sleep depth in HIV+ subjects. These results suggest sleep EEG could be a valuable brain aging biomarker for the HIV population.



391 NEUROINFLAMMATION AND REACTIVE GLIOSIS DURING LONG-TERM cART INITIATED IN ACUTE HIV

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Background: We previously revealed neuroinflammation on magnetic resonance spectroscopy (1.5T MRS) in acute HIV infection (AHI). The aim of this study is to use high field proton MRS (3T MRS) to assess neuroinflammation before and after long-term cART (up to 60 months) initiated during AHI.

Methods: Individuals with AHI completed single voxel proton brain MRS on a 3T Phillips MR scanner using standard single voxel double spin echo data acquisition with an echo time of 35ms and a 4-test neuropsychological assessment (NPZ4) before cART (M0, n=109) and at 6 months (M6, n=45), 24 months (M24, n=62) and 60 months (M60, n=25) after cART initiation with sustained viral suppression. A subset of 31 individuals completed both NPZ4 and MRS at M0 and M24. Thai HIV negative participants were included as healthy controls (HC, n=21). Single voxel MRS was acquired from the basal ganglia (BG) and the left frontal white matter (WM) regions. LCModel was used to quantify brain metabolites using GAMMA simulated reference basis sets. The LCModel outputs were corrected for T1, T2 relaxation times as well as gray, white and CSF contribution within the MRS voxel of interests. Non-parametric Mann-Whitney and Wilcoxon test were used for comparisons.

Results: All 109 participants were male. At baseline, median age (27; range = 18-65), self-reported duration of infection (19 days; range = 3-49), CD4 count (343; range = 101-1302 cells/mm$_3$), and plasma HIV RNA 6.06 (log, copies/mL). In BG, total choline (tCho) and glutamate (Glu) were elevated at M0 compared to HC (p<0.0001) and decreased to HC levels after cART (Figure 1a). Median CD4 count, plasma HIV RNA, and NPZ4 improved significantly with cART. Within the subset of 31 matched individuals, tCho was elevated at M0 (p=0.0002) and remained elevated after 24 months of cART (p=0.048) compared to HC. Baseline levels of WM myo-inositol (Ins) were similar between groups (HC and M0), but differed at M24, with higher levels observed among AHI compared to M0 (p<0.0001, Figure 1b).

Conclusion: This high field (3T) MRS study reveals distinct signatures of neuroinflammation in treatment naïve AHI. (increased tCho and Glu) and after 24 months of cART (increased tCho and Ins). The development of increased Ins after cART suggests the possibility of reactive gliosis despite early cART.

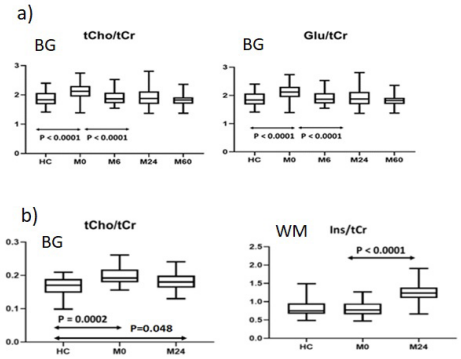


Figure 1a: tCho/tCr and Glu/tCr from the basal ganglia between HC and HIV at M0, M6, M24, and M60. 1b: Basal ganglia tCho/tCr and white matter Ins/tCr of the 31 subset between HC and HIV at M0 and M24.

392 LOWER PHYSICAL ACTIVITY AND FITNESS LEVELS ARE ASSOCIATED WITH SMALLER BRAIN VOLUMES

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Background: The average age of people living with HIV (PLWH) is now greater than 50 years. Older PLWH are more sedentary and more frail than similarly aged HIV-seronegative (HIV-) people. Previous studies in HIV- individuals have shown an association between sedentary lifestyle and smaller brain volumes. In this study, we evaluated the relationship between physical activity and fitness levels, and brain volumes in PLWH.

Methods: Fifty-six older (>/=50 years old), sedentary (exercise <2 hours a week), virologically controlled (< 50 copies/mL) PLWH underwent 7-day activity monitoring (wrist actigraphy, Actigraph), graded exercise testing on a cycle ergometer (VO2max), structural neuroimaging using MRI, and neuropsychological tests examining multiple domains, including executive function, learning, memory, psychomotor speed and language. We measured the relationship between VO2max, levels of physical activity and nine brain regions commonly affected by HIV (thalamus, caudate, putamen, hippocampus, amygdala, cerebellum, cortical white matter, and total and subcortical gray matter), using partial correlations after correcting for age, race, and sex.

Results: By design, subjects were sedentary and spent 89% of the day in sedentary or light activity and only 11% of the day in moderate physical activity. Physical fitness (VO2max , ml/kg/min) was positively correlated with brain volumes including thalamus (p= .009), temporal lobe (p= .025), and total gray matter (p= .017). In addition, actigraphy measures of percent of time spent in sedentary activity also correlated inversely with brain volumes in cortical white matter (p= .025), thalamus (p= .015), caudate (p= .014), and putamen (p= .027). In contrast, we did not observe any significant relationships between VO2max or actigraphy measures of percent sedentary time and neuropsychological performance.

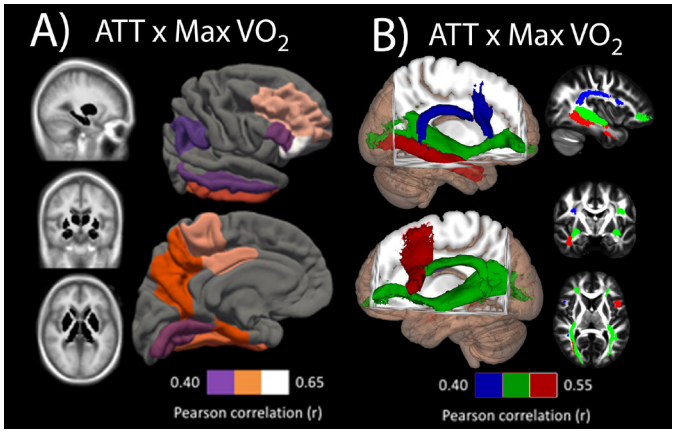
Conclusion: These results suggest that lower physical activity within sedentary PLWH is associated with smaller brain volumes (subcortical and cortical).

These subtle changes on neuroimaging were not captured using standard neuropsychological tests and suggest that neuroimaging may be important in the evaluation of sedentary PLWH. Future studies should evaluate the effects of exercise training or increasing physical activity on brain volumes in sedentary PLWH.

393 ACTIVE LIFESTYLE IS ASSOCIATED WITH BETTER BRAIN FUNCTION IN PERSONS LIVING WITH HIV

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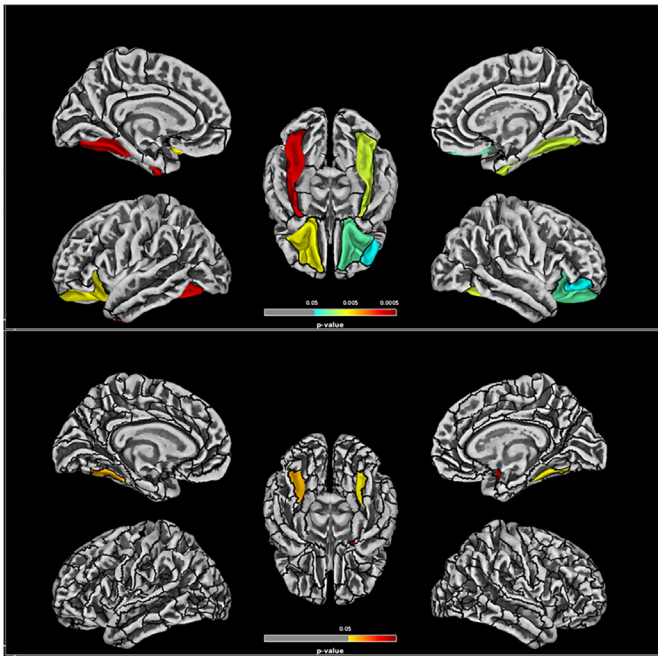
Background: Mortality due to HIV has dramatically reduced due to the introduction of combination anti-retroviral therapy (cART). Despite virologically suppression many PLWH still develop cognitive impairment can occur. On average, PLWH have reduced physical exertion and a reduction in active lifestyles. A reduction in physical function may affect both brain function and structure in PLWH. We evaluated whether physical fitness (as measured by VO2 maximum) relates to metrics of brain structure (diffusion tensor imaging (DTI)) and function (arterial transit time (ATT)).
Methods: Forty-one sedentary elderly virologically well-controlled PLWH underwent neuroimaging (DTI and CBF). Each participant completed a graded exercise test on a cycle ergometer with 12-lead electrocardiography. Measurements of oxygen uptake, carbon dioxide production, heart rate, and blood pressure will be continuously monitored during testing to compute peak VO2. DTI fractional anisotropy (FA) was processed using tract-based spatial statistics FSL 5.0.9. CBF was processed with in-house scripts to calculate regional arterial transit time (ATT) that corresponds to how long the blood takes to perfuse into the brain tissue. ATT maps were registered to their corresponding T1 scan and regional volumes were extracted based on Freesurfer 5.3 parcellations. Partial correlations were performed between VO2 max and imaging metrics for both structure and function. Each correlation was adjusted for age and gender with a statistical threshold set at $p<0.05$.
Results: FA was positively associated with VO2 max in the Frontal Aslant Tract, frontal occipital fasciculus, inferior longitudinal fasciculus and superior longitudinal fasciculus (Figure 1B). ATT positively associated with VO2 max in several gray matter regions that correspond to the white matter projections (Figure 1A). The strongest correlations were seen in the paracentral, posterior cingulate, and dorsal lateral prefrontal regions.
Conclusion: We found that current fitness associated with both structure and function in an aviremic sedentary older PLWH. Higher VO2 max related to improved brain structure and function diversely throughout the cortex. Together, this bolsters the claim that physical fitness may improve brain integrity of virologically stable HIV participants.



394 EFFECTS OF PERINATAL HIV INFECTION ON THE CORTICAL THICKNESS IN YOUNG ADULTHOOD

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Background: Brain atrophy has been observed in perinatally HIV-infected patients (PHIV) despite initiation on combined antiretroviral treatment (cART), but studies measuring cortical thickness (CT) are limited. We aimed to evaluate the neurologic state and CT of immunovirological stable PHIV youths with good daily functioning.
Methods: A total of 25 PHIV patients on cART and 25 healthy controls (HC) matched by age, sex, level of education and socioeconomic status underwent a Magnetic Resonance Imaging scan. CAT12 toolbox was used to extract cortical thickness values from T1w images using parcellations from to two atlases (Human Connectome Project multi-modal parcellation (HCP-MMP1) and Desikan–Killiany atlas (DK40)). Mean thickness values for all ROIs in both atlases were compared between HIV+ and HC with a two-independent-samples t-test with age and gender as covariates.
Neuropsychological assessments were conducted, which consist of fluid intelligence (FI) scale for overall functioning, and composite Z-score for executive functions (EFZ-10). Psychopathological symptoms were also obtained.
Results: 50 participants were included (60% females, median age 20 years [IQR 19-23], 64% caucasian). Regarding PHIV: 40% had history of AIDS (3 had encephalopathy), median CD4% nadir 11.9% (IQR 5-17). At assessment, 84% had viral load <50 cp/ml (uVL), median viral load in detectable patients 416 cp/ml (IQR 185-530), median CD4 687 cel/mm_3 (IQR 497-830), median time on cART 17.12 years (IQR 14.82-18.54) and median time with uVL 10.85 years (6.83-13.13). No significant differences regarding FI, EFZ-10 or psychopathological symptoms were found.
When comparing CT, significant differences ($p<0.05$, Holm-Bonferroni corrected) were found using both atlases, where PHIV-infected patients showed thinner cortices compared with their non-HIV peers. According to HCP-MMP1, differences were found in left and right Ventral Visual Complexes and right Pirform cortex. Based on DK40, differences were located in left and right fusiform gyri, left and right lateral-orbitofrontal gyri and right parsobitalis gyrus. No significant differences were found in the opposite contrast (HIV+ > HC).
Conclusion: Despite good control of HIV infection and no differences in neurocognitive evaluation, PHIV showed thinner cortices of the temporal, orbito-frontal and occipital lobes. Longitudinally studies are required to determine the impact of HIV on brain in PHIV patients during adulthood.



395 EFFECT OF ANTICHOLINERGIC MEDICATIONS ON BRAIN INTEGRITY IN OLDER HIV-POSITIVE ADULTS

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Background: The aging population of people living with human immunodeficiency virus (HIV) (PLWH) has resulted in an increase in comorbidities requiring medications. While anticholinergic (AC) medications are sometimes prescribed to older adults for a limited period of time, they have been linked to a greater risk of cognitive impairment in the HIV- population. The effect of AC in older PLWH with regards to brain volumetrics has not yet been well-established. We compared AC burden between older (age ≥50 years) PLWH and HIV- controls (HC) and assessed the interaction of HIV status and AC burden on neuropsychological performance (NP) and brain volumes cross-sectionally and longitudinally at two-year follow-up.
Methods: The Anticholinergic Cognitive Burden Scale (ACB; Boustani et al., 2008) was used to categorize 105 HC and 215 PLWH with undetectable viral load (<50 copies/mL) aged ≥50 years as low (ACB score ≤3) or high AC burden (ACB score >3). NP (learning/memory, executive function (EF), psychomotor speed (PM)) and brain volumetrics were acquired. A chi-square test compared rates of high AC burden in HC and PLWH. General linear models examined main effects and interactions of HIV status and ACB group on NP and within the frontal, parietal, temporal, occipital lobes; cortical, subcortical, and total gray matter (GM); and total white matter volumes. Linear mixed models examined change in NP and volumes over two years for a subset of 30 HC and 94 PLWH who had no change in AC burden.
Results: PLWH (n=53; 25%) had a greater proportion of individuals with high ACB compared to HC (n=13; 12%) (p=0.01). Overall, PLWH had significantly worse NP and greater reductions in brain volumes compared to HC (p <.001). Individuals with a higher ACB had worse NP and greater reductions in brain volumes compared to individuals who had a low ACB. No significant interactions were observed between HIV status and ACB (p >.05). Longitudinally, both HC and PLWH who had a higher ACB displayed a greater decline in subcortical GM volume over time compared to individuals with low ACB (Figure 1). The observed decline in brain volumetrics significantly correlated with worse PM over time.
Conclusion: The significant effect of higher ACB on NP and GM volumes in older adults (regardless of HIV status) supports concerns over their continued use in older individuals. Although both HIV and high ACB are associated with worse NP and reductions in brain volumetric, no interaction was observed.

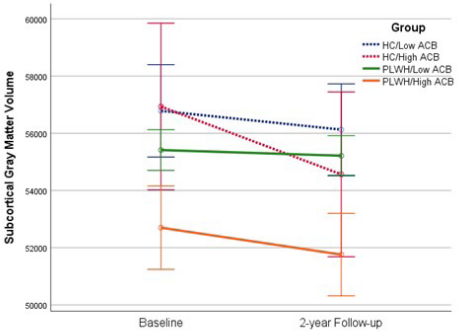


Figure 1. HIV- controls (HC) and persons living with HIV (PLWH) who had a higher anticholinergic cognitive burden (ACB) had lower subcortical gray matter volumetrics. Individuals with a higher ACB demonstrated significantly more loss of subcortical gray matter volume compared to individuals with lower ACB (regardless of HIV serostatus).

396 EFFECTS OF VIRAL LOAD ON NEUROIMAGING AND NEUROPSYCHOLOGICAL PERFORMANCE

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Background: Previous studies have investigated the relationship between viral load (VL) and brain atrophy in people with HIV (PLWH). However, these studies often combine PLWH on and off antiretroviral therapy (ART) including those with and without detectable VL. Here we compare brain volumetrics and neuropsychological performance (NP) in HIV- controls (HIV-) and PWHL receiving ART who are further categorized into: 1) virologic suppression (VS, VL ≤ 20 copies/mL), low-level viremia (LL, 21 - 200 copies/mL) and virologic failure (VF > 200 copies/mL).
Methods: 128 HIV- (mean age 42.4, 50% male) and 239 PLWH (mean age 43.7, 62% male) on stable ART regimen completed NP testing (executive function, learning and memory, psychomotor speed, and language domains) and structural neuroimaging. Of the 239 PLWH, 175 (73.2%) demonstrated VS (≤ 20 copies/mL) and 64 had detectable VL (38 LL, 26 VF). NP scores, cortical volumes (frontal, occipital, parietal, and temporal) and subcortical volumes were converted into demographically-corrected z-scores. T-tests analyzed differences in NP domains, global cognition and volumetric z-scores between PLWH and HIV-. Analyses of variance with post-hoc Tukey's tests were used to examine differences in NP scores and volumetrics between groups.
Results: In general, PLWH had significantly decreased NP z-scores in the executive function, language, and psychomotor speed domains as well as significantly smaller subcortical volumes compared to HIV- (p <0.05). When PLWH were subgrouped by VL, results indicated no significant differences between the VS, LL, and VF groups in any of the NP domains, global cognition or volumetric z-score (p¬ >0.05). The VS group had significantly lower executive function and language z-scores compared to HIV-, and both the VS and LL groups had lower subcortical z-scores compared to HIV-. The VF group exhibited larger subcortical volume compared to the LL group, although this was non-significant (Figure 1).
Conclusion: Results suggest an HIV effect on subcortical volumes and NP scores but not a VL effect. Higher subcortical volumes in the VF group compared to the LL group may indicate inflammation, but increased group sizes are needed to determine if this effect is significant. The lack of a significant VL effect may signify that ART use is critical rather than viral suppression, but longitudinal studies are needed.

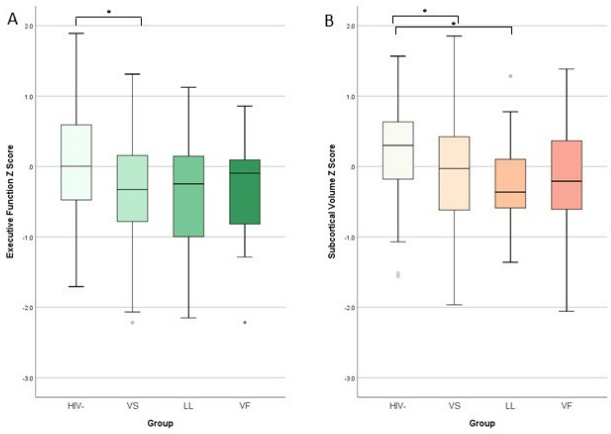


Figure 1. Executive function (A) and subcortical volume Z scores (B) by group (HIV- = HIV-negative controls; VS = virologic suppression (≤ 20 copies/mL); LL = low-level viremia (21 - 200 copies/mL); VF = virologic failure (> 200 copies/mL)).

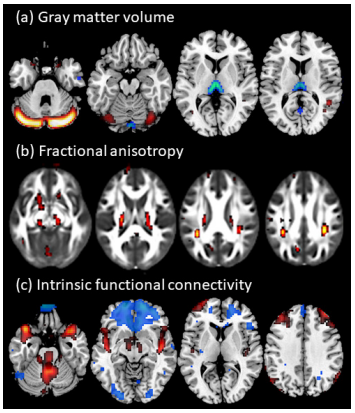
397 MULTIMODAL BRAIN ABNORMALITIES ASSOCIATED WITH COGNITIVE IMPAIRMENT IN HIV INFECTION

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Background: HIV-associated neurocognitive impairment (NCI) remains a prevalent comorbidity that impacts daily functioning and increases morbidity. While HIV infection is known to cause widespread disruptions in the brain, different MRI modalities have not been effectively integrated. This study applied 3-way supervised fusion to investigate how structural and functional co-alterations affect cognitive function.
Methods: Participants completed comprehensive neuropsychological testing and had a multi-modal MRI scan to acquire high-resolution anatomical, diffusion-weighted, and resting-state functional images. Pre-processed data was reduced using voxel-based morphometry (gray matter volume), probabilistic tractography (fractional anisotropy), and regional homogeneity (intrinsic functional connectivity), respectively. We applied multi-modal canonical correlation analysis with reference plus joint independent component analysis (MCCAR+jICA), using global neurocognitive functioning as the reference.
Results: The sample includes 70 HIV+ and 69 HIV- adults who were matched on age (M=38.7), gender (70% male), and race (68% African-American). HIV+ participants had lower global neurocognitive functioning (p=.005), with differences in the domains of learning (p=.006), memory (p=.006), and

executive function (p=.026). Figure 1 shows the independent joint component that significantly correlated with global neurocognitive functioning in all three modalities. Gray matter regions included thalamus and cerebellum. White matter regions included the cingulum tract of the cingulate and hippocampus, inferior and superior longitudinal fasciculus, and uncinate fasciculus. Functional regions included posterior parietal, lateral prefrontal, orbitofrontal, anterior cingulate, precuneus, and insular cortices. HIV+ status was associated with lower gray matter volume (p=.038) and lower fractional anisotropy (p=.028) in this component. Duration of HIV disease and nadir CD4 cell count were also associated with gray matter volume and functional connectivity in identified independent components.

Conclusion: These results suggest that linked structural and functional deficits in several brain networks are related to HIV-associated NCI. As MRI becomes more commonplace in HIV care, multimodal fusion may provide neural biomarkers to support diagnosis and treatment of NCI.



398 IMPAIRED COGNITION AND REDUCED BRAIN VOLUMES IN YOUTH WITH BEHAVIORALLY ACQUIRED HIV

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Background: Behaviorally acquired HIV infection during adolescence and young adulthood occurs during key brain developmental processes (frontal lobe pruning, network selection). Our prior work suggests deep gray volumes are significantly lower in HIV+ youth vs historical controls; the magnitude of these differences are larger than those reported in adult HIV cohorts despite shorter infection durations and higher CD4+ T-cell nadirs. Here, we aim to compare cognition and deep gray volumes in 16-20-year-old youth with behaviorally acquired HIV versus age-, sex-, and demographically-matched uninfected controls.

Methods: Cross sectional analysis of seventeen 16-20-year-old Philadelphia youth with behaviorally acquired HIV (infected for ≥ 1 year) and 18 age-, sex-, and demographically-matched uninfected controls. Participants underwent brain MRI. Brain volumes were measured using FreeSurfer. To evaluate within-structure volumes, voxel-based volume differences between study participants and a standard age-matched atlas were calculated using deformation based T1 morphometry.

Results: HIV+ youth and uninfected controls were similar in age (median 20.0 vs 19.5 years), sex (94% vs 94% male), race (88% vs 94% African American), insurance status, and average alcohol and marijuana consumption. The median infection duration for HIV+ youth was 1.9 years (IQR 1.4-2.9), and median CD4 nadir was 410 cells/uL (IQR 335-478). 69% (11/16) of HIV+ youth qualified for a diagnosis of HIV-associated neurocognitive disorder, 9 with functional impairment. Total intracranial volume did not differ between HIV+ youth and controls, but HIV+ youth had 7% lower caudate volumes compared to controls (p=0.052); volume differences within the caudate were more pronounced in regions proximal to the CSF interface. Cognitive impairment was associated with lower thalamic volumes in HIV (p=0.002), but not in controls.

Conclusion: These data support the concept that youth with behaviorally acquired HIV have early volume loss in deep gray structures despite robust CD4+ T-cell counts, and that volume loss is associated with cognitive impairment. Larger longitudinal studies with adult comparators are needed to further define patterns of volume loss (and potential implications on pathophysiology), and to determine whether age-specific mitigation strategies are warranted in youth.

399 ALCOHOL USE IS ASSOCIATED WITH DEGRADATION OF BRAIN WHITE MATTER IN HIV INFECTION

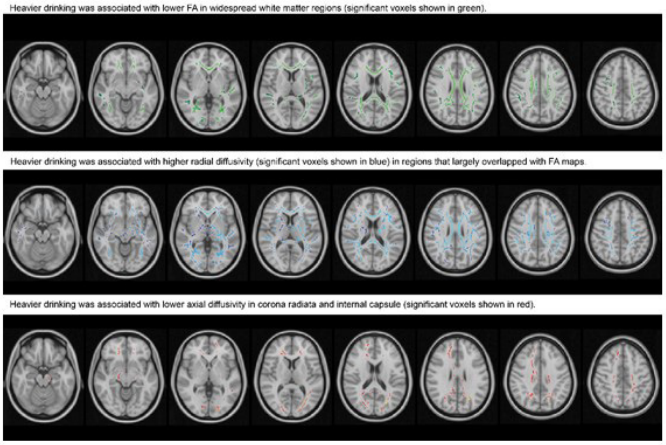
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Background: Heavy drinking and HIV infection are independently associated with damage to the brain's white matter. As most neuroimaging studies of people living with HIV (PLWH) exclude heavy drinkers, effects of alcohol use on white matter in the context of HIV are not well understood. We examined associations of current alcohol use, HIV status, and clinical characteristics with indices of white matter integrity in PLWH and seronegative controls.

Methods: PLWH and controls were recruited from an immunology clinic for a study of alcohol- and HIV-associated brain dysfunction. Participants were categorized as non-drinkers, moderate drinkers, or heavy drinkers per NIH guidelines. Diffusion tensor imaging was used to derive measures of fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD). Whole-brain voxelwise analyses were performed using tract-based spatial statistics (TBSS), corrected for multiple comparisons. Confirmatory region-of-interest (ROI) analyses were conducted to probe group differences.

Results: The sample of 108 participants (62 PLWH, 46 controls) averaged 45.2±11.1 years of age and was 42% female. Most PLWH were on antiretroviral therapy (94%) and were virally suppressed (69%). PLWH and controls were matched on rates of heavy drinking, smoking, and other drug use. In voxelwise analyses, heavier alcohol intake was significantly associated with lower FA, higher RD, and lower AD in widespread areas (p's<.05; Figure 1). ROI analyses confirmed that non-drinkers had higher FA than heavy drinkers in corpus callosum, cingulate gyrus, posterior thalamic radiation, and left external capsule (p's<.05). Non-drinkers had higher FA than moderate drinkers in genu and body of corpus callosum (p's<.05). Moderate drinkers had higher FA than heavy drinkers in body of corpus callosum, posterior thalamic radiation, and left external capsule (p's<.05). Older age extensively predicted lower FA (p<.05). Neither HIV status nor clinical characteristics were associated with FA, and the HIV by drinking group interaction was not significant (p's>.05).

Conclusion: Alcohol use significantly predicted white matter microstructural degradation in this sample of PLWH in care and seronegative controls. Results are consistent with a dose-dependent association of alcohol use with lower white matter microstructural coherence. The overlap between FA and RD maps points to dysmyelination as a possible mechanism. Findings underscore the need to address unhealthy alcohol use in HIV-positive and seronegative individuals.



400 MICROSTRUCTURAL MRI CHANGES ASSOCIATED WITH COGNITIVE IMPAIRMENT IN CONTROLLED HIV

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Background: Despite cART, cognitive impairment and brain MRI abnormalities are still prevalent in people with HIV (PWH). Diffusion tensor imaging (DTI) can be used to detect microstructural changes in both white matter (WM) and grey matter (GM), and it may be possible to detect subtle and early changes prior to neurocognitive decline. In this cross-sectional study, we investigated integrity of the brain parenchyma in virologically controlled PWH (HIV+) and socio-economically similar control subjects (HIV-). DTI parameters were also correlated with neuropsychological (NP) measures in both groups.
Methods: All participants underwent 3T MRI which included DTI at 2mm isotropic resolution and 30 diffusion directions, a comprehensive battery of NP testing, and clinical evaluation. Fractional anisotropy (FA) and mean diffusivity (MD) were determined from various regions of interest (ROIs). We analyzed group differences of FA and MD in various ROIs and conducted multivariate regressions with NP testing and DTI adjusted for age and sex.
Results: 134 HIV+ patients on long-term ART with viral load of <100c/mL and 47 HIV- controls were included in this study. In the HIV+ group, compared to HIV- controls, MD was higher (more abnormal) and FA lower (also more abnormal) in various WM ROIs including the cerebral WM (MD p=0.02, FA p=0.03). However, the white matter abnormalities were not associated with worse cognition in the HIV+ group (p=0.38 for overall T-score). Instead, it was the grey matter abnormalities that were associated with worse cognition including overall T-score (p=0.03), memory (p=0.02), and information processing (p=0.03).
Conclusion: DTI detected microstructural abnormalities in numerous brain parenchymal ROIs of HIV+ compared to HIV- participants. These changes are present even despite sustained virologic suppression with long-term ART. Both WM and GM were more abnormal in the HIV+ group, with the GM abnormalities more clearly associated with current NP outcomes in this cross-sectional study. Serial MRIs and NP testing with this cohort will evaluate whether the WM abnormalities are also associated with NP outcomes in the future.

	HIV+ (n=134)	HIV- (n=47)	p-value
Female sex, % (n)	31% (41)	49% (24)	0.016
Age, years ± SD	51 ± 9	50 ± 10	0.825
African American race, % (n)	64% (90)	67% (32)	0.803
Nadir CD4	217.1	-	-
Current CD4	641.3	-	-

401 COGNITIVE IMPAIRMENT AMONG HIV-INFECTED MEN WITH LONGITUDINAL FOLLOW-UP

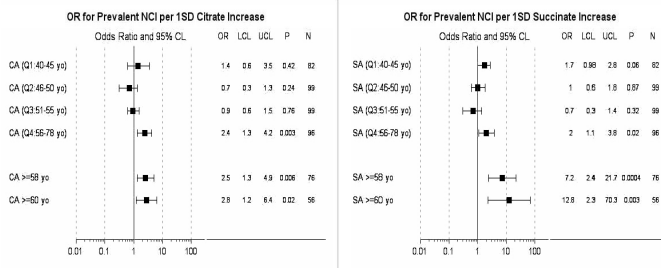
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Background: To control false discovery rate (FDR) in identifying cognitive impairment among individuals infected with HIV, the multivariate normative comparisons (MNC) method has been used to account for intercorrelations among cognitive domains. However, the existing MNC is for cross-sectional data and does not account for the intercorrelations among repeated visits. That is, the best predictor of future test performance is current test performance. This work developed a novel longitudinal MNC (LMNC) to classify cognitive status for individuals with multiple visits, yielding more accurate results than naïvely applying the cross-sectional MNC to each visit.
Methods: Data used in this work were collected before April 2017 among MSM from the Neuropsychological (NP) Substudy of the Multicenter AIDS Cohort Study. Six cognitive domains were evaluated bi-/semi-annually among these men: learning, memory, executive functioning, working memory & attention, motor speed & coordination, and speed of information processing. The final analysis included data from 22,900 visits by 3,701 men (mean age 34.9, 55.0% HIV+, mean 6.2 visits, mean follow-up 8.3 yrs) with complete data from all 6 domains. T-scores, at every domain, were adjusted for race, age, education and number of tests. HIV- men without comorbidities (n=922) were treated as healthy controls, and the LMNC was used to classify cognitive impairment among HIV- and HIV+ men. Also, the cross-sectional MNC was applied to each visit with and without Benjamini-Hochberg (BH) corrections.
Results: Among healthy controls the LMNC identified 5.5% with cognitive impairment. This suggests that the LMNC guarded FDR at the pre-determined 5% level. With the cross-sectional MNC applied with and without the BH correction, impairment rates were 19.8% and 9.5% in the healthy controls, respectively. In the HIV+ group, 7.3% men were identified as impaired with the LMNC, compared with 16.4% and 29.5% using the MNC method (with and without the BH correction). In the HIV- group, the rates are 9.3%, 11.7% and 24.1%, respectively. The rates of impairment and mean T-scores across visits did not differ between the HIV- and HIV+ men.
Conclusion: This newly developed LMNC successfully controlled the FDR at the pre-specified level across study visits. This means that the estimates of impairment over repeated testing is more accurate than simply applying cross-sectional criteria multiple times.

402 PLASMA CITRATE AND SUCCINATE PREDICT NEUROCOGNITIVE IMPAIRMENT IN OLDER PWH

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Background: Neurocognitive impairment (NCI) is associated with monocyte activation, implicating a role for neuroinflammation. Activated macrophages increase glycolysis and accumulate the tricarboxylic acid (TCA) metabolites citrate and succinate, which may promote disease by engaging diverse cellular pro-inflammatory pathways or may be markers of mitochondrial dysfunction. We hypothesized that this metabolic shift contributes to NCI and frailty in people with HIV (PWH).
Methods: Fasting plasma citrate and succinate were quantified at entry by liquid chromatography/mass spectrometry in AIDS Clinical Trials Group HIV Infection, Aging, and Immune Function Long-Term Observational (HAILO) study participants. Adjusting for clinically relevant variables, logistic regression and proportional hazard models examined associations of these TCA metabolites with prevalent and incident NCI, respectively; repeated measures analyses examined associations with neuropsychologic testing (NPZ-4) and 4-meter gait speed, a feature of frailty, over time.
Results: 376 participants were included (276 without NCI; 100 with NCI at entry). Participants with NCI were more likely to be Hispanic (35% vs 20%; p=0.01), have less education (p<0.001) and shorter antiretroviral therapy (ART) duration (p<0.01). Overall, median age was 51 (range 40-77) yrs; 81% were male; 60% were current or former smokers. Median entry and nadir CD4 counts were 613 (IQR 449-825) and 203 (68-317) cells/mm$_3$, respectively; 93% had HIV RNA <50 copies/ml. Age modified citrate associations with: prevalent NCI (figure); NPZ-4 scores and gait speed over time (p<0.01, p=0.02 and p=0.04, respectively, for interaction with age). In the oldest age-quartile (ages 56-78; n=96) each 1 SD increase in citrate was associated with a 2.4 (95% CI 1.3, 4.2) increased odds of prevalent NCI; -0.17 SD (-0.28, -0.07) lower NPZ-4 scores over time; and 0.22 second [0.12, 0.31] slower gait speeds over time. Interactions between succinate and age were not significant, but the strength of the succinate association with NCI increased with age (figure). Further, in the oldest age-quartile, each 1 SD increase in succinate was associated with a 1.9-fold (1.1, 3.9) increased hazard of incident NCI and -0.24 SD (-0.47, -0.02) lower NPZ-4 scores over time.
Conclusion: The identified associations suggest common pathways in the pathogenesis of NCI and gait speed, involving mitochondrial dysfunction or inflammation, to which older PWH appear more susceptible.



All odds ratios adjusted for sex, race/ethnicity, antiretroviral therapy duration, education years, nadir CD4+ counts, HIV RNA levels and smoking.
CA, citrate; SA, succinate

403 AGE-ASSOCIATED DEMENTIA AMONG OLDER PEOPLE WITH HIV IN THE US: A MODEL-BASED ANALYSIS

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Background: Approximately 25-30% of people with HIV (PWH) in the US (~300,000) are ≥55y and at risk for age-associated dementias (AAD), including Alzheimer's disease and vascular dementias. We project the lifetime cumulative incidence and mortality associated with AAD among PWH in the US.

Methods: We expanded the validated Cost-effectiveness of Preventing AIDS Complications (CEPAC) model to incorporate age- and sex-stratified risk of AAD with increased mortality among those who develop AAD. We first validated the model in the general population (age, mean±SD [62y±6]). Next, we simulated a population of people at high risk for HIV acquisition given risk behaviors, so mortality is adjusted by a relative mortality rate (RMR) for MSM, IDU, and socio-economic status. We then simulated the 2015 US population of people ≥55y diagnosed with HIV (CD4, mean±SD [490/μL±209]) of whom 73% are in care and 63% are virologically suppressed. Loss to follow-up (LTFU) is 13%/year, and mortality is due to HIV, AAD, and RMR-adjusted other causes. We estimated AAD prevalence, AAD incidence, and AAD-associated mortality using published data from populations without HIV. Model outcomes included AAD cumulative lifetime incidence and life expectancy (LE). We performed sensitivity analysis on HIV-specific (e.g., LTFU) and AAD-specific (e.g., AAD incidence) parameters, as well as the impact of a 5y forward-shift in AAD incidence and non-HIV-associated mortality (i.e., premature aging).

Results: Among older males/females with HIV, we projected AAD cumulative incidence of 18%/17% and LE of 14.5y/14.6y, compared to higher cumulative incidence and longer LE among people at high risk for HIV or in the general population (Table). Without LTFU, AAD cumulative incidence and LE increased among PWH because competing HIV-related mortality was reduced. If PWH experienced premature aging, AAD cumulative incidence increased with decreased LE. If AAD incidence among PWH was 2x that of the population without HIV, then AAD cumulative incidence increased but with a smaller impact on life expectancy. Limitations included uncertain estimates of AAD incidence and AAD-associated mortality among PWH.

Conclusion: Using current data and a validated simulation model, we project that almost 20% of PWH now ≥55y in the US are likely to develop AAD over their lifetime. Cumulative incidence of AAD will be greater if the competing risk of mortality from HIV is reduced or if the risk of AAD is higher among PWH than among those without HIV.

Table. Model projected lifetime cumulative incidence of age-associated dementia (AAD) and life expectancy among people with and without HIV ≥55y

	Lifetime AAD cumulative incidence (%)			Life expectancy (years)		
Population	Males	Females	All*	Males	Females	All*
Base case:						
PWH	18	17	18	14.5	14.6	14.5
People at high risk for HIV	23	22	23	17.0	17.2	17.0
General population	36	44	38	21.2	24.2	21.9
Sensitivity analyses:						
PWH if no LTFU	22	20	22	16.3	16.5	16.3
PWH if 5y premature aging	27	25	27	14.0	14.2	14.0
PWH if 2x AAD incidence	29	26	28	14.2	14.4	14.2

*Assuming 77% males and 23% females as per 2015 CDC data regarding people ≥55y diagnosed with HIV.
Abbreviations: AAD: age-associated dementia; PWH: people with HIV; LTFU: loss to follow-up

404 A RANDOMISED CONTROLLED TRIAL ON THE EFFECT OF B VITAMINS ON NEURONAL INJURY IN PLHIV

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Background: We have previously found an association between plasma homocysteine levels and cerebrospinalfluid neurofilament light protein (NFL) –a marker of neuronal injury– in people living with HIV (PLHIV). Elevated levels of homocysteine is an indicator of B12 and/or folate deficiency. The aim of this study was to investigate if B-vitamin substitution would lead to decreased levels of plasma NFL.

Methods: We performed a single center, randomised, open, controlled trial in Gothenburg, Sweden. Neuroasymptomatic PLHIV with stable antiretroviral therapy (ART) for >12 months and with HIV RNA <50 copies/mL who consented to participate in the study were screened. Individuals who had plasma homocysteine >12 μmol/L were eligible for the study. Patients were randomised to either treatment with Triobe (cyanocobalamin 0,5 mg, folic acid 0,8 mg, and pyridoxine 3 mg) or to no treatment for 12 months.

Results: One hundred and twenty-four PLHIV matching the inclusionciteria were screened for p-homocysteine levels. There was a significant correlation between p-homocysteine levels and p-NFL levels at screening ($r = 0.62$, $p < 0.0001$). Sixty-one patients were randomised to either treatment with Triobe ($n = 31$) or to no treatment ($n = 30$). P-homocysteine levels decreased from a median of 15.9 (interquartile range (IQR) 13. 5–17.2) to 9.9 (IQR 8.5–11.4) ($p < 0001$) between baseline and month 12 in the B-vitamin arm, but not in controls: 14.6 (IQR 13.4–16.9) and 16 (IQR 13.9–18) at baseline and month 12, respectively. At baseline, median plasma NFL was 12.6 (IQR 8.8–21.1) pmol/L in the B-vitamin arm and 10.2 (IQR 8.02–14.9) in the control arm. The levels did not change significantly to month 12 in either arm, 13.8 (IQR 10.3-18.8) and 12.8 (IQR 8.4–14.7) pmol/L, respectively.

Conclusion: We found a significant correlation between p-homocysteine and p-NFL levels in neuroasymptomatic PLHIV on ART. B-vitamin substitution for 12 months had no effect on p-NFL. The mechanism behind the correlation between homocysteine and NFL at baseline, also seen in the earlier study, is unknown and needs to be further investigated. The study will continue until 24 months of follow-up.

405 CONSERVED CSF HIV ANTIBODY RESPONSE IN PATIENTS WITH DIVERSE NEUROLOGIC PHENOTYPES

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Background: The CNS is exposed to HIV during primary infection and likely continuously during untreated chronic infection. ART that suppresses plasma HIV RNA also usually suppresses CSF HIV RNA with occasional asymptomatic episodes of detectable HIV RNA. A rare exception is development of neurosymptomatic (NS) CSF escape in which CNS HIV infection develops despite plasma viral suppression. While drug resistance and incomplete drug penetration predispose to this, the origins of NS escape are not fully understood.

Methods: To assess whether NS escape might be triggered by an unidentified CNS pathogen and/or whether the CSF anti-HIV antibody repertoire might distinguish NS escape, CSF was collected from 25 HIV-infected participants, some longitudinally, with diverse neurologic phenotypes and treatment status (Table 1). CSF samples were incubated with a VirScan T7 bacteriophage library expressing 481,966 peptides tiled across all known vertebrate and arbovirus genomes that previously identified CSF enteroviral antibodies in pediatric acute flaccid myelitis. Antibody-bound phage were immunoprecipitated and after two rounds of enrichment, were deep sequenced to quantify enriched viral peptides. Separately, unbiased metagenomic next-generation sequencing (mNGS) of total CSF RNA was performed to look for unidentified infections and HIV.

Results: mNGS was 100% concordant with HIV RNA PCR for samples with 530 viral copies (n=15) and 0% concordant from samples with £ 113 viral copies (n=8). In addition, mNGS detected the two known infections in the secondary escape patients. Additionally, the CSF anti-HIV antibody repertoire primarily enriched two distinct epitopes within the HIV envelope (env) protein in the VirScan assay, regardless of neurologic or treatment status. These epitopes mapped to the V3 loop near the binding site for CCR5 and to the C-terminal heptad repeat domain.

Conclusion:
CSF mNGS did not identify additional infections in HIV NS escape. Preliminary VirScan data suggest that immunodominant epitopes in the CNS are highly conserved across patients, regardless of neurologic status. However, compared to similar epitopes described in sera, we identified CSF antibodies specific for the R306S mutation in the gp120 V3 region which has been associated with brain-derived env sequences and increased macrophage tropism.

Neurologic status	Treatment status	Number of patients	Number of CSF samples	Additional Information
Variable	Off ART (viremic)	4	16	
Variable	On ART (suppressed)	4	12	
Neurosymptomatic CSF escape	On ART (peripherally suppressed)	4	4	
Secondary CSF escape	On ART (peripherally suppressed)	2	2	varicella zoster virus (n=1), human cytomegalovirus (n=1)
CNS opportunistic infection	Off ART (viremic)	2	8	varicella zoster virus (n=1), JC virus n=1
HIV-associated neurocognitive disorder (HAND)	On ART (suppressed)	9	9	

406 A RANDOMIZED TRIAL OF ADJUNCTIVE TELMISARTAN TO REDUCE CNS INFLAMMATION IN ACUTE HIV

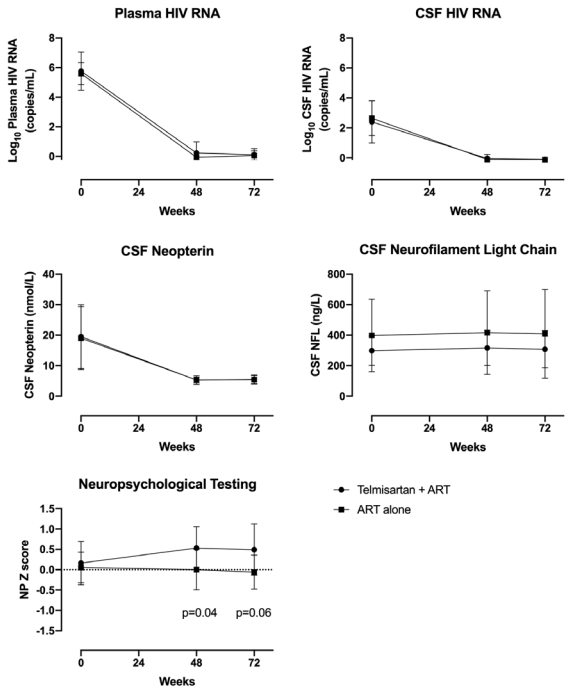
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Background: Telmisartan is an angiotensin II receptor antagonist that inhibits inflammatory cytokines and macrophage activity. We hypothesized that initiation of antiretroviral therapy (ART) with adjunctive telmisartan in acute HIV infection (AHI) would reduce inflammation and immune activation and alter the pathogenesis of HIV within the central nervous system (CNS).

Methods: 21 participants with AHI were randomized 2:1 to initiate treatment with ART +/- telmisartan; after 48 weeks, all individuals received ART alone. At baseline, 48, and 72 weeks, we measured blood and cerebrospinal fluid (CSF) biomarkers of HIV infection, inflammation, and neuronal injury. Brain magnetic resonance spectroscopy (MRS) metabolites and neuropsychological (NP) performance assessed by a battery of 16 tests (summarized as NPZ) were evaluated at baseline and weeks 48 and 72. Wilcoxon rank sum and Mann Whitney tests examined differences within individuals and between groups at each time point.

Results: All participants were Thai men who have sex with men. At enrollment, median age was 29 years (IQR 24-34), CD4+ T cell count 479 (95-688), and estimated duration of infection 16 days (13-22). Pre-ART median log plasma and CSF HIV RNA levels were 5.95 (5.36-6.48) copies/mL and 2.82 (2.17-4.36) copies/mL. Plasma and CSF HIV RNA using highly sensitive assays (lower limit of quantitation of 0.3 copies/mL) did not differ between groups at 48 or 72 weeks. While levels of CSF inflammatory biomarkers declined in both arms, there were no significant differences between arms in levels of CSF neopterin, IP-10, sCD14, MCP-1, sCD163, neurofilament light chain or YKL-40 at 48 or 72 weeks. MRS metabolites in basal ganglia and white matter remained stable over time in both arms and there were no significant differences between arms at 48 or 72 weeks. Individuals on telmisartan had higher (better) overall NPZ scores at 48 weeks (0.64 vs 0.05; p=0.04) and 72 weeks (0.70 vs 0.08; p=0.06), although this difference appeared to be driven by a subsample in the telmisartan group (n=3) who exhibited significant improvement from baseline.

Conclusion: In this pilot study of telmisartan as an adjunct to ART during AHI, telmisartan did not affect CNS biomarkers of inflammation or injury. The association with NP performance warrants further investigation.



407 INFLAMMATORY MARKERS SHOW DYNAMIC CHANGES IN ACUTE HIV AND PREDICT COGNITIVE OUTCOMES

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Background: HIV-associated neurocognitive disorder (HAND) has been associated with elevated inflammatory markers in the peripheral blood and cerebrospinal fluid (CSF) in chronic HIV. We investigated the dynamics of viral load and inflammatory markers in CSF and plasma during acute HIV infection and their impact on longitudinal neurocognitive performance (NP) after antiretroviral therapy (ART) in Peru.

Methods: MSM and transgender women in the Sabes study were followed with monthly testing (HIV Ab & RNA) and enrolled within 3 months of HIV acquisition. In ART-naïve HIV+ participants, 39 inflammatory markers were measured in plasma (N = 87) and 37 in CSF (N = 29) at enrollment. Time from infection to enrollment (ITE) was estimated by an algorithm using testing history (type, date and result of test). NP was assessed with a 15-test battery, averaged as a total Z score derived from Peruvian normative data and administered every 24 weeks. Linear regression was used to evaluate associations between VL, biomarkers, and ITE. In a subset analysis of 42 participants who started ART at enrollment, 13 of whom provided CSF samples, biomarker levels were used as predictors of change in standardized NP score from baseline (ΔNP). We adjusted for multiple comparisons with the Benjamini-Hochberg (BH) method.

Results: Longer ITE was associated with lower VL in CSF ($\beta = -0.024$ $\log_{10}$ copies/mm_3/day, $p = 0.03$) and plasma, ($\beta = -0.037$ $\log_{10}$ copies/mm_3/day, $p = <0.0001$). In univariate analysis, longer ITE was associated with lower levels of 24 and higher levels of 4 biomarkers. After adjustment with BH, ITE was negatively associated with baseline levels of VCAM-1, and IFN-γ in both plasma and CSF, negatively associated with CSF CD-163 and positively associated with plasma CD-163. In the unadjusted subset analysis, higher levels of the following biomarkers predicted a negative βNP at α2 time points: plasma YKL40; plasma and CSF IL-16, plasma IL-6, CSF TNF-β, CSF IL-16, CSF TNF- α, and CSF IP-10.

Conclusion: Higher baseline values of key inflammatory biomarkers in plasma and CSF in early HIV were correlated with greater reductions in NP score over time after ART. There was also a novel pattern of CSF and plasma inflammatory marker dynamics observed in the first two months of untreated HIV infection.

Additional investigation of inflammatory events during acute HIV infection could offer key information on longitudinal neurological outcomes.

Table 1: Baseline plasma and CSF biomarkers in ART-naïve, acutely HIV infected participants with association to estimated time of infection (ITE)

(A) ITE vs Baseline Biomarker Level				
Name	Plasma B-coefficient (log10 copies/mm3/day)	Plasma p-value	CSF B-Coefficient log10 copies/mm3/day	CSF P-value
Viral Load	-0.04	<0.0001	-0.02	0.03
VCAM-1	-0.006	0.0003*	-0.006	0.002*
IFN-Y	-0.01	0.0045*	-0.015	0.0235*
CD-163	0.004	0.0472*	-0.005	0.0015*

*Table 1: ITE as a predictor of enrollment biomarker levels. * = adjusted for multiple comparisons with Benjamini-Hochberg.*

408 PROTEOMIC CHARACTERIZATION OF CSF EXTRACELLULAR VESICLES IN HIV PATIENTS

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Background: Extracellular vesicles (EVs) are nano-sized particles present in most body fluids including cerebrospinal fluid (CSF). Little is known about CSF EV proteins in HIV+ individuals. In this cross-sectional study, we characterized the CSF EV proteome in HIV+ subjects and its relationship to neuroinflammation, stress responses, and HIV-associated neurocognitive disorders (HAND).

Methods: CSF EVs isolated from 20 age-matched HIV+ subjects with (n=10) or without (n=10) cognitive impairment were characterized by electron microscopy, nanoparticle tracking analysis, immunoblotting, and untargeted LC/MS/MS mass spectrometry. Functional annotation was performed by gene ontology (GO) mapping and expression annotation using Biobase Transfac and PANTHER software. Cultured astrocytic U87 cells were treated with hydrogen peroxide for 4 hours to induce oxidative stress and EVs isolated by ultracentrifugation. Selected markers of astrocytes (GFAP, GLUL), inflammation (CRP), and stress responses (PRDX2, PARK7, HSP70) were evaluated in EVs released by U87 cells following induction of oxidative stress, and in CSF EVs from HIV+ patients by immunoblotting.

Results: Mass spectrometry identified 2727 and 1626 proteins in EV fractions and EV-depleted CSF samples, respectively. CSF EV fractions were enriched with exosomal markers including Alix, syntenin, tetraspanins, and heat-shock proteins, and a subset of neuronal (ENO2, NFL, NPTN, NRXNs), astrocyte (GFAP, PEA15, S100B, SLC1A3), oligodendrocyte (MAG, MBP, MOG), and choroid plexus (ACO2, CLIC6, COMT, EZR, TTR) markers in comparison to EV-depleted CSF. Proteins related to synapses, immune/inflammatory responses, stress responses, metabolic processes, mitochondrial functions, and blood-brain barrier were also identified in CSF EV fractions by GO mapping. HAND subjects had higher abundance of CSF EVs ($p<0.005$) and proteins mapping to GO terms for synapses, glial cells, inflammation, and stress responses compared to those without HAND. GFAP, GLUL, CRP, PRDX2, PARK7, and HSP70 were confirmed by immunoblotting of CSF EVs of HAND subjects and were also detected in EVs released by U87 cells under oxidative stress.

Conclusion: CSF EVs derived from neurons, glial cells, and choroid plexus carry synaptic, immune/inflammation-related, and stress response proteins in HIV+ individuals with cognitive impairment, representing a valuable source for biomarker discovery.

409 EFFECT OF NON-HIV DRUGS ON NEUROCOGNITIVE DOMAINS IN A WELL-TREATED HIV POPULATION

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Background: Neurocognitive impairment (NCI) remains a problem in people with HIV (PWH) despite advances in HIV management. Medications with anticholinergic (ACH) activity have been associated with NCI in aging, HIV-negative persons. Previously we described ACH use in PWH >65 years old in the Swiss HIV Cohort Study (SHCS) and the association with self-reported NCI using SHCS screening questions for memory, attention, and reasoning difficulties. The current study aimed to further assess the effect of ACH and sedative drugs on neurocognitive function in PWH who underwent detailed neuropsychological evaluation using a standardized testing battery.

Methods: A medication review was performed in PWH >45 years old enrolled in the prospective Neurocognitive Assessment in Metabolic and Aging Cohort (NAMACO), a sub-cohort of the SHCS. NAMACO participants were included regardless of self-reported NCI. Neurocognitive function was evaluated for 7 domains by trained neuropsychologists. Binary outcomes (presence/absence of impairment) were assessed for each individual domain and combined to determine overall neurocognitive function. The effect of ACH and sedative drugs on neurocognitive function was evaluated using multivariable logistic regression models adjusted for patient demographic characteristics, HIV history, comorbidities, illicit substance use, alcohol binge and efavirenz/dolutegravir use.

Results: 963 PWH (80% male, 92% Caucasian, 96% virologically suppressed, median age 52 [IQR: 49-57]) were included. 16% of participants were prescribed >1 sedative drug and 14% >1 ACH drug, with 82% of these drugs having an ACH activity score <3. 41% of participants had NCI, mainly related to impairment of motor domain. Sedative drugs were associated with impairment of attention and verbal learning domains (OR 1.98; 95% CI 1.28-3.07; and OR 1.77; 95% CI 1.07-2.93), and ACH drugs with impairment of motor and sensory skills domains (OR 1.71; 95% CI 1.08-2.71; and OR 3.09; 95% CI 1.43-6.66). Increased risk of overall NCI was associated with sedative drugs (OR 1.55; 95% CI 1.00-2.40; p=0.048) and was borderline for ACH drugs (OR 1.58; 95% CI 0.98-2.55; p=0.06). Other significant associations with overall NCI were older age, lower education and being non-Caucasian.

Conclusion: Non-HIV drugs can contribute to NCI with sedative drugs altering attention and learning functions and ACH drugs impairing motor and sensory functions. HIV clinicians need to consider these drugs when assessing NCI.

410 ANTICHOLINERGIC DRUG USE IN PATIENTS ≥ 65 YEARS OLD IN THE SWISS HIV COHORT STUDY

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Background: Medications with anticholinergic (ACH) activity have been associated with neurocognitive impairment (NCI), particularly in elderly due to a reduced number of cholinergic receptors. People with HIV (PWH) are more likely to have NCI as they age. Additional risk factors include viral replication, chronic inflammation, antiretroviral therapy (ART) toxicity, higher rates of depression, and previous central nervous (CNS) infections, making this population especially vulnerable to ACH effects. This study determined the prevalence of prescribed ACH drugs and their association with self-reported NCI in elderly PWH of the Swiss HIV Cohort Study (SHCS).

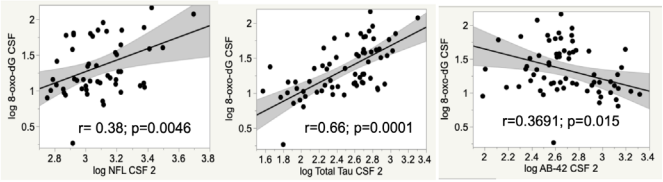
Methods: A literature review was performed to identify ACH drugs with documented ACH activity, supporting side effect profile, and CNS penetration. The degree of ACH activity was scored from 0 to 3, a higher score indicating more ACH activity. A medication review was performed in July 2019 for all SHCS participants >65 years old to assess the prevalence of prescribed medications with ACH properties. Association between ACH burden and neurocognitive complaints was evaluated using the SHCS self-reported NCI questions addressing memory loss, attention difficulties, and slowing of reasoning ability.

Results: 1019 PWH (82% male) with a median age of 70 [IQR: 67-74] years were included. Most patients were on ART (99%); 50.8% were integrase inhibitor regimens. The average number of non-HIV drugs was 5.1+3.6, representing a polypharmacy (i.e. >5 non-HIV drugs) prevalence of 50.2%. 200 participants (19.6%) were on >1 drug with ACH activity, with an average ACH score of 1.7. Overall, 131, 22 and 46 PWH had an ACH score of 1, 2 and >3, respectively. Antidepressants were the most prescribed ACH drugs (49.8%). Gender and age were not associated with ACH drug use however polypharmacy was ($p<0.001$). Self-reported NCI, adjusted for age, gender, and polypharmacy was associated

with depression (OR=2.69; 95% CI 1.72-4.21) and a trend was observed with being on >1 ACH drug (OR=1.42; 95% CI 0.97-2.09; p=0.07). In a subgroup analysis of patients without depression (N=911), adjusted for age, gender, and polypharmacy, self-reported NCI was associated with the use of >1 ACH drug (OR=1.66; 95% CI 1.08-2.55; p=0.02).
Conclusion: ACH drug use is common in elderly PWH and may contribute to self-reported NCI. The effect of ACH drugs on NCI warrants further evaluation using neurocognitive tests.

411 BIOMARKERS OF NUCLEIC ACID OXIDATION AND NEURODEGENERATION IN CSF IN PWH

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Background: Oxidative stress is common in HIV, even among virologically suppressed individuals, and may contribute to or result from neurodegeneration. 7,8-dihydro-8-oxoguanine (8-oxo-dG), representing oxidatively damaged guanine, is a marker of oxidative DNA damage. Important markers of age-related neurodegeneration include Aβ-42 reduction, reflecting amyloid deposition in brain, and CSF total Tau and neurofilament light (NFL), reflecting neuronal damage. We aimed to examine whether oxidative stress is associated with markers of AD-related neurodegeneration.
Methods: Participants were enrolled at six U.S. centers in the CNS HIV Antiretroviral Effects Research (CHARTER) study. Inclusion criteria included HIV RNA ≤50 copies/ml in plasma. Exclusions included significant CNS confounding conditions. Total Tau and Aβ-42 were measured in CSF and plasma by bead suspension array. NFL in CSF and 8-oxo-dG in CSF and plasma were measured using ELISA. Peripheral blood mitochondrial (mt) DNA copy number was obtained from genome-wide genotyping data as a ratio of mtDNA single-nucleotide polymorphism probe intensities relative to nuclear DNA single-nucleotide polymorphisms.
Results: Participants were 53 PWH, mean age 55 (+/-9.3), 19% women, 48% non-Hispanic white. Higher 8-oxo-dG correlated with markers of neurodegeneration including lower CSF Aβ-42 (r=-0.34; p=0.012), higher CSF NFL (r=0.39; p=0.0091) and higher total Tau (r=0.6696; p<0.0001). CSF 8-oxo-dG was not related to age, sex, or ethnicity. Aβ-42 was significantly lower in women and African Americans. Higher NFL levels were seen in men and older individuals. Higher total Tau was seen with increasing age. Relationships between 8-oxo and neurodegeneration markers remained after adjusting for demographic variables. 8-oxo-dG was higher among PWH exposed to dideoxynucleoside antiretrovirals. Levels of protein carbonyls, a marker of protein oxidation, were not related to neurodegeneration. Higher 8-oxo-dG, but not protein carbonyls, correlated with lower mtDNA copies per cell (r = -0.59; p = 0.027 and r = -0.31; p = 0.27, respectively).
Conclusion: Among virologically suppressed PWH, nucleic acid oxidation was associated with CSF biomarkers of neurodegeneration. Potential sources of oxidative stress in PWH include low-level HIV replication, inflammation, and specific ART drugs. Results suggest that the higher levels of oxidative stress among PWH may play a role in neurodegeneration.



412 PREDICTIVE VALIDATION OF AN UGANDAN INFANT EYE-TRACKING TEST OF MEMORY OF HUMAN FACES

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Background: Neurodevelopmental assessments in early childhood followed by neurocognitive assessments during the preschool-age years are sometimes used to monitor HIV-affected children in resource-constrained settings. Using an automated neurocognitive performance test at one-year of age, we evaluated its predictive validity with neuropsychological performance on validated preschool measures several years later.
Methods: 58 uninfected children (25 boys, 33 girls) of mothers with HIV were evaluated at one year of age with the Mullen Scales of Early Learning (MSEL) and the Fagan test of Infant Intelligence (FTII). FTII tests for recognition for pictures of local adult and children faces, usingTobii eye tracking instrumentation to measure gaze direction and duration during successive trials where familiar (previously presented) and novel faces were presented together. After familiarization trials, longer gaze to novel faces is expected. Total screen viewing duration (either face combined) was used as a measure of attention. Most of these children were then tested several years later with the Kaufman Assessment Battery for Children, 2nd Edition (KABC-2) and the visual computerized Tests of Variables of Attention (TOVA). Evaluation took place at the Tororo District Hospital in eastern Uganda.
Results: FTII proportion of time viewing novel (vs. familiar) faces was significantly related to overall KABC-2 performance (eta2=0.07), related especially to auditory working memory (KABC Number Recall; p<0.05). FTII proportional preference for novel faces was significantly related to TOVA percent omission errors (vigilance attention). FTII overall attention was related to KABC-2 Hand Movements (eta2=0.11), Rebus (symbol coding learning; eta2=0.13) and TOVA D prime (signal detection; eta2=0.06). MSEL and FTII performance were not significantly related to one another, suggesting they measure different things. MSEL cognitive ability did predict several TOVA performance measures.
Conclusion: An eye-tracking based measure of infant measure of attention and working memory (human faces) can predict aspects of neurocognitive performance several years later. Gathering test results automatically, eye tracking-based cognitive assessments in infants can be beneficial in evaluating neurocognitive risk in HIV-infected and affected children; gauging benefits from early treatment and supportive care. We thus provide an innovative performance-based window into the integrity of brain/behaviour development in infancy.

Table 1. Summary of associations between Fagan and school-age measures: Correlation and partial eta squared coefficients adjusted for age and sex.

	Fagan sample p		Fagan prop_visit		Fagan prop_fixation		Fagan VisitDuraFull ScreenAdjSample Perc		Fagan FixedPlus VisitDuraFull ScreenAdjβ		MSEL	
	r	Eta-squared	r	Eta-squared	r	Eta-squared	r	Eta-squared	r	Eta-squared	r	Eta-squared
KABC meanZKABCrawAllSubtests	.07	.00	.26	.04	.35*	**.07****	.06	.01	.04	.00	-.12	.00
KABC ssmpi	.08	.04	.04	.00	.00	.02	.00	.01	.04	.00	.27	.03
KABC numbreO	.12	.01	.50*	**.20*, ****	.52*	**.19*, ****	.01	.00	.05	.00	-.15	.00
KABC HANDM00	.13	**.11****	.09	.04	.08	.01	.02	.00	.02	.00	-.10	.01
KABC REBUS0	.26	**.13****	.19	.00	.18	.02	.11	.01	.17	.02	.07	.01
TOVA ommission errors	-0.38	.02	-.33	**.07****	-.45*	.01	.07	.04	-.05	.03	**-.25**	**.17****
TOVA comission errors	.20	.05	.42	.05	.47*	.03	-.29	**.14****	-.23	**.11****	**.35**	**.11****
TOVA D'prime	.01	**.06****	.03	.03	.11	.00	.19	.03	.10	.01	**-.31**	**.10****

*Significantly different from zero at .05 level of significance
** Medium or large eta squared

413 LOW NEUROSTEROIDS IDENTIFIES A BIOLOGICAL SUBTYPE OF DEPRESSION IN PEOPLE WITH HIV

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Background: The prevalence and mortality risk of depression in people with Human Immunodeficiency Virus infection (PWH) on antiretroviral therapy (ART) is higher than in the general population, yet biomarkers for therapeutic targeting are unknown. Here, we aimed to identify plasma metabolites associated with depressive symptoms in PWH on ART.
Methods: This is a prospective study of 99 ART-treated HIV-infected adults (94% with plasma VL < 200 copies/ml) with or without depressive symptoms assessed using the Beck Depression Inventory (BDI) from the NNTC and HNRC cohorts. Participants with BDI scores > 20 were classified as having high depressive symptoms. Plasma metabolite profiles from 55 participants comprised the discovery set; profiles from 44 additional participants were used to validate the accuracy of models. Metabolite profiling was performed using

ultra high-performance liquid chromatography and tandem mass spectrometry (UHLC/MS/MS2) and gas chromatography/MS.

Results: Median age, CD4+ T-cell count, and nadir CD4+ T-cell count were 50y, 373 cells/µl, and 66 cells/µl in the discovery cohort and statistically similar to the validation set. Seventeen (31%; median BDI 32) and 18 (41%; median BDI 23) participants were classified as having high depressive symptoms in the discovery and validation cohort, respectively. Participants with depressive symptoms had lower neuroactive steroids (dehydroepiandrosterone sulfate (DHEA-S), androstenediols, pregnenolone sulfate) compared to those without depressive symptoms. Cortisol/DHEA-S ratio, an indicator of hypothalamic-pituitary-adrenal axis imbalance, was associated with depressive symptoms due to low DHEA-S (Figure), and discriminated between participants with high vs. low depressive symptoms with AUC of 0.70 (P=0.03, discovery) and 0.80 (P=0.02, validation). When cortisol/DHEA-S was coupled with androstenediol and pregnenolone sulfate, discrimination improved with AUC of 0.81 (discovery) and 0.85 (validation). The odds of having depressive symptoms increased with higher cortisol/DHEA-S ratios [odds 2.5 per z-score, 95% confidence interval 1.3-4.7], independent of age and gender. Kynurenine to tryptophan ratio showed no significant associations.

Conclusion: These findings suggest that altered neuroactive steroid metabolism may contribute to the pathophysiology of depression in ART-treated HIV-infected adults, representing a potential biological pathway for therapeutic targeting.

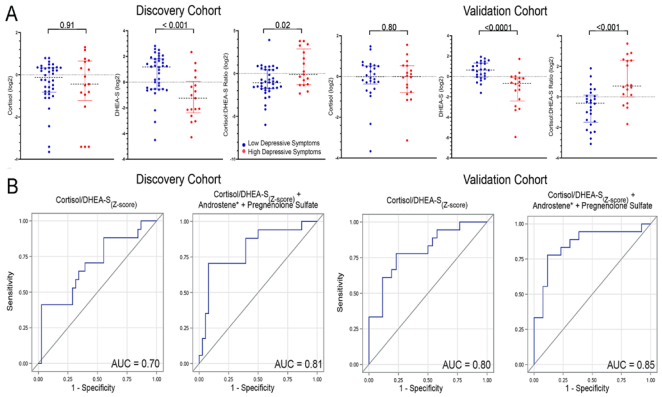


Figure: (A) Beeswarm plots illustrating the median and interquartile range for cortisol and dehydroepiandrosterone sulfate (DHEA-S) metabolites, and cortisol/DHEA-S ratios in participants with low versus high depressive symptoms in discovery (left) and validation (right) cohorts. **(B)** Receiver operating characteristic (ROC) curve from logistic regression models assessing low versus high depressive symptom participant classification using cortisol/DHEA-S ratio (z-score) or cortisol/DHEA-S ratio with androstene and pregnenolone sulfate in the discovery and validation cohorts. AUC denotes the area under the ROC curve. *Androstene: androstenediol 3β,17β monosulfate (1)

414 ANTICHOLINERGIC BURDEN IS ASSOCIATED WITH DEPRESSIVE SYMPTOMS IN PERSONS WITH HIV

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Background: Persons with HIV (PWH) have a higher risk of depression and neurocognitive (NC) impairment (NCI) than the general population. PWH are also at greater risk for polypharmacy, which increases the risk of adverse events. Many prescribed drugs have anticholinergic (AC) effects, which are a risk factor for depression and NCI in the general population and could contribute to the risk of these conditions in PWH.

Methods: To determine the relationships between AC effects and either depressive symptoms or cognitive performance, we analyzed data from 608 PWH on ART who had plasma HIV RNA ≤ 200 copies/mL. AC effects were quantified using the published AC burden (ACB) method. Depressive symptoms were quantified using the Beck Depression Inventory (BDI). Cognitive performance was assessed using a standardized, comprehensive neuropsychological test battery that assessed seven cognitive domains and was summarized by global and domain T scores. Analytical methods included correlation, analysis of variance, and multivariable regression that included demographic, HIV, and ART characteristics as well as medical, psychiatric, and addiction diagnoses.

Results: Participants were mostly middle-aged (mean 44.6 years), European ancestry (55.4%) men (85.4%) who had taken ART for more than 4 years (53.0%) and whose current CD4+ T-cell count was >500/µL (54.2%). Median global T-score was 45.8 and median BDI was 12.7. Two hundred fifty-seven (42.3%) took at least one AC drug: The most common were codeine (9.0%), bupropion (8.9%), and trazodone (7.3%). Higher ACB was associated with worse BDI (ρ=0.22, p<0.0001) and global T score (ρ=-0.19, p<0.0001). All seven cognitive domains were affected (p range 0.006 to <0.0001). In multivariable regression models, ACB remained associated with worse BDI (p=0.0001, model R2=0.41, p<0.0001) and trended toward association with global T score (p=0.07, model R2=0.21, p<0.0001). Addition of number of prescribed drugs to models weakened the association of ACB with Global T score below statistical significance (p=0.73) but not with BDI (p=0.003). The AC drugs most strongly associated with BDI were paroxetine, trazodone, atropine, olanzapine, and hydroxyzine.

Conclusion: AC drugs are associated with more depressive symptoms, even after accounting for other influential characteristics, including psychiatric diagnoses. This cross-sectional analysis cannot establish causality but eliminating AC drugs from medication regimens may improve depressive symptoms.

415 ASSOCIATION BETWEEN LUNG AND COGNITIVE DYSFUNCTION IN MEN WITH HIV INFECTION

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Background: Lung dysfunction associated with chronic obstructive pulmonary disease (COPD) is common in HIV and a risk factor for developing cognitive dysfunction, a well-recognized comorbidity among persons with HIV infection. We evaluated the relationship between lung and cognitive function in men with and without HIV infection.

Methods: We performed a cross sectional analysis of participants in the Multicenter AIDS Cohort Study (MACS). Participants underwent pulmonary function testing including, diffusion capacity for carbon monoxide (DLCO; a measure of oxygen diffusion from the lungs to blood) and forced expiratory volume in one second/forced vital capacity ratio (FEV1/FVC; a measure of airway obstruction used to diagnose COPD). The neuropsychological test battery assessed Executive Function, Speed (of information processing), Attention and Working Memory, Learning, Memory, and Motor functional domains. A T score was derived for each functional domain. Multivariable linear regression models estimated the association between the measures of lung and cognitive function.

Results: Among 866 participants, 477 (55.1%) had HIV infection. The mean age (standard deviation) of the participants was 55 (12) years. The majority were Caucasian (58.1%). Although a lower DLCO was associated with a lower Executive Function among men without HIV infection (β=0.10; p=0.01), this was not the case among the HIV-infected men (β=0.07; p=0.11). Lower levels of DLCO were associated with lower Speed scores among HIV-infected men (β=0.10; p=0.03), but not among the uninfected men (β=0.00; p=0.91). Among men without HIV infection, a lower FEV1/FVC was associated with reduced Learning (β=19.64; p=0.02) and Memory scores (β=21.63; p=0.01). However, among the HIV-infected men, the associations of FEV1/FVC with Learning (β=8.02; p=0.27) and Memory (β=4.71; p=0.53) did not reach statistical significance.

Conclusion: Reduced lung function was associated with poorer cognitive function in the domains of Executive Function, Speed, Learning, and Memory. However, these associations differed by HIV status. appear to be modified by HIV status. Future studies are needed to better elucidate the pathophysiologic mechanisms by which airway obstruction and reduced oxygen diffusion in the lungs interact with HIV status to contribute to cognitive dysfunction.

Table 1. Relationship between lung and cognitive function in individuals with and without HIV

Cognitive Functional Domains	Pulmonary Function Test	Individuals with HIV		Individuals without HIV		Interaction p†
		β (95% CI)*	p	β (95% CI)*	p	
Executive	FEV1/FVC	6.59 (-9.48–22.65)	0.92	-2.94 (-18.42–12.53)	0.71	0.92
	DL_{CO}	0.07 (-0.02–0.15)	0.11	**0.10 (0.02–0.18)**	**0.01**	0.24
Speed	FEV1/FVC	1.24 (-15.30–17.78)	0.88	-7.44 (-25.80–10.92)	0.43	0.93
	DL_{CO}	**0.10 (0.01–0.19)**	**0.03**	0.00 (-0.08–0.09)	0.91	0.27
Attention and Working memory	FEV1/FVC	-9.19 (-22.25–3.88)	0.17	-4.27 (-18.26–9.71)	0.55	0.26
	DL_{CO}	0.04 (-0.04–0.11)	0.35	-0.02 (-0.09–0.06)	0.65	0.78
Learning	FEV1/FVC	8.02 (-6.20–22.23)	0.27	**19.64 (3.03–36.25)**	**0.02**	0.13
	DL_{CO}	0.01 (-0.06–0.08)	0.83	0.06 (-0.01–0.14)	0.09	0.07
Memory	FEV1/FVC	4.71 (-10.09–19.51)	0.53	**21.63 (4.89–38.37)**	**0.01**	**0.04**
	DL_{CO}	-0.01 (-0.07–0.05)	0.82	0.05 (-0.02–0.13)	0.18	**0.02**
Motor	FEV1/FVC	0.74 (-19.65–21.12)	0.49	-2.75 (-20.19–14.69)	0.76	0.49
	DL_{CO}	0.02 (-0.09–0.13)	0.73	0.09 (0.00–0.18)	0.06	0.48

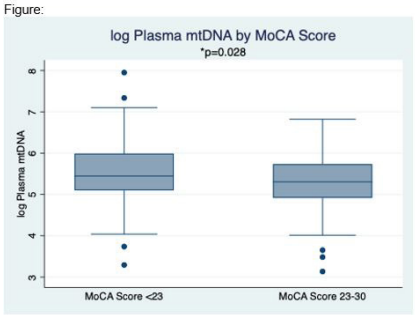
FEV1/FVC = forced expiratory volume in one second/forced vital capacity; DL_{CO} = diffusing capacity for carbon monoxide
*Adjusted for age, race, education, recruitment site, hypertension, diabetes mellitus, hepatitis C, intravenous drug use, and smoking
†Interaction p for HIV status

416 MITOCHONDRIAL DNA, COGNITIVE FUNCTION, AND FRAILTY IN OLDER ADULTS WITH HIV

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Background: Older PLWH experience more comorbidities and geriatric syndromes, including cognitive impairment and frailty. Mitochondrial DNA (mtDNA), released from dying cells, is a biomarker of inflammation, a mediator of immune activation and has been detected at elevated levels in the plasma of PLWH. We hypothesized that in older PLWH, plasma mtDNA would be associated with lower cognitive performance, frailty, and higher serum IL-6 level.
Methods: We analyzed cross-sectional data from PLWH over age 55 at a single urban medical center. Participants completed a psychosocial questionnaire, biomedical visit, cognitive assessment (Montreal Cognitive Assessment, MoCA) and frailty testing by Fried criteria. Plasma and urine cell-free mtDNA were measured by qPCR detection of mitochondrial NADH dehydrogenase-1.
Results: There were 164 participants; mean age 61 (SD: 6) range 54-87 years. One-third (55) were female. Half identified as Black, 29% as White, and 21% as other. Median time living with HIV was 25 years (IQR 22-29). The majority (93%) had HIV-1 viral load <200 copies/mL and median CD4 count was 582 cells/uL (IQR 402-795). Geometric mean mtDNA level in plasma was 221 copies/µl (geometric SD: 2) and 2.4x108 copies/gram of urine creatinine (geometric SD: 4) in urine. Levels of plasma and urine mtDNA (Spearman correlation rho, ρ=0.05, p=0.54) were unrelated. Median MoCA score was 24 (IQR 21-26); 63 (39%) scored <23. 49 (30%) were non-frail, 95 (58%) pre-frail and 20 (12%) frail. Age was not related to MoCA score (ρ=-0.1, p=0.19), but was associated with frailty status by Jonckheere-Terpstra (JT) test (p=0.008). Plasma mtDNA level was higher in those with low MoCA score (p=0.028) by t-test [Figure 1]. Higher plasma mtDNA level was associated with slow walk (p=0.007) and exhaustion (p=0.04), but not weight loss (p=0.62), grip strength (p=0.06), low physical activity (p=0.71) or composite frailty score (p=0.98). Serum IL-6 levels were associated with frailty status (p=0.018) but not with low MoCA score (p=0.89 by JT). Neither plasma nor urine mtDNA levels were correlated with IL-6 level, ρ-0.05 (p=0.55) and 0.09 (p=0.29), respectively.
Conclusion: In this study we show a relationship between elevated levels of plasma mtDNA and lower performance on the MoCA, greater exhaustion, and slower walk, suggesting mtDNA may have a role as a novel biomarker in assessing pathogenic inflammation associated with cognitive dysfunction and some components of frailty in PLWH.

Figure:



417 IMPACT OF WEB-BASED COGNITIVE TRAINING ON WORKING MEMORY IN COCAINE USERS WITH HIV

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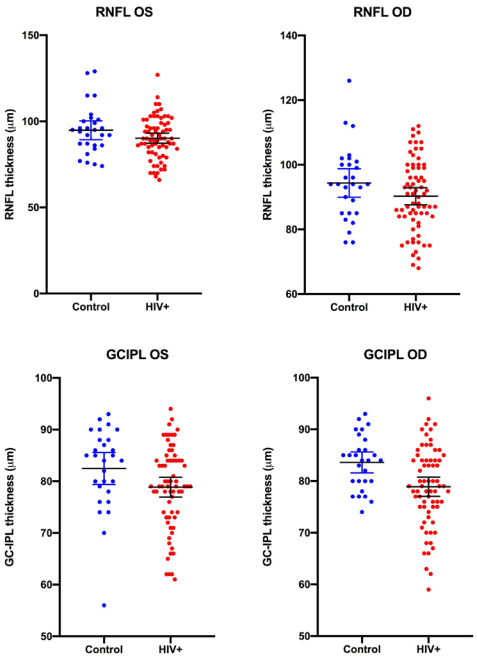
Background: Cocaine use is disproportionately prevalent among persons with HIV, and it is known to exacerbate HIV-associated neurocognitive impairments, specifically working memory, that contribute to impulsive decision making. This study tested the effectiveness of a web-based cognitive training intervention to improve working memory and reduce impulsivity in HIV-infected cocaine users.
Methods: In this randomized controlled trial, participants were assigned to one of two conditions of 48 cognitive training sessions, each lasting 20-30 minutes, over 10 weeks. Games in the active condition (ACT) targeted working memory, while games in the control condition (CON) targeted other domains. Each session included a random sampling of 4 out of possible 8 games repeated once back-to-back. Participants completed clinical interviews and comprehensive neuropsychological testing at baseline and post-intervention, as well as a process measure to provide feedback on the intervention.
Results: The sample of 58 participants was 48.6 years old on average, mostly male (71%) and African American (88%). Participants completed 37.3 of the 48 possible sessions on average, with no difference by condition, and 56 participants (97%) completed the post-intervention follow-up. We conducted repeated measures ANCOVAs on working memory (domain deficit score) and delay discounting (natural log k-value), controlling for age, education, and number of games improved (as proxy of intervention engagement). In the intent-to-treat sample, there was a significant group-by-time interaction for working memory with a medium effect size [$F(1, 51) = 4.470$, $p = .039$, eta squared = 0.081], such that ACT had greater improvements relative to CON. For delay discounting, there was a similar pattern, again with a medium effect, but the interaction effect was not significant [$F(1, 48) = 3.546$, $p = .066$, eta squared = 0.069]. Overall, participants rated the sessions as helpful (M=4.09, on 5 point scale), but those in ACT perceived greater improvement on the games over time [M=4.39 (0.69) vs. 3.89 (0.92); $t(54) = 2.31$, $p = .025$].
Conclusion: Our findings support the acceptability and potential effectiveness of cognitive training to improve working memory in HIV-infected cocaine users. A larger trial with a longer duration of training targeting more domains is needed to test the durability of effects and improvement in daily living.

418 RETINAL THINNING CORRELATES WITH BRAIN ATROPHY IN WELL-CONTROLLED HIV INFECTION

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Background: Retinal measurements correlate well with neurologic disease in multiple sclerosis, however whether such measurements correlate with neurologic disease in well-treated persons living with HIV (PLWH) is unknown. We evaluated differences in retinal measures by spectral domain optical coherence tomography (SD-OCT) between PLWH and uninfected controls and correlations with the retinal measures and brain volumes, neuropsychological (NP) function, and markers of neuronal injury and neuroinflammation.
Methods: SD-OCT was performed on 69 PLWH on antiretroviral therapy (ART) and 28 uninfected controls. Participants also underwent brain MRI, neuropsychological testing, and an optional lumbar puncture. All procedures, including the SD-OCT, were completed for research only and there were no

clinical indications. Mean retinal nerve fiber layer (RNFL) and ganglion cell inner plexiform layer (GC-IPL) thicknesses were compared between groups using ANCOVA, and means were correlated with pre-selected MRI brain volumes, NP domain scores, and CSF cytokines and neurofilament light chain.
Results: There were no differences in age, race or visual acuity between the two groups; there were more women in the control group (p=0.006). In the HIV+ group, the median time since diagnosis was 19 years and all had an HIV RNA level <100 copies/ml for at least one year prior to the SD-OCT. Multiple regression analyses indicated that the HIV+ group had thinner adjusted-mean RNFL (78.17µm, 95% CI 76.3, 80.0; control = 84.0µm, 95% CI 81.3, 86.5; p < 0.005) and GC-IPL (90.0µm, 95% CI 87.0, 92.6; control = 96.6µm, 95% CI 92.2, 101.0; p = 0.01). In the HIV+ group, retinal thicknesses were negatively associated with the fraction of CSF volume (i.e. brain atrophy) on MRI (p=0.01 for RNFL and 0.006 for GC-IPL). There were few associations with NP domains and CSF measurements.
Conclusion: PLWH on ART had thinning of the RNFL and the GC layer of the retina. This retinal thinning was asymptomatic but was strongly associated with measures of brain atrophy. This suggests that there is widespread neurodegeneration including the retina despite adequate ART.



419 GUT MICROBIOTA REGULATE IMMUNE CELL HOMEOSTASIS IN THE CNS

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Background: The CNS is an important site of HIV infection, pathogenesis, and persistence. We recently demonstrated that CD4+ T cells are present in the brain and that they are susceptible to HIV infection. We also showed that HIV infection results in CD4+ T cell depletion in the CNS and that CD4+ T cell homeostasis could be restored by ART. Recently, it was shown that gut microbiota influences T cell trafficking to the brain in certain disease states via the gut-brain axis. Based on these observations, we hypothesized that gut microbiota regulates immune cell homeostasis in the CNS which could modulate HIV infection, pathogenesis, and persistence in the CNS.
Methods: Direct experimentation in humans to establish gut microbiota's role in CNS immune homeostasis is not possible. We established an in vivo platform to investigate gut microbiota's role in human hematopoietic cell homeostasis in the brain. We generated germ-free (GF) bone marrow/liver/thymus (BLT) humanized mice and BLT mice colonized with human (HuM-BLT mice) or murine (MuM-BLT mice) gut microbiota. First, we rederived GF immunodeficient NSG mice. GF NSG mice were implanted with human thymus/liver tissue and transplanted with autologous stem cells in a GF surgical isolator. HuM-BLT and MuM-BLT mice were constructed by colonizing GF mice with human or mouse fecal microbiota. Using flow cytometry, we quantitated human T cells (CD4+ and CD8+), B cells and myeloid cells in the brains of GF BLT (n=10), HuM-BLT (n=14), and MuM-BLT (n=10) mice.
Results: Our results revealed higher levels of human hematopoietic cells in the brains of MuM-BLT (p=0.0076) and HuM-BLT (p=0.0534 [7.4x higher]) mice compared to GF BLT mice. Total human T cell, CD4+ T cell and CD8+ T cell numbers were significantly higher in the brains of HuM-BLT (p=0.0034, p=0.0034 and p=0.0106 respectively) and MuM-BLT (p=0.0041, p=0.0030, p=0.0076 respectively) mice compared to GF BLT mice. Human B cell and myeloid cell levels were not significantly different. We confirmed that these results were not due to the humanization procedure by performing a similar analysis of murine immune cell levels in the brains of GF and colonized wild-type mice.
Conclusion: Collectively, our results demonstrate that gut microbiota regulate immune cell homeostasis in the CNS and provide the first evidence that gut microbiota may have a direct role in HIV pathogenesis and the establishment and maintenance of the CNS HIV reservoir.

420 CSF1R INHIBITION TARGETS CNS MACROPHAGES IN AN SIV/MACAQUE MODEL OF HIV CNS DISEASE

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Background: CNS macrophages, including microglia, serve as a latent HIV cellular reservoir. Colony stimulating factor 1 receptor (CSF1R) is expressed exclusively on cells of myeloid lineage and is essential for microglial survival. CSF1R protein levels increase with SIV and HIV infection and remain elevated in the CNS despite suppressive ART. Consequently, CSF1R is an ideal drug target to reduce the CNS latent reservoir.
Methods: Primary brain and spinal cord microglia were isolated from uninfected macaques. Cells were cultured for one week before treatment with 10uM PLX3397, a small molecule inhibitor of CSF1R, or vehicle. Calcein and ethidium staining was used to identify live and dead cells. Live cells were also quantified using interferon-beta qPCR. In vivo studies were conducted using daily oral treatment of 165mg/kg PLX3397 in ART-suppressed SIV-infected pigtailed macaques (N = 2). Two weeks after the start of PLX3397 treatment, ART was stopped while PLX3397 treatment continued. Plasma and CSF were collected every four days after release to measure viral loads. Animals were euthanized 16 days post-release from ART. Brain and spinal cord microglia were isolated after euthanasia to measure viral RNA, DNA, and replication competence.
Results: PLX3397 treatment in vitro significantly reduced the number of primary microglia over 72 hours (P < 0.0001, Two-Way ANOVA). In vivo, PLX3397 treatment was well tolerated; animals did not show side-effects or develop monocytopenia. PLX3397 did not significantly affect plasma viral rebound kinetics. However, treatment did prevent CSF rebound in one animal. In addition, neither SIV RNA or DNA was detected in cultured primary microglia from this animal. In the second animal, viral RNA was isolated from CNS macrophages cultured from both brain and spinal cord.
Conclusion: PLX3397 reduced CNS macrophage viability in vitro, demonstrating that targeting CSF1R may reduce CNS macrophages, including those harboring HIV. PLX3397 treatment was associated with a lack of SIV rebound from the CNS and a decrease in IBA1+ CNS macrophages in one of two animals after stopping ART. These studies demonstrate the potential of targeting CSF1R to reduce the HIV latent reservoir in the CNS.

421 METAGENOMIC NEXT-GENERATION SEQUENCING FOR DIAGNOSIS OF CNS INFECTION IN PLWH

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Background: Central nervous system (CNS) infection is still the leading cause of death in people living with HIV. Metagenomic next-generation sequencing (mNGS), which could identify a comprehensive spectrum of pathogens by a single assay, has recently shown its efficacy in the diagnosis of infectious diseases. However, its clinical utility in HIV-infected patients is still not well established.
Methods: HIV-infected patients with clinically suspected CNS infection admitted to Shanghai Public Health Clinical Center, China underwent lumbar puncture. Cerebrospinal fluid (CSF) samples were sent to conventional testing,

including bacterial and fungal smear, acid-fast stain, cryptococcal antigen test, GeneXpert MTB/RIF, Treponema pallidum particle agglutination assay, rapid plasma reagin test, as well as culture of bacteria, fungal organisms and Mycobacterium species. Patients with negative results of all the above-mentioned tests were enrolled and had a mNGS test on CSF.
Results: A total of 45 eligible patients were enrolled. The majority of them were middle-aged male with CD4 T cell counts of 75 (2-504) cells/ul. An etiologic diagnosis was identified in 57.8% (26/45) of the study participants. CD4 T cells counts in patients with pathogens detected in CSF by mNGS were significantly lower than that in those without a definite diagnosis [44(2-414) vs 180(5-504) cells/ul, P=0.02]. Among the 26 patients with confirmed CNS infection, pathogens including John Cunningham virus (10), Cytomegalovirus (9), Varicella-zoster virus (4), Toxoplasma gondii (3), Aspergillus (3), Penicillium (2), Torque teno virus 19 (1), Human herpesvirus 8 (1), Methylobacterium (1), Mesorhizobium (1), and Acinetobacter (1) were identified by mNGS. Multiple infections were diagnosed in 11 cases (24.4%). The results of mNGS led to the modification of treatment in 33.3% patients (15/45), while they increased confidence in maintaining original therapy in 24.4% patients (11/45). During a median of 20 days hospitalization, the overall mortality was 2.2% (1/45). 66.7% (30/45) of the patients showed improvement, 28.9% (13/45) stable and 2.2% (1/45) deteriorated, respectively.
Conclusion: Our data show that clinical mNGS of CSF represents a helpful tool in the diagnosis of CNS infection among HIV-infected patients.

422 EXPRESSION OF HIV-1 INTRON-CONTAINING RNA IN MICROGLIA INDUCES INFLAMMATORY RESPONSES

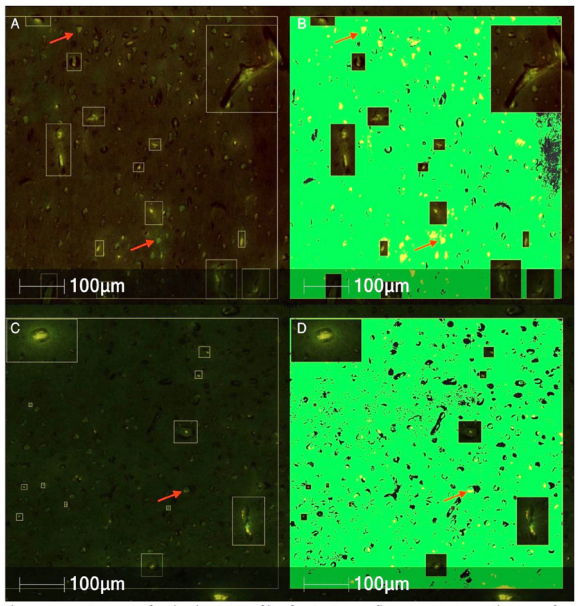
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Background: Chronic immune activation is observed in HIV-1+ individuals on long-term combination antiretroviral therapy (cART) and is thought to lead to HIV-associated non-AIDS complications (HANA) such as neurocognitive impairment. We have recently reported that expression of HIV intron-containing RNA (icRNA) alone in productively infected monocyte-derived macrophages induces proinflammatory responses (PMID 30150664). Hence, in this study, we tested the hypothesis that persistent expression of HIV icRNA in microglia (MG), the brain-resident macrophage, contributes to neuroinflammation.
Methods: Monocyte-derived microglia (MDMGs) were derived from CD14+ cells purified from PBMCs. Human iPSC (induced pluripotent stem cell)-derived microglia (hiMG) were generated by co-culturing yolk-sac-derived primitive macrophages and iPSC-neurons. Expression of MG markers such as P2RY12, IBA-1 and TMEM119 was confirmed by qRT-PCR or flow cytometry. Microglia were infected with HIV-1, and extent of viral infection and induction of proinflammatory responses was determined by mRNA analysis (NanoString, qRT-PCR), flow cytometry and ELISA.
Results: HIV-1 infection in MDMGs up-regulated expression of ISGs and proinflammatory cytokines such as IP-10 and MCP-1. Treatment of infected MDMGs with raltegravir or a CRM1 inhibitor that blocks Rev–CRM1-dependent nuclear export of HIV-1 icRNA, or infection of MDMGs with Rev-mutant (M10) deficient for icRNA export did not induce IP-10 expression, suggesting that nuclear export of HIV icRNA but not Rev or Tat expression is the trigger for proinflammatory responses in MDMGs. To better mimic the yolk-sac origin of MG, we generated hiMG and found that hiMGs were robustly infected with replication competent CCR5-tropic HIV-1 (YU2). Importantly, establishment of productive infection led to secretion of proinflammatory cytokines IP-10 and MCP-1, which was inhibited upon pre-treatment with raltegravir or CRM1 inhibitor. Interestingly, HIV-infected hiMGs displayed poor phagocytic activity, suggesting that HIV infection negatively impacts homeostatic functions of MG.
Conclusion: Collectively, our findings suggest that viral gene expression and nuclear export of HIV icRNA, even in the absence of viral spread, induces proinflammatory responses in microglia and suppresses their homeostatic functions. Since none of the current cART regimens inhibit viral RNA expression, novel strategies are needed to suppress HIV icRNA expression-induced immune activation.

423 ACCELERATING CELLULAR SENESCENCE IN THE BRAIN OF SIV-INFECTED YOUNG RHESUS MACAQUES

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Background: HIV infection plays a role in accelerating aging. Limited studies have found cellular senescence can occur in some tissues in HIV-infected individuals. However, it is unclear whether HIV infection can accelerate senescence in the brain partially due to challenges of access to human brain tissues. Here we used the SIV infected rhesus macaque model to determine whether SIV contributes to aging of the brain.
Methods: Four groups of rhesus macaques were studied, which included SIVmac251-infected young (Mean 6.65 ± SD 0.94 years) and old aged animals (Mean 20.26 ± SD 3.91 years), and SIV-naïve age-matched animals for comparison. Brain frontal lobes were collected and formalin-fixed paraffin-embedded. Lipofuscin, p16, p21, Cyclin D1 (CCND1), and Caveolin 1 (CAV1) were used as biomarkers of brain cellular senescence, and measured by RNAScope, RT-qPCR, and/or immunohistochemistry. Image data quantification analysis was performed by HALO and ImageJ software.
Results: As expected, in healthy SIV-naïve groups, a significantly higher amount of lipofuscin was observed in old animals than young animals. However, interestingly, this age-dependent discrepancy disappeared between groups of young and old animals with SIV infection, although both groups had higher levels of lipofuscin than young uninfected group. Moreover, the increase of lipofuscin was significantly higher in SIV-infected young animals than those age-matched animals without SIV infection, this was not observed between the older groups of animals with or without SIV infection. CAV1 gene expression was significantly increased in the SIV-infected young animals. CCND1 was significantly higher in uninfected older animals than uninfected young animals, but SIV infection of young animals reduced this difference to insignificant. In the young groups, SIV infected animals had a higher expression levels of p21, CCND1, and CAV1 than uninfected cohorts.
Conclusion: Our results demonstrate that SIV infection contributes to accelerating brain cellular senescence in young rhesus macaques. Given that senescent cells in the brain contribute to the cognitive decline and neurodegeneration, our findings indicate that they play an important role in the acceleration of brain aging in young hosts and possibly towards to the development of HIV-associated neurocognitive disorders.



Fluorescent microscopy for the detection of lipofuscin via autofluorescence. Frontal cortex of SIV infected (A&B) and naïve (C&D) young, rhesus macaques. SIV infected, young, rhesus macaques have higher numbers of cells that contain lipofuscin (A). In naïve, young, rhesus macaques, only rare cells contain lipofuscin (C). Overlays of the HALO analysis results illustrate the autofluorescent area detected (yellow) in SIV infected and naïve, young rhesus macaques (B&D respectively). Arrow: example of lipofuscin. Dotted box: nonspecific autofluorscent area, exclusion from analysis.

424 CNS HIV BEARS ENVELOPE MARKERS CONSISTENT WITH T-CELL ORIGIN IN THE FACE OF ART

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Background: One line of evidence that the CNS may be a source for HIV in the face of ART is cerebrospinal fluid (CSF) escape, where HIV is suppressed in the blood but detectable in the CSF. However, it is unclear if CSF HIV is CNS restricted or can transmit to other sites. For the latter, HIV requires high-level drug resistance and infection of a cell able to traffic out of the CNS. Here we investigated the cell of origin of HIV in the CSF of CSF escape study participants, as well as whether the ART concentrations found in the CSF could result in the evolution high level resistance necessary for HIV replication outside the CNS compartment.

Methods: We collected blood and CSF from 122 South African participants clinically indicated for lumbar puncture. We performed a viral load assay and detected concentrations of antiretroviral drugs in the blood and CSF and chose participants on the first line regimen of efavirenz, emtricitabine, and tenofovir for further study to avoid confounding effects of regimen type. For CSF escape participants (22% of total), we used the CD26 and CD36 host cell surface markers on the virion envelope to determine the cellular source of HIV using binding to anti-CD26 and CD36 antibody columns, followed by viral load assay of bound virus. The cell type specific signature of CD26 and CD36 was determined from in vitro infected macrophages and T cells and was unambiguous for these cell types. We also examined the effect of measured ART levels of CSF escape participants on HIV replication and evolution using in vitro infection.

Results: We observed that the CD26/CD36 signature on the viral surface of HIV from CSF escape was consistent with T cell origin of the CSF virus. This was also the case for CSF HIV from participants who were viremic in both compartments. ART levels of efavirenz, emtricitabine, and tenofovir were not significantly different between individuals with CSF escape and those who were fully suppressed. Furthermore, HIV replication at CSF ART levels was required in in vitro infection for the progression to high level, multidrug resistance and replication at ART levels found in the blood.

Conclusion: The combination of an infected cell type able to disseminate infection and ART levels conducive to stepwise evolution of resistance implicates the CNS as a source for the spread of drug resistant virus in the face of ART.

425 HIV-1 VIRAL DIVERSITY AND RESISTANCE IN CENTRAL NERVOUS SYSTEM BY DEEP SEQUENCING

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Background: The central nervous system (CNS) compartment is one of several sites in which compartmentalized HIV-1 replication has been observed. Most studies assessed viral compartmentalization in the CNS via cerebrospinal fluid, however, information about tissue compartmentalization of HIV-1 is still limited.

Methods: We used ultra-deep sequencing (UDS) to study viral diversity and resistance patterns in different brain areas by analyzing reverse transcriptase (RT) gene. Twelve samples from 3 patients (P1, P2 and P3) with possible or certain HIV-encephalopathy were studied and sequencing was performed on MiSeq (Illumina®). HIV proviral DNA reservoir quantification was performed with Generic HIV DNA Cell® kit and diversity by (i) phylogenic analysis with approximately-maximum-likehood phylogenic trees with Fastree 2.1, (ii) single-nucleotide polymorphism on Geneious Prime software and (iii) HIV-1 genotypic drug resistance identification with algorithms 2018 administered by ANRS.

Results: HIV-proviral DNA was undetectable in all P1 samples and in P2 cerebellum and thalamus sample. P2 temporal lobe and medulla oblongata sample as well as all P3 specimens showed detectable proviral-DNA loads by increasing order: cerebellum (23 cp/ 10^6 cells), medulla oblongata (31 cp/ 10^6 cells), temporal lobe (91 cp/ 10^6 cells), substantia nigra (92 cp/ 10^6 cells), caudate nucleus (130 cp/ 10^6 cells), and frontal lobe (544 cp/ 10^6 cells). Overall, RT phylogenic analysis revealed (i) a high diversity in each site analyzed, and (ii) HIV compartmentalization within different brain areas with a majority of them harboring a distinct HIV subpopulation. However, some cerebral sites also shared HIV variants; caudate nucleus and spinal cord in P1 or caudate nucleus, cerebellum and frontal lobe in P3 [figure 1]. On the other hand, brainstem (substantia nigra and oblongata specimen) area harbored a specific subpopulation in both P2 and P3. Some non-synonymous conferring resistance to Nucleoside and Non-Nucleoside Reverse Transcriptase Inhibitors were found, specifically M41L, V90L and V106I. However, the presence or proportion of variants carrying these mutations varied within different brain areas of a same patient.

Conclusion: This work showed by UDS significant inter-regional and intra-regional viral diversity in CNS reflecting viral replication. It also confirmed HIV-compartmentalization in different brain areas suggesting that there is not a single but several reservoirs within CNS.

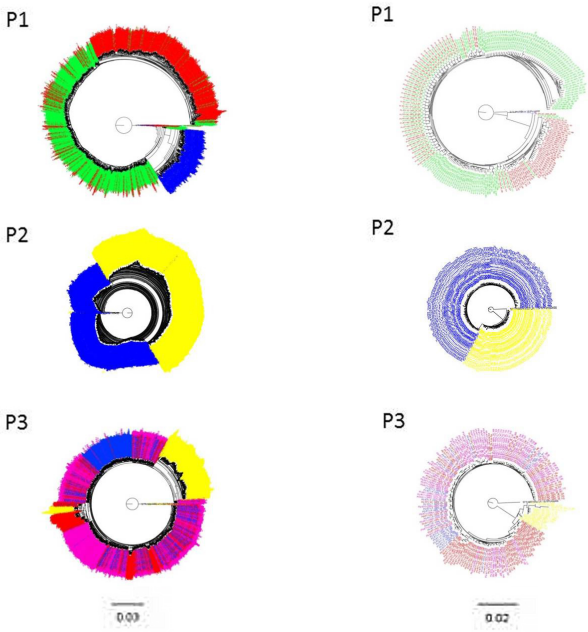


Figure 1: Approximately maximum-likelihood phylogenetic trees constructed with Fastree (2.1) of RT consensus viral sequences issued from different brain aeras. *Trees on the left side correspond of phylogenetic analysis with all viral consensus sequences and those on the right of phylogenetic analysis after cleaning viral consensus sequences found less than 100 times in each brain area.*

Red: caudate nucleus; blue (P1 and P2: temporal lobe, P3: frontal lobe); green: spinal cord; yellow: brainstem (P2: medulla oblongata and P3: substantia nigra); pink: cerebellum

426 HIV DIVERSITY IN CSF AND PLASMA OF INDIVIDUALS WITH HIV AND CRYPTOCOCCAL MENINGITIS

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Background: HIV-1 can compartmentalize in reservoir sites e.g. the central nervous system (CNS) and this is a barrier to complete HIV eradication. We compared cerebrospinal fluid (CSF) and plasma viral load (VL), drug resistance mutations (DRMs) and co-receptor usage in HIV-1 strains from individuals co-infected with HIV-1C and Cryptococcal meningitis (CM) in Botswana

Methods: This was a cross-sectional study utilizing CSF and plasma paired samples from 60 participants enrolled in a clinical trial evaluating the early fungicidal activity of 3 short-course, high-dose liposomal amphotericin B regimens for CM between 2014-2016. HIV VL was measured in 38/60 (63%) paired samples. Viral escape was defined as HIV-1 RNA ≥0.5 $\log_{10}$ in CSF than plasma and HIV-1 VL discordance as CSF/Plasma ratio >1. HIV-1 protease, reverse transcriptase and envelope were sequenced using big dye sequencing chemistry and analyzed for DRMs using Stanford HIV drug resistance database. Geno2pheno was used for prediction of co-receptor usage.

Results: A total of 34/38 participants (89.5%) had detectable VL in plasma and CSF with medians of 5.1 (IQR:4.7-5.7) and 4.6 (IQR:3.7-4.9) $\log_{10}$copies/ml, respectively ($p \leq 0.001$). The prevalence of CSF viral escape was 1/34 (2.9%) [95% CI: 0.07-15.3]. HIV-1 VL discordance was observed in 7/34 (21%) pairs. Discordance was not associated with CD4 count, ART status, duration or regimen, abnormal mental status, or mortality. A total of 26/45 (58%) pairs were sequenced and 14% were on ART. Frequency of DRMs in the plasma and CSF was 9 and 11, respectively. The most predominant DRM in the plasma was K101E (n=2) whilst the other mutations occurred at equal frequency of 1 in

plasma and CSF (table 1). HIV DRM discordance was present in 3/26 (12%) paired samples. Of these, one had I84T and the other had M46I in CSF only, the third one had K101E in plasma and V106M in CSF. V3 loop was sequenced from 18/45 (40%) pairs; 94% and 83% were CCR5-using strains in the CSF and plasma, respectively (p=0.8).

Conclusion: Low rates of CSF viral escape were observed and co-receptor usage was similar in both compartments. PI-associated DRMs were found in the CSF but not in plasma. Studies investigating the clinical effectiveness of PIs are warranted.

Table 1: Protease and Reverse transcriptase associated mutations in CSF and plasma

ID	ART regimen	Plasma DRM			CSF DRM		
		NRTI	NNRTI	PI	NRTI	NNRTI	PI
1930	ART naïve	None	None	**None**	None	None	**I84T**
1736	TDF+3TC/FTC +EFV	D67N, K70G, M184V, K129E	K101E, K103N, E138A, G190A	None	D67N, K70G, M184V, K129E	K101E, K103N, E138A, G190A	None
1134	ABC+3TC/FTC +EFV	None	**K101E**	None	None	**V106M**	None
1895	ART naïve	None	None	**None**	None	None	**M46I**
1528	TDF+3TC/FTC+NVP	M184M/I	None	None	M184M/I	None	None

427 HERPES ZOSTER IN HIV: THE ROLE OF PLEOCYTOSIS IN SECONDARY CSF ESCAPE AND DISCORDANCE

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Background: HIV cerebrospinal fluid (CSF) escape is defined by higher HIV RNA levels in CSF than plasma in the presence of treatment-related plasma viral suppression, while CSF discordance is similarly defined by higher CSF than plasma HIV RNA in untreated individuals. Secondary escape or discordance implies that the disproportionate CSF HIV RNA relates to another infection in addition to HIV.

Methods: A retrospective review of people living with HIV enrolled in a cohort study or receiving clinical care at Sahlgrenska Infectious Diseases Clinic in Gothenburg, Sweden who developed uncomplicated herpes zoster (HZ) and underwent lumbar puncture (LP) within the ensuing 150 days. Based on treatment status and the relationship between CSF and plasma HIV RNA concentrations, they were divided into 4 groups: i) antiretroviral treated with HIV CSF escape (N=4), ii) treated without CSF escape (N=5), iii) untreated with HIV CSF discordance (N=8), and iv) untreated without CSF discordance (N=8). We augmented these with two additional cases of secondary CSF escape related to neuroborreliosis and HSV-2 encephalitis and analyzed this experience for factors contributing to CSF HIV RNA concentrations.

Results: HIV CSF escape and discordance were associated with higher CSF white blood cell (WBC) counts than their non-escape (P<0.01) and non-discordant (P<0.01) counterparts.The CSF WBC counts correlated with the CSF HIV RNA levels in both the treated (P<0.01) and untreated (P<0.01) group pairs. Moreover, the CSF WBC counts correlated strongly with the CSF:plasma HIV RNA ratios of the entire group of 27 subjects (P=<0.0001) indicating a strong effect of the CSF WBC count on the relation of the CSF to plasma HIV RNA concentrations across the entire sample set. The inflammatory response to HZ and its augmenting effect on CSF HIV RNA was found up to 5 months after the HZ outbreak in the cross-sectional sample, and continued for one year after HZ in one individually followed longitudinally.

Conclusion: HZ provides a useful 'model' of secondary CSF escape and discordance. Likely, the inflammatory response to HZ pathology within the neuraxis provokes or augments local HIV production by enhanced trafficking or activation of HIV-infected CD4+ T lymphocytes. Whereas treatment and other systemic factors determine the plasma HIV-1 RNA set-point, the CSF WBC count strongly influences the relation of the CSF HIV RNA level to that set-point.

428 BRAIN HIV LATENCY BIOMARKERS

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Background: The presence and quantification of HIV in the brain is important for eradication as neuropathological studies suggest that latent brain HIV varies considerably amongst individuals. HAND, both past and stable in virally suppressed (VS) patients is associated with brain latency and may serve as a latency biomarker discovery approach. We hypothesized that putative brain latency biomarkers would differ in VS past/stable HAND vs. non-HAND.

Methods: 24 HIV+ men (age M=52.67±12.72; HIV infection duration: M=17.75±12.69 years) who were VS (in plasma <100cpml and CSF <100cpml) on cART underwent lumbar puncture and neuropsychological testing. Patients with past HAND from which they had recovered and patients with stable HAND (past/stable HAND group) were compared to patients with no known past or current CNS involvement (non-HAND group) for putative markers of HIV brain latency: CSF HIV RNA by single copy assay (SCA), HIV tat, BCL11b, neurofilament-light chain (NFL), neopterin, CCL2, and CSF:serum albumin ratio (Q-Alb). CSF markers were classified as normal/abnormal using normal references and a combined CSF latency biomarker risk score was created by summing the number of abnormal values. HAND status was defined using Global Deficit Score (GDS≥0.5). Past HAND was determined from medical record review.

Results: Low level HIV persistence (CSF HIV RNA SCA >1-12.4 cpml) was detected in CSF in both groups (17% of past/stable HAND and 24% of non-HAND; p=73) and HIV tat was also detected in both groups (17% of past/stable HAND and 6% for non-HAND; p=.42) (SCA was <1cpml in each case). BCL11b levels were similar across the board. However, the past/stable HAND group showed higher NFL levels (p=.05) than the non-HAND group. Neopterin was abnormal in many patients (57% of past/stable HAND and 31% of non-HAND; p=.24). CCL2 and Q-Alb levels were largely normal and similar in both groups. Consequently, the combined CSF latency biomarker risk score did not differ across groups (p=.58).

Conclusion: Past/stable HAND is not a useful model for identifying brain latency biomarkers using the latter markers. Past/stable HAND remains an active virological immunological and degenerative process. The concept of a "legacy effect" from past HAND is not supported.

Table 1. Demographic characteristics and CSF biomarker levels

	Past/stable HAND	*non-HAND*	*Mann-Whitney z/χ²*	*p*
Description	*Past HAND + NP-Normal on study (n=2); Past HAND + HAND on study (n=5)*	*No Past HAND + NP-Normal on study (n=17)*		
N	7	17		
Age [mean (SD)]	60.86 (7.24)	49.29 (13.10)	1.94	.05
Education [mean (SD)]	15.29 (2.64)	13.44 (2.15)	1.67	.10
Sex (% male)	100	100	0.00	.
<200 Nadir CD4+ (%)	71	18	6.45	.02
Current CD4+ (cells/μL) [median (IQR)]	674 (631)	678 (356)	-0.19	.85
HIV duration (years) [median (IQR)]	32 (14)	10 (20)	2.45	.01
Plasma HIV RNA PCR undetectable (<20cpmL) (%)	86	94	0.46	.51
Plasma HIV RNA SCA undetectable (<1cpmL) (%)	59	86	1.61	.35
CSF HIV RNA PCR undetectable (<80cpmL) (%)	100	100	0.00	.
CSF HIV RNA SCA undetectable (<1cpmL) (%)	83	76	0.12	.73
CSF HIV-Tat (pg/mL) detectable (%)	17	5	0.65	.46
Log_{10} CSF BCL11b (pg/mL) [mean (SD)]	2.02 (0.23)	1.85 (0.48)	0.64	.53
Log_{10} CSF NFL (pg/mL) [mean (SD)]	3.21 (0.31)	2.93 (0.21)	1.97	.05
CSF NFL (pg/mL) abnormal (%)	57	24	2.52	.17
Log_{10} CSF neopterin (mmol/L) [mean (SD)]	1.15 (0.26)	1.07 (0.20)	0.37	.71
Neopterin abnormal (≥13mmol/L) (%)	57	31	1.38	.36
Log_{10} CSF MCP-1 (pg/mL) [mean (SD)]	5.88 (0.33)	5.95 (0.40)	-0.32	.75
CSF MCP-1 (pg/mL) abnormal (%)	0	0	0.00	.
Log_{10} CSF/serum albumin ratio [mean (SD)]	0.68 (0.33)	0.70 (0.19)	-0.51	.61
CSF/serum albumin ratio abnormal (%)	14	12	0.03	1.00
CSF latency biomarker risk score	2.00 (1.41)	1.65 (1.11)	0.56	.58

429LB HIGH LEVELS OF CELL-ASSOCIATED HIV-1 TRANSCRIPTION IN CSF DESPITE EFFECTIVE cART

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Background: CSF is a possible compartmentalized HIV reservoir though the cells involved and their level of HIV-1 transcriptional activity remain obscure. We used a novel highly sensitive assay of HIV-1 RNA/DNA and flow cytometry to study both CSF cells and PBMC.
Methods: We studied 10 HIV+ subjects (2 with current HAND) on cART with both plasma and CSF HIV RNA (Roche) <50 copies/ml.DNA and RNA were extracted from paired samples of CSF (13-20 ml) and PBMC. Cell-associated HIV-1 transcriptional activity and HIV-1 DNA levels were determined by a newly described quantitative piCode End-Point PCR assay, based on the extremely sensitive piCode MicroDiscs platform (>27-fold sensitivity of real-time PCR; Suzuki et al J AIDS HIV Treat. 2019; 1(2):69). It detects transcripts of HIV LTR, including unspliced RNA (gag/pol), incompletely spliced RNA (tat, vpr, vpu), and multiply spliced RNA (rev, nef), with a sensitivity of 3 infected cells/10^6 cells. Immunological profiles of CSF cells and PBMC were determined by 18-colour flow cytometry and compared by Wilcoxon signed rank test. MR spectroscopy (MRS) evaluated the frontal white matter (FWM), posterior cingulate cortex (PCC), and caudate nucleus.
Results: 9/10 patients' CSF had high levels of cell-associated HIV-1 RNA transcriptional activity (median 4711 copies per 10^6 cells, vs 270 in PBMC; p=0.004). 8/10 patients had HIV-1 DNA in CSF cells (median 1314 copies per 10^6 cells vs 752 in PBMC; p=0.09). Higher HIV-1 RNA in CSF cells was correlated with lower N-acetyl aspartate in FWM (r=-0.78; p=0.038) and PCC (r=-0.76; p=0.012). 95% of CSF cells were T cells, of which 95% were memory CD4 and CD8 T cells (median counts of 8,818 and 7,503 cells, respectively). 2.8% of CSF cells were CD14+CD16+ monocytes, 1.7% were NK cells and 0.4 % were B cells. CSF CD4 T cells consisted of 75% CXCR3+ CD49d+ integrinß7- cells (vs 15% of CD4 in PBMC); 48% CCR5+ (vs 16% in PBMC); and 18% expressing CD38 and/or HLA-DR activation markers (vs 7% in PBMC).
Conclusion: CSF cellular HIV-1 LTR transcriptional activity is compartmentalised and its biological significance is strongly indicated by the MRS correlations. The cellular origin is likely the dominant CXCR3+ CD49d+ integrinß7- non-gut homing memory CD4+T cells; monocytes may be less important. Transcriptional products eg tat (vs whole virus) are likely neuropathogenetically significant. These data support HIV-1 transcription inhibitor development.

	HIV RNA Copies /10^6 cells	HIV DNA Copies /10^6 cells	Total CSF cell counts Median (IQR)			% of CD4 Median (IQR)		
	Median (IQR)	Median (IQR)	Memory CD4	Memory CD8	Mono-cytes CD14+ CD16+	CXCR3+ CD49d+ Integrin ß7-	CCR5+	CD38+ and/or HLA-DR+
CSF	**4,711** (1647-6780)	**1,314** (427-3804)	**8,818** (2609-21797)	**7,503** (2530-12984)	**455** (206-1453)	**75 %** (71-86)	**48** (40-59)	**18** (7-30)
PBMC	**270** (263-1025)	**752** (236-1025)	N/A	N/A	N/A	**15** (10-19)	**16** (11-22)	**7** (5-11)
p value	*0.004*	0.09	-	-	-	*0.008*	*0.004*	*0.02*

430 PLASMA RAMs IN REVERSE TRANSCRIPTASE GENE ASSOCIATE WITH CSF HIV-1 ESCAPE

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Background: Several risk factors for cerebrospinal fluid HIV-1 escape (CSFE) have been reported: length of HIV infection, cART interruptions, low CD4 nadir/CPE score, persistent low-level viremia and the use of ABC+3TC, boosted PIs or unboosted ATZ. We sought to assess whether the presence of previous plasma RAMs may be a determinant behind the reported risk association between CSFE and ARVs class composing cART.
Methods: Retrospective cross-sectional study on HIV+ adult patients on cART undergoing lumbar puncture (LP) for any reason (2007-July 2019) at 4 Italian hospitals (Brescia, Torino, Roma, Milano). Inclusion criteria: being on cART for at least 6 months, available coupled plasma and CSF HIV-RNA measurements, available historical cumulative plasma genotypic resistance testing (HGRT) for reverse transcriptase (RT) and protease (PI) genes. Exclusion criteria: secondary CSFE. CSFE was defined as any measurable CSF HIV-RNA coupled with a plasma HIV-RNA <50 copies/mL and any difference ≥0.5 Log_{10} between CSF and plasma HIV-RNA when the latter was detectable
Results: 197 patients were enrolled: 50 years (43-54), current and nadir CD4 count 312 (115-560) and 82 (24-200) cells/µL; median length of cART treatment 54 months (17-171). 126 patients (63.9%) had plasma HIV-RNA<50 cp/mL and 28 (14.2%) showed CSFE. The main reasons for LP were diagnostic assessment in diseases without eventually CNS involvement (25.4%), HIV-associated neurocognitive disorders (28.4%), CNS infections (19.8%) and research purposes (16.2%). CSFE was not associated with PIs use in the whole cohort (16.6% vs 8.6%, p.14) nor in any subgroup identified by cART type (3 different-classes-, 3 drugs-NRTIs- and ≥4 drugs-based cART). Instead, PIs use was more common in patients with a positive HGRT for RAMs in RT (44.9% vs 29.3%, OR 2.0 [1.1-3.8], p.04). Having a cumulative HGRT positive for RAMs in RT associated with a higher risk of CSFE (21.5% vs 9.3%, OR 2.7 [1.2-6.0], p.01), while no such an association was observed for RAMs in PI (17.4% vs 13.8%). Interestingly, at the CSFE diagnosis patients showed higher proportion of positive CSF RAMs in RT compared to patients without CSFE with available CSF GRT (55.6% vs 19.0%, p.04). At multivariable analysis, only RAMS in RT and CD4 nadir were independent predictors of CSFE (tab.1)
Conclusion: In this cohort, CSFE prevalence was slightly higher than what reported in recent studies. Besides low CD4 nadir, the positivity of HGRT for plasma RAMs in the RT gene and not the use of PIs per sé was an independent predictor of CSFE

Table 1. Predictors of primary CSF HIV-1 escape at multivariable logistic regression model

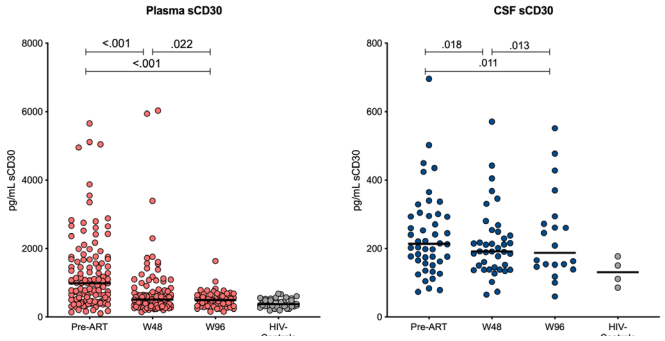
Parameter	AOR (IC95%)	p
Nadir CD4+ T cell, per every 100 CD4+ T-cells/mmc more	0.42 (0.18-0.99)	***.047***
Plasma HIV-RNA (cp/mL)	NS	.96
Time on continuous plasma virological suppression (months)	NS	.14
cART including PIs	NS	.73
Presence of plasma RAMs in Reverse Transcriptase	9.9 (1.9-52.9)	***<.01***
Presence of plasma RAMs in Protease	NS	.99
CPE score	NS	.36

431 PLASMA AND CSF SCD30 DYNAMICS BEFORE AND AFTER ART INITIATED IN ACUTE HIV

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Background: Soluble CD30 (sCD30) is a potential marker of persistent immune activation and/or viral persistence in people living with HIV (PLWH). Surface CD30 co-localizes with HIV RNA and DNA in CD4+ T cells from blood and gut tissue and depletion of cells expressing CD30 reduces the total amount of HIV-1 DNA detected. Evalution of sCD30 in cerebrospinal fluid (CSF) compared to blood before and after antiretroviral therapy (ART) in acute HIV (AHI) may be valuable in understanding HIV neuropathogenesis.
Methods: We measured pre-ART sCD30 in plasma (n=117; 71 Fiebig 1-2, 46 Fiebig 3-5) and CSF (n=71; 39 Fiebig 1-2, 32 Fiebig 3-5) in the Thai RV254/SEARCH010 AHI cohort and examined correlations with HIV disease parameters and inflammatory biomarkers. A subset had sCD30 levels measured at 48 and 96 weeks on ART in plasma (n=109 and n=56, respectively) and CSF (n=40 and n=20, respectively). We used non-parametric tests to compare sCD30 levels between AHI participants and HIV-uninfected Thais and to assess relationships between covariates. We used mixed effects models to examine changes within individuals over time.
Results: The median age was 26.5 years (IQR 23-31), pre-ART CD4 count 381 (276-519), and estimated duration of infection 18 (15-23) days. The sample was 96% male. Compared with controls, pre-ART sCD30 levels were elevated in plasma (984 vs 374 pg/mL, p<0.001) and CSF (165 vs 131 pg/mL, p=0.01). Pre-ART plasma sCD30 levels correlated with plasma HIV RNA (r=0.44, p<0.001) and CD4/CD8 ratio (r=-0.5, p<0.001) as well as plasma neopterin (r=0.29, p=0.01), sCD163 (r=0.26, p=0.03), and IP-10 (r=0.28, p=0.02). Pre-ART CSF sCD30 correlated with CSF HIV RNA (r=0.24, p=0.03) as well as CSF sCD14 (r=0.44, p=0.001), sCD163 (r=0.46, p<0.001), and IP-10 (r=0.26, p=0.02). Plasma and CSF sCD30 did not correlate. In longitudinal analyses, sCD30 levels in both compartments declined at 48 and 96 weeks. This decline was more substantial in plasma (-1.9-fold change, p<0.001) than CSF (-1.14-fold change, p=0.0015).
Conclusion: In untreated AHI, sCD30 is elevated in plasma and CSF and correlates with markers of HIV disease activity and inflammation. With ART initiation in AHI, sCD30 levels decline in both compartments; this is distinct from

previous findings that CSF sCD30 rises after ART in chronic HIV and warrants further investigation to assess a possible distinct impact of very early ART.



432 QUANTITATION OF CEREBROSPINAL FLUID PLEOCYTOSIS AND HIV-1 RNA DURING ACUTE INFECTION

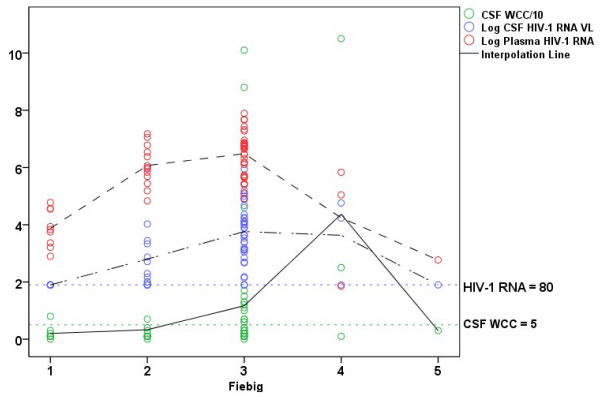
Phillip Chan[1], Camilla Muccini[2], Carlo Sacdalan[1], Eugène Kroon[1], Donn J. Colby[1], Nitiya Chomchey[1], Peeriya Prueksakaew[1], Suteeraporn Pinyakorn[3], Nittaya Phanuphak[1], Linda Jagodzinski[3], Victor Valcour[4], Sandhya Vasan[3], Jintanat Ananworanich[1], Serena S. Spudich[5], for the RV254 Study Team
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Background: HIV-1 RNA can be detected in cerebrospinal fluid (CSF) within days after viral transmission. CSF leukocyte level (clinically determined as white blood cell count, or WBC) is linked with levels of systemic and CSF HIV-1 RNA in untreated chronic HIV infection. We quantitated CSF WBC and investigated its associations with HIV-1 in blood and CSF during untreated acute HIV infection (AHI).

Methods: Individuals with AHI were enrolled in the RV254 cohort in Bangkok, Thailand. A subset underwent optional lumbar puncture (LP). We measured WBC, protein and glucose in whole CSF. HIV-1 RNA was tested in CSF supernatant by Roche COBAS TaqMan HIV-1 V2.0 with a lower limit of quantification (LLQ) of 80 copies/mL. A level of 79 copies/mL was assigned to samples with levels below LLQ. Logistic regression was used to determine factors predicting CSF pleocytosis (WBC>5 cells/mm_3).

Results: From March 2016 to March 2019, 61/246 RV254 participants underwent LP. 60 (98%) were male, and median age was 26, CD4 count 335 (IQR 247-553) and CD8 count 540 (IQR 357-802) cells/ul. 22 (37%) presented at Fiebig stage I & II and 36 (59%) had acute retroviral syndrome but none had overt neurologic signs or symptoms. 7 had untreated syphilis and 2 had hepatitis C. 16 (26%) CSF samples had HIV-1 RNA below LLQ. Median HIV-1 RNA levels in plasma and CSF were 6.10 (IQR 5.15-6.78) and 3.15 (IQR 1.90-4.11) log_{10} copies/ml respectively. The median CSF WBC was 2 (IQR 1-8; range 0-105) cells/mm_3. Median CSF protein and glucose were 27 (IQR 23.2-31.9) mg/dL and 62 (IQR 57-69) mmol/L respectively. 20 (33%) CSF samples had pleocytosis. Four extreme outliers had levels >40 cells/mm_3 of whom 2 were later diagnosed with neurosyphilis. Paring plasma and CSF HIV-1 RNA with CSF WBC by Fiebig stages revealed that CSF pleocytosis lagged behind the rise in CSF HIV-1 (Figure). In the multivariate analysis, CSF pleocytosis was independently predicted by CSF HIV-1 levels (adjust odd ratio (aOR)=2.69 (95%CI 1.44 – 5.04); p=0.002) and CD8 T-cells (aOR=1.24)(95%CI 1.00 – 1.54); p=0.046).

Conclusion: CSF pleocytosis is present in one third of neuroasymptomatic individuals during AHI. It appears to emerge temporally after CSF viremia, suggesting that marked CSF lymphocytosis is not necessary to early CNS viral transmigration. Future studies should examine the functionality of the excessive T-cells among those with CSF pleocytosis and whether the presence of pleocytosis may impact central nervous system outcomes in long term follow up after ART.



433 EVOLUTION OF IMMUNE ACTIVATION BIOMARKERS IN CSF IN FIEBIG I-V ACUTE HIV INFECTION

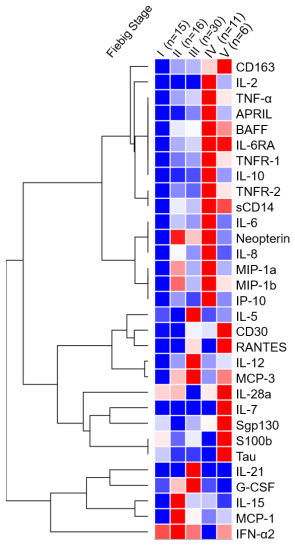
Julian Weiss[1], Phillip Chan[2], Carlo Sacdalan[2], Eugène Kroon[2], Siriwat Akapirat[3], Jennifer Chiarella[1], Victor Valcour[4], Nittaya Phanuphak[2], Ningbo Jian[5], Sandhya Vasan[5], Jintanat Ananworanich[2], Bonnie Slike[5], Shelly J. Krebs[5], Serena S. Spudich[1], for the RV254/SEARCH 010 study
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Background: The initial immune response in the central nervous system (CNS) during acute HIV infection (AHI) may set the trajectory for HIV-associated neurocognitive disorders (HAND). A better understanding of immune activation pathways and dynamics in the CNS during AHI could inform therapeutic modalities to lessen the neurological impacts of HIV.

Methods: We analyzed 41 biomarkers of immune activation in the cerebrospinal fluid (CSF) in the RV254/SEARCH010 Thai AHI cohort prior to antiretroviral initiation. We compared biomarker levels across Fiebig stages by univariate analysis and explored bivariate correlations with CSF HIV RNA levels. Temporal expression patterns were visualized by heatmap analysis (Figure 1), and pathway kinetics were identified through hierarchical clustering using Spearman's correlation of biomarkers differentially expressed between Fiebig stages. To quantify the heatmap data, post-hoc Dunn's test was performed for pairwise comparisons of biomarker levels between stages.

Results: CSF was collected for biomarker analysis from 78 enrollees (99% male, median age 28 (IQR 23-33) years, median duration of infection 18 (IQR 15-23) days, median CD4 T cells 400 (IQR 280-543) cells/mL, median log_{10} plasma HIV RNA 5.69 (IQR 5.01-6.51) copies/mL). Analysis of median CSF biomarker levels across Fiebig stages revealed temporal patterns of immune activation. Univariate analysis showed a set of biomarkers with statistically significant increases at Fiebig II compared to Fiebig I, and continued to increase until peak CSF viremia, primarily at Fiebig IV. The diverse subset of markers exhibiting this pattern included IL-2, TNF-α and its receptors TNFR-1 and TNFR-2, and IL-6RA, among others. Most biomarkers that followed this induction pattern had strong positive associations with CSF HIV RNA level, such as IL-2 (R2=0.36, P<0.0001) and TNFR-2 (R2=0.20, P<0.0001). Others, such as IL-15 and MCP-1, were also induced following Fiebig I, but peaked prior to peak viremia with inconsistent correlations with CSF HIV RNA level.

Conclusion: This analysis revealed temporal pathways of multiple CSF biomarkers with differential dynamics of immune activation during AHI. The predominant pattern displayed significant increases at Fiebig II compared to Fiebig I, with peak biomarker concentration occurring at peak CSF HIV RNA level during Fiebig IV. The levels of these CSF biomarkers correlated with CSF HIV RNA levels, and may provide insight into early immunological mechanisms contributing to HAND.



434 ROLE FOR PLATELET ACTIVATION AND ENDOTHELIAL ASSOCIATION IN HIV ENTRY INTO THE BRAIN

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Background: The brain is an important sanctuary site and barrier to cure in HIV. Platelet decline is associated with perivascular cuffs of infected cells in the brain in HIV infected humans and SIV infected macaques, but is considered subclinical and often untreated. Platelet activation and interactions with vascular endothelium can contribute to platelet decline, and impact the permeability of the blood brain barrier in the context of other diseases. We sought to determine if platelet-endothelial associations (PEAs) contribute to platelet decline and are associated with the presence of infiltrates of infected cells in the brain in the SIV-infected pigtailed macaque model of HIV infection, to confirm that PEAs exist in people living with HIV (PLWH), and to define how these interactions affect the blood brain barrier.

Methods: The effect of platelets on microvascular endothelial integrity in the brain was determined using a transwell cell culture assay system. PEAs and perivascular macrophages in the brain were identified using immunohistochemistry on tissue from SIV-infected pigtailed macaques and uninfected controls and from PLWH, and associations between PEAs and macrophage subsets determined using unbiased stereology. Platelet activation was monitored throughout infection using flow cytometry of platelet p-selectin on peripheral blood.

Results: Permeability of brain microvascular endothelium (BMEC) decreased two-fold following incubation with platelets from SIV-infected macaques compared with uninfected macaques (P=0.01), and that effect was abrogated by preventing contact between the platelets and BMECs. PEAs were observed in the brains of PLWH and in SIV-infected macaques. PEAs were more common in SIV-infected than control macaques during acute (RR = 4.0, P = 0.03) and asymptomatic (RR = 3.6, P = 0.04) infection, and were more likely to be associated with blood vessels surrounded by SIV-infected non-resident macrophages (RR = 1.5, P = 0.007). Macaques that did not develop perivascular infiltrates of cells in their brains during terminal infection demonstrated higher platelet activation during acute (P = 0.04) and asymptomatic (P < 0.0001) infection compared to those that developed infiltrates.

Conclusion: Platelet activation and PEA formation may represent a protective mechanism against entry of SIV-infected cells into the brain. Platelet decline in HIV infection may have clinical impacts and contribute to the development of latent viral reservoirs.

435 HIV SUPPRESSION AND CHANGES IN CSF MARKERS IN PATIENTS RANDOMLY SWITCHED TO DTG + 3TC

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Background: A major concern of dual therapy is the potential lower efficacy in viral reservoirs, especially in the central nervous system (CNS). The aim of this study was to evaluate the maintenance of HIV viral suppression as well as changes in neuronal injury and inflammatory markers in cerebrospinal fluid (CSF) in asymptomatic stable patients switching antiretroviral therapy within a clinical trial.

Methods: Prospective, single arm study. HIV+ virologically suppressed patients on triple therapy were randomly selected to switch to Lamivudine 300 mg + Dolutegravir 50 mg once daily within the DOLAM Study (EUDRA CT 2015-000274-35). A small group consented to participate in the Neuro-Substudy. All pts were on stable triple therapy and had no history of virological failure to regimens containing 3TC/FTC or INSTI as per inclusion/exclusion criteria. CSF and blood samples were taken at baseline and week 48. Plasma and CSF HIV-1 RNA were assessed by real-time PCR. CSF neurofilament light chain (NFL) as well as inflammatory markers (sTREM2, Neopterine, MCP-1, IL-6) were measured in CSF by sandwich ELISA method.

Results: 15 pts had baseline and week 48 plasma and CSF samples. 12 (80%) pts were male. Median (IQR) age was 46 (14) years, baseline and nadir CD4 count 746 (356) and 302 (165) cells/µl respectively. Most patients switched from a NNRTI based regimen (60%) followed by INSTI (26.7%). All subjects maintained plasma viral suppression at baseline, week12, 24, 36 and 48. HIV RNA in CSF was undetectable at baseline and week 48 in all participants (LOD 40 copies/ml). NFL median change from baseline to week 48 was not statistically significant [Median (Min-Max) NFL at baseline: 499 ng/L(268-734); Median (Min-Max) NFL at W48: 457(226-886); p:0.3]. No significant changes were observed in the rest of inflammatory markers in CSF.

Conclusion: Treatment simplification from triple therapy to Dolutegravir+Lamivudine resulted in no changes in viral suppression in plasma and CSF. No evidence of neuronal damage or changes in inflammatory markers were found in CSF after 48 weeks of dual therapy. These data suggest that dual therapy with Dolutegravir+Lamivudine maintains viral control within the CNS reservoir, but larger studies are needed.

436 BILIRUBIN AS A SURROGATE MARKER OF DOLUTEGRAVIR-ASSOCIATED CNS ADVERSE EVENTS

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Background: In Phase 3 trials, dolutegravir (DTG) was well tolerated, with only 2% prevalence of adverse events (AE) leading to discontinuation. However, in post-marketing data, use of DTG has been associated with central nervous system (CNS) events. Higher DTG plasma levels have previously been associated with CNS AE. Given that both DTG and bilirubin (BIL) are metabolised by the UGT1A1 enzyme, we aimed to assess if BIL levels, as a surrogate marker for DTG and UGT1A1 activity, could predict CNS effects with DTG.

Methods: Analysis of subjects treated with DTG within the UCD ID Cohort, a prospective cohort study, with BIL levels recorded pre and at weeks 4, 12, 48 and 96 after DTG initiation. Reported CNS AE were obtained at same time points. Subjects were divided into those who did or did not reported CNS AE (CNS group vs no-CNS groups). Between group differences in BIL levels were assessed using Mann-Whitney tests and linear mixed effects model as appropriate. Contribution of BIL levels to development of CNS AE was assessed using logistic regression models.

Results: 372 subjects were included in the study, mean age (SD) 44.6 (9.3) years, 59% males, 61% Caucasian, 28% acquired HIV via intravenous drug use, median CD4-T cell count 515.5 (IQR 321, 720) cells/mm$_3$, 66% HIV RNA<40c/mL, 14% co-infected with HCV and 3% co-infected with HBV. A total of 102 (33%) subjects reported AE, of which 94% were CNS AE, with insomnia (40%), depression (15%) and headache (15%) most commonly reported. Median (IQR) time to develop CNS AE was 17 (5, 51) weeks. Although no between-group differences were observed in changes of BIL levels overtime (p=0.79), BIL levels at the time of reporting CNS AE were significantly higher in the CNS group compared to the same time point from non-CNS subjects matched by age and gender (mean (SD) 12.3 (8.9) vs 9.4 (5.9) µmol/L, p=0.02). In analysis adjusted

for demographic factors, HCV co-infection and HIV acquisition risk, higher BIL levels at the time of reporting CNS AE were independently associated with 6.5% increased risk of developing CNS AE (OR=1.065 (95% CI (1.001, 1.134) p=0.04)).
Conclusion: The prevalence of CNS AE with DTG was higher than clinical trials had suggested but in line with those reported with real world use. BIL levels were independently associated with increased risk of developing CNS AE. How BIL levels relate to DTG levels or UGT1A1 activity requires further investigations.

437 ART INITIATED AT HIGH CD4 NADIR DOES NOT NORMALIZE CSF MARKERS OF IMMUNE ACTIVATION

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Background: HIV infects cells in the central nervous system (CNS), mainly microglia and perivascular macrophages, and induces a chronic intrathecal immune activation. Similar to its effect outside the CNS, antiretroviral treatment (ART) substantially decreases CNS inflammation and CD4+ T-cell trafficking through the cerebrospinal fluid (CSF) is often reduced to near normal levels. Yet, CSF levels of neopterin, a pteridine marker of primarily macrophage/microglia activation, have been found to be stably increased in the majority of persons living with HIV (PLWH) who begin treatment during the chronic phase of HIV infection when the immune function is impaired. By contrast, CSF neopterin is essentially normalized when ART is initiated early, during acute HIV infection (AHI). The aim of this study was to evaluate if CSF immune activation biomarkers normalize to a larger extent in PLHIV with chronic HIV who start ART at high, as compared to starting treatment at low CD4-cell counts.
Methods: 176 neuroasymptomatic patients who started ART during chronic HIV were retrospectively included from the longitudinal prospective Gothenburg CSF cohort study and followed for in median 5.0 years (mean 6.1 years). Lumbar punctures were performed at baseline before ART, after 1, and >3 years. Twenty-five participants had a CD4 nadir <50; 52 between 50 and 199; 61 between 200 and 349; 22 between 350 and 499; and 16 ≥500 cells/µL. Neopterin concentrations were measured using a commercially available immunoassay (NEOPT-SCR.EIA 384 Det., Thermo Fisher Scientific – BRAHMS GmbH, Henningsdorf, Germany) with an upper normal reference value of 5.8 nmol/L in CSF.
Results: A significant inverse correlation between CD4 cell count and CSF neopterin was found at baseline ($r = -0.25$, $p < 0.01$) while no correlations between CD4 nadir and CSF neopterin were found after 1, or >3 years ART. 15% of participants with the highest CD4 nadir (>500) had normal CSF neopterin (<5.8 nmol/L) compared to 0% of those with the lowest CD4 nadir (<50). After >3 years of ART, 57% and 50% respectively had normal CSF neopterin.
Conclusion: CSF Neopterin does not normalize in many patients initiating ART during chronic HIV.
This also applies to ART-initiation at high CD4 cell counts.

438 INTEGRASE INHIBITOR START OR SWITCH IMPACTS LEARNING IN WOMEN WITH HIV

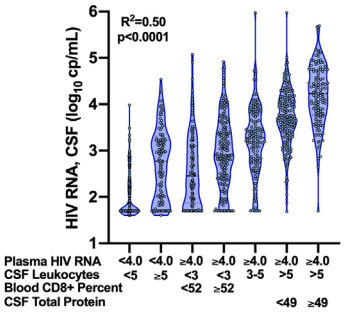
Jane A. O'Halloran[1], Kunbo Wang[2], Dionna W. Williams[3], Raha Dastgheyb[3], Kathryn Fitzgerald[3], Asante R. Kamkwalala[3], Amanda B. Spence[4], Anjali Sharma[5], Pauline M. Maki[6], Deborah Gustafson[7], Kathleen M. Weber[8], Adaora Adimora[9], Margaret Fischl[10], Yanxun Xu[3], Leah H. Rubin[3]
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Background: In recent years, the integrase strand transfer inhibitor (INSTI) class of antiretroviral therapy (ART) has become an integral component of HIV treatment. Despite concerns regarding neuropsychiatric adverse events there are limited data on cognitive side effects, particularly in women with HIV (WWH).
Methods: WWH enrolled in the Women's Interagency HIV Study (WIHS), who started or switched to INSTI-based ART and had completed one comprehensive neuropsychological (NP) test battery before and after the start/switch, were included. The NP battery assessed learning, memory, fluency, attention/working memory, executive function, processing speed, and motor function. The primary NP outcomes were demographically-corrected T-scores (M=50, SD=10) for each cognitive domain. Linear mixed effects models adjusted for relevant covariates (e.g., age, race, education, income, substance use, body mass index, HIV RNA) were used to examine the effect of start/switch of any INSTI as well as each individual drug within the INSTI class on NP function.
Results: 628 WWH, median age 48 (interquartile range 36, 60) years, 65% black non-Hispanic, had NP data before and after INSTI start/switch. While 14% started INSTI-based ART, the remainder switched primarily from protease inhibitor (PI)-based ART (51%) or a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART (27%). Raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG) were introduced in 38%, 24% and 38% of WWH, respectively. Overall, any INSTI use was associated with poorer performance in learning after start/switch ($p<0.001$). Specifically, use of EVG ($p=0.02$) and DTG ($p=0.002$), but not RAL, was associated with poorer learning. In analyses restricted to INSTI switch, any INSTI use was associated with poorer performance in learning ($p<0.009$), as was use of DTG specifically ($p=0.004$). INSTIs and DTG remained associated with poorer learning among those switching from a PI-based regimen. DTG also remained associated with poorer learning among those switching from an NNRTI (p's<0.05). Switching from an NNRTI to an INSTI was also associated with better processing speed.
Conclusion: Switching or starting an INSTI was primarily associated with poorer performance in learning among WWH. These changes were mainly observed in EVG and DTG users, and not with RAL, indicating that the impact of INSTI on cognition in WWH may not be a class effect.

439 HIV RNA IN CEREBROSPINAL FLUID OFF ART PREDICTS MORE DEPRESSIVE SYMPTOMS ON ART

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Background: HIV RNA in blood substantially differs between individuals without antiretroviral therapy (ART) due, in part, to differences in the immune response, such as endogenous interferons. Elite controllers suppress HIV RNA without ART but are at greater risk for vascular and central nervous system (CNS) complications than PWH on suppressive ART, possibly due to their robust immune response to HIV. HIV RNA in CSF also substantially differs between PWH without ART but relatively little is known about the effects of the antiviral immune response on CNS health trajectory.
Methods: The project aimed to determine a) the correlates of HIV RNA in CSF in 1,008 PWH without ART and b) the association between HIV RNA in CSF without ART and cognition or depression over time with ART (1,555 assessments in 300 PWH). All participants had plasma HIV RNA ≤ 200 copies/mL and were comprehensively assessed with neuropsychological (NP) testing, Beck depression inventory (BDI), and lumbar puncture. Statistical methods included univariable and stepwise multivariable regression using Bayesian Information Criterion and false discovery rate correction, recursive partitioning, and mixed models.
Results: Participants were mostly middle-aged (mean 39 years), European ancestry (50.4%) men (83.1%) with a mean duration of HIV of 7.5 years. Without ART, HIV RNA in CSF was ≤ 50 copies/mL in 161 (16.0%) and was less than HIV RNA in blood in 95% (median difference -1.4 $\log_{10}$ copies/mL, range -4.8 to +1.3). Multivariable regression identified that higher HIV RNA in CSF was associated with higher HIV RNA in blood, higher CSF leukocyte count, fewer CD4+ T-cells, higher CD4+ and CD8+ percent, lower serum albumin, higher total protein in CSF and blood, and lower CSF glucose (model $R2=0.27$, $p<0.0001$). Recursive partitioning identified that four variables explained 50% of the variance in HIV RNA in CSF (Figure). PWH who had lower HIV RNA in CSF without ART had worse BDI values ($p=0.034$) over time while on ART (but not worse NP performance), even after accounting for demographic, disease, and treatment covariates (model $p<0.0001$).
Conclusion: The relationship between HIV RNA in CSF and blood is highly variable with 1 in 6 having undetectable HIV RNA in CSF without ART and 1 in 20 having HIV RNA in CSF higher than HIV RNA in blood. PWH who better control HIV RNA in CSF without ART have more depressive symptoms on ART, which could reflect bystander injury from a more effective antiviral immune response.



440 CSF CXCL-10 IS ASSOCIATED WITH THE PRESENCE OF LOW-LEVEL CNS HIV DURING ART

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Background: The central nervous system (CNS) is a reservoir of HIV persistence during antiretroviral therapy (ART). Our group and others have demonstrated that both HIV RNA by single copy assay (SCA) and HIV p24 antigen by single molecule digital ELISA can be detected in cerebrospinal fluid (CSF) during ART. However, these markers require specialized protocols and are not always quantifiable during ART. Therefore, surrogate markers of HIV CNS persistence are needed that are widely available and readily quantifiable.

Methods: We performed a cross-sectional analysis of persons with HIV (PWH) on combination ART with both plasma and CSF HIV RNA <50 copies/ml by conventional PCR. In addition to HIV RNA by SCA and p24 antigen by digital ELISA, we measured CSF CXCL10 and sCD30, immune activation markers that may reflect HIV persistence in the CNS. We also measured CSF neurofilament light chain (NFL) and neuron specific enolase (NSE), markers that reflect neuronal damage. Results are reported in pg/ml, with comparisons made with Wilcoxon rank sum. Logistic regression was performed with CSFHIV+ as outcome.

Results: 66 adult PWH with virologic suppression on ART were analyzed. 19 (29%) were CSFHIV+ (positive by either SCA or p24). CSFHIV+ participants did not differ from those without detectable CSF HIV (CSFHIVneg) in terms of age, gender, race, current/nadir CD4+ T-cell count, CSF total protein, or duration of current ART regimen (all p>0.2). CXCL10 was significantly higher in the CSFHIV+ group compared to the CSFHIVneg group (median= 411 [IQR= 344-640] versus median= 312 [IQR= 205-468], p=0.008). In contrast, sCD30 was not significantly different (p=0.43) between the two groups (median= 8.97 [IQR= 4.05-14.58] in CSFHIV+ versus median= 7.04 [4.19-10.76] in CSFHIVneg). There was no significant difference in NFL between the two groups (p=0.85), but there was a trend towards higher NSE values (p=0.096) in the CSFHIV+ group. In logistic regression accounting for the effect of detectable plasma HIV by SCA, increasing IP-10 concentration (Odds Ratio= 1.33, 95% CI= 1.01-1.77) remained significantly associated with CSFHIV+.

Conclusion: In this study of PWH on suppressive ART, there was a significant relationship between CSF CXCL10 and the presence of low-level HIV in CSF. CSF CXCL10 merits further study as a candidate marker of CNS persistence that may be useful in the evaluation of HIV eradication interventions.

441 USE OF D/C/F/TAF WITH NEUROLOGIC/PSYCHIATRIC COMORBIDITIES: AMBER SUBGROUP ANALYSIS

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Background: Patients with human immunodeficiency virus (HIV)–1 and neurologic or psychiatric comorbidities (NPCs) may face challenges with HIV-1 care.

Methods: The phase 3 AMBER trial (ClinicalTrials.gov: NCT02431247) enrolled treatment-naïve, HIV-1–infected adults who were randomized 1:1 to receive once-daily darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10mg or control (D/C+F/tenofovir disoproxil fumarate). Here we report a subgroup analysis evaluating efficacy/safety in those with and without NPCs at baseline. NPCs were based on verbatim medical history; terms were coded and NPCs were defined as those within the MedDRA v22 system organ class Nervous System Disorders or Psychiatric Disorders. The primary objective was assessment of virologic response (HIV-1 RNA <50 copies/mL) at Week 48 by intent-to-treat FDA snapshot analysis in patients with or without NPCs in each treatment arm.

Results: Among 725 patients in AMBER, 88 (D/C/F/TAF) and 99 (control) had NPCs. Overall, psychiatric comorbidities (125/187 [67%]) were more common than neurologic comorbidities (81/187 [43%]). Patients with NPCs, vs those without, were more likely to be black (17% vs 9%), from North America (37% vs 18%), use nicotine (52% vs 45%), and be drug users (26% vs 14%). Patients with NPCs had higher rates of early study discontinuation vs those without NPCs (D/C/F/TAF, 10% vs 5%; control, 10% vs 7%), which was largely driven by loss to follow-up. High virologic response rates (85-93%) were achieved at Week 48 regardless of NPCs (Table); while patients with NPCs had numerically lower response rates, no patients in either arm discontinued due to lack of efficacy or developed darunavir, primary protease inhibitor, or TAF resistance. Rates of discontinuation due to related adverse events (AEs) were low regardless of NPCs (Table). Patients with NPCs did not experience a higher incidence of neurologic or psychiatric AEs related to D/C/F/TAF. The most common (≥5%) neurologic AE, regardless of treatment arm or NPCs, was headache. For patients with NPCs, the most common (≥5%) psychiatric AEs were anxiety and depression (D/C/F/TAF), and depression and insomnia (control); no psychiatric AEs met this threshold among patients without NPCs.

Conclusion: In AMBER, the presence of NPCs did not preclude virologic response in either treatment arm. Patients with NPCs were not at added risk of discontinuing due to AEs and did not experience a higher incidence of neurologic or psychiatric AEs related to D/C/F/TAF.

Table. Virologic Response and Summary of Adverse Events

	D/C/F/TAF		Control	
	With NPCs	Without NPCs	With NPCs	Without NPCs
N	88	274	99	264
ITT-FDA snapshot, n (%) [95% CI]				
Virologic response (HIV-1 RNA <50 copies/mL)	76 (86) [77; 93]	255 (93) [89; 96]	84 (85) [76; 91]	237 (90) [85; 93]
Virologic failure	6 (7) [3; 14]	10 (4) [2; 7]	3 (3) [1; 9]	9 (3) [2; 6]
No viral load data	6 (7) [3; 14]	9 (3) [2; 6]	12 (12) [6; 20]	18 (7) [4; 11]
AEs, n (%)				
Any related	36 (41)	90 (33)	43 (43)	108 (41)
Any related serious	0	0	2 (2)	4 (2)
≥Grade 2 related	12 (14)	31 (11)	17 (17)	38 (14)
≥1 related leading to discontinuation of study drug	2 (2)	5 (2)	2 (2)	12 (5)
≥1 neurologic*	18 (20)	47 (17)	20 (20)	28 (11)
Related	4 (5)	13 (5)	5 (5)	8 (3)
≥1 psychiatric†	17 (19)	26 (9)	19 (19)	18 (7)
Related	1 (1)	8 (3)	1 (1)	3 (1)

ITT, intent-to-treat; CI, confidence interval.
*System organ class of nervous system disorders. †System organ class of psychiatric disorders.

442 CLINICAL FEATURES AND OUTCOMES OF PATIENTS STOPPING DTG FOR NEUROPSYCHIATRIC SYMPTOMS

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Background: Dolutegravir is a safe and effective integrase strand transfer inhibitor used in combination in people living with HIV (PLWH). In several, but not all, cohorts a high rate of discontinuation for neuropsychological side effects (NPS) has been reported: age, female gender, older age and abacavir co-administration have been suggested as potential risk factors while pharmacological and genetic features are still under study. Aim of this analysis is to describe the clinical features and outcomes of patients stopping DTG for NPS.

Methods: In a cohort study involving two Italian outpatient clinics we enrolled patients starting DTG and recorded clinical, therapeutic, pharmacokinetic and pharmacogenetic features. The study was approved by the two Ethics Committees and patients signed a written informed consent. In this analysis we focused on patients stopping DTG for NPS in terms of pre-existing psychiatric comorbidities and outcomes after drug withdrawal. Symptoms were clinically assessed and no/partial/complete resolution was recorded.

Results: 112 (out of 561) patients stopped DTG after a median follow up of 27 months (18-37): 66 for NPS. They were mostly sleep disorders (30.3%), headache (27.3%), anxiety (25.8%), depression (18.2%), psychosis (4.5%), vertigo (4.5%) and confusion (3%). Pre-existing psychiatric comorbidities were reported in 21 subjects (31.8%) mostly anxiety/depression in 24.2%: the latter was associated with the discontinuation for worsening depression (p=0.021, OR=4.4) but

not other symptoms. Outcome was available in 57 participants: within 30 days a complete (61.4%) or partial (33.3%) improvement in symptoms was reported. Headache (p=0.039) and sleep disorders (p=0.083) were associated with complete resolution of symptoms. Patients were switched to raltegravir (30.3%), elvitegravir/cobicistat (28.8%), darunavir/cobicistat (25.8%) or rilpivirine (12.1%)-containing regimens. Partial/complete regression of NPS was observed in 66.7%/33.3%(DRV/c), 43.5%/52.2% (RA), 12.5%/62.5% (RPV) and 11.1%/72.2% (EVG/c) (Chi2 1.99, p=0.158).

Conclusion: In our cohort study 11.7% of participants stopped DTG due to NPS: they were mostly sleep disorders and headache and a full regression of both was observed after switching to other drugs. In most cases a complete resolution of symptoms was observed; the incomplete resolution in almost one third of participants suggests alternative reasons.

443 LONG-TERM ADHERENCE MONITORING OF EMTRICITABINE IN HAIR BY MASS SPECTROMETRY IMAGING

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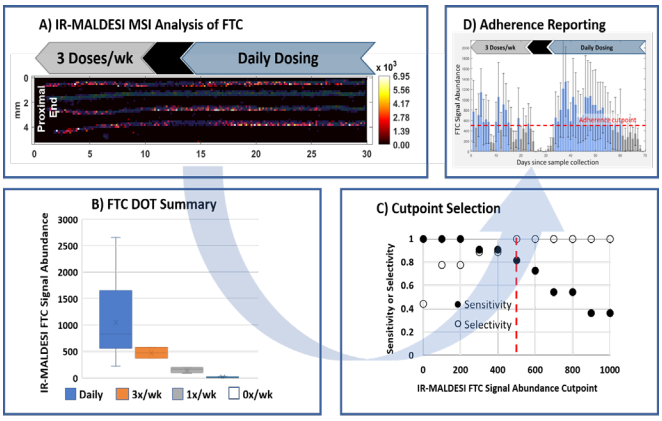
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Background: Adherence to antiretroviral therapy is critical for effective treatment and prevention of HIV. Incorporation of drug in hair creates a long-term record of adherence behavior, and mass spectrometry imaging (MSI) using infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) offers a means of monitoring changes in this record as an objective measure of adherence. Here we benchmark longitudinal profiles of emtricitabine (FTC) in hair strands using IR-MALDESI MSI following directly observed therapy (DOT). We also identify adherence thresholds and develop a tool for real-time evaluation of patient adherence in a clinical setting.

Methods: Benchmarking was performed in hair samples cut close to the scalp from 12 volunteers undertaking 28-day phases of daily and then differentiated (0x, 1x, or 3x/wk; n=4 in each group) tenofovir+FTC dosing as part of a DOT study (NCT03218592). The proximal 2cm (~2 months growth) of hair strands (n=4) were collected on day 28 of each phase and fixed to glass slides with double-sided tape before analysis with an IR-MALDESI source coupled to a Thermo QE+ mass spectrometer. MSI data were processed with MSiReader, and longitudinal profiles of FTC over time were generated using custom Matlab software. Quantification of the response was performed based on calibration from blank strands incubated in an FTC solution (lower limit of quantitation: 0.27 ng/mg hair; relative standard deviation (RSD): 20%).

Results: FTC was measured in strands from 11 volunteers (1 reported recent hair salon treatment). A representative IR-MALDESI image (Fig. A; daily-to-3x/wk dosing) shows distinct and localized bands of FTC in each strand associated with proximal differentiated dosing and distal daily dosing periods. Delineating these periods across all study samples, we evaluated average IR-MALDESI response associated with each dosing frequency (Fig. B). While interindividual variability in hair accumulation was observed (daily dosing RSD = 69%), an adherence cutpoint with high sensitivity (81%) and selectivity (100%) was derived from these data based on a receiver operating characteristic curve (Fig. C). A cutpoint-based analysis tool was developed to classify daily adherence in FTC longitudinal profiles (Fig. D).

Conclusion: Longitudinal dose granularity for FTC can be visualized in hair strands by IR-MALDESI MSI. This approach provides a non-invasive long-term, daily adherence report for patients and clinicians, applicable to both treatment and prevention efforts.



444 ADHERENCE BY DBS, SELF-REPORT, AND PILL COUNT IN YOUNG ADULTS WITH PERINATAL HIV

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Background: Concentrations of tenofovir-diphosphate (TFV-DP) in dried blood spot (DBS) can objectively measure ART adherence and predict viral suppression. We explored if TFV-DP, self-reported adherence, and unannounced phone pill counts were associated with viral suppression needed for individual health (HIV viral load [VL]<20 copies/mL) and treatment as prevention (TasP) in the context of Undetectable=Untransmittable (U=U, VL<200) in young adults living with perinatal HIV infection (YAPHIV).

Methods: We quantified adherence using TFV-DP and emtricitabine-triphosphate (FTC-TP) in DBS, self-report, and pill counts, and concomitant VL in YAPHIV from New York City, 18-28 years, receiving tenofovir-based regimens. Self-reported adherence and pill counts were assessed using validated measures. Mean and median TFV-DP levels (by regimen: tenofovir disoproxil fumarate/emtricitabine [TDF]/FTC, tenofovir alafenamide [TAF]/FTC), self-reported adherence, and pill counts were estimated, stratified by VL level (<20 copies/mL or <200 copies/mL). Differences in mean adherence levels were assessed with t-tests. Predictive accuracy of each measure to predict VL<200 copies/mL was compared using Receiver Operator Characteristic analysis. 'White coat adherence' (lowest TFV-DP with quantifiable FTC-TP) was assessed.

Results: Of 34 YAPHIV on TDF/FTC, 41% had VL<20 (mean TFV-DP 1293 fmol/punch [95% CI 1059, 1580]), and 59% had VL<200 (mean TFV-DP 658 fmol/punch [95% CI 356, 1218]) (Table). Of 27 on TAF/FTC, 52% had VL<20 (mean TFV-DP 2250 fmol/punches [95% CI: 1446, 3500]), and 63% had VL<200 (mean TFV-DP 1996 fmol/punches [95% CI (1340, 2974]). White coat adherence was detected in 1 person. Of YAPHIV with all three adherence measures (TFV-DP level, self-report, pill counts; n=42), TFV-DP from TAF/FTC (0.97 [95% CI: 0.89, 1.00; p=0.001]) had the highest area under the curve for predicting VL<200, followed by TFV-DP from TDF/FTC (0.87 [95% CI: 0.68, 1.00; p=0.007]), pill count (0.72 [95% CI: 0.53, 0.90; p=0.03]), and self-report (0.69 [95% CI: 0.53, 0.86; p=0.05]).

Conclusion: TFV-DP concentrations required to prevent transmission (VL<200 copies/mL) are lower than for individual health (VL<20 copies/mL) and different for TDF vs. TAF, suggesting differential thresholds for TasP/U=U vs. individual health, while self-reported adherence and pill counts were less sensitive. All adherence measures were associated with HIV VL<200, making the choice of a specific method dependent on context, preference, and available resources.

Table. Tenofovir-diphosphate (TFV-DP) drug (fmol/punch[es]) in dried blood spots (DBS), unannounced phone pill count, self-reported adherence, and HIV viral load among young adults living with perinatal HIV-infection (YAPHIV) in New York City

	Overall	VL <20	VL ≥20	p-value	VL <200	VL ≥200	p-val
Tenofovir-diphosphate (TFV-DP) (fmol/punch): Participants on TDF/FTC (n=34)							
Mean (95% CI)[A]	321 (175, 587)	1293 (1059, 1580)	121 (56, 261)	<.0001	658 (356, 1218)	115 (45, 195)	0.004
Median (IQR)	847 (13, 3482)	1135 (986, 1704)	111 (24, 550)		992 (694, 1344)	111 (13, 497)	
Tenofovir-diphosphate (TFV-DP) (fmol/punches): Participants on TAF/FTC (n=27)							
Mean (95% CI)[A]	800 (443, 443)	2250 (1446, 3500)	263 (124, 557)	<0.0001	1996 (1340, 2974)	169 (78, 367)	<0.00
Median (IQR)	1241 (324, 2416)	2358 (1424, 3832)	324 (135, 662)		2300 (1374, 3060)	217 (104, 339)	
Unannounced telephone pill count (n=42)							
Mean (95% CI)	77% (69%, 86%)	89% (82%, 96%)	60% (45%, 76%)	0.002	85% (77%, 93%)	60% (41%, 80%)	0.02
Median (IQR)	88% (58%, 100%)	97% (83%, 100%)	49% (35%, 93%)		95% (76%, 100%)	47% (34%, 97%)	
Self-reported adherence (n=42)							
Mean (95% CI)	81% (74%, 87%)	84% (77%, 92%)	75% (63%, 87%)	0.1	84% (78%, 91%)	72% (58%, 87%)	0.08
Median (IQR)	84% (75%, 95%)	84% (77%, 100%)	78% (64%, 92%)		91% (77%, 100%)	77% (64%, 91%)	

A Drug concentrations were log-transformed and back-transformed to estimate geometric means with 95% confidence intervals (CIs)

445 COMPARING TFV-DP & FTC-TP IN PBMC, RBC, NEUTROPHILS, & PLATELETS WITH F/TDF VS F/TAF

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Background: Emtricitabine (FTC) plus tenofovir alafenamide (F-TAF) or tenofovir disoproxil (F-TDF) undergo cell-specific conversion, resulting in differential pharmacokinetics (PK) of tenofovir-diphosphate (TFV-DP) and FTC-triphosphate (FTC-TP) across cell types. The selective cleavage of TAF via cathepsin A allows for more targeted delivery of TFV to cell types expressing that enzyme, such as peripheral blood mononuclear cells (PBMC). The PK of TFV-DP and FTC-TP has been evaluated in PBMC and red blood cells (RBC) measured with dried blood spots (DBS), but not in other major blood cell types, such as neutrophils and platelets.
Methods: Paired DBS, PBMC, neutrophils, and platelets were obtained from HIV-negative individuals receiving F-TDF for PrEP, or directly observed F-TAF in the TAF-DBS study that evaluated 33%, 67% and 100% of daily dosing (NCT02962739). DBS, PBMC, neutrophils, and platelets were isolated from whole blood using a stepwise ficoll and centrifugation process. TFV-DP and FTC-TP were determined using a validated LC-MS/MS assay. Concentrations in fmol or pmol/10^6 cells were converted to fmol or pmol/µL to normalize across varying cell sizes.
Results: Five F-TDF and 29 F-TAF participants had all cell types available. Median TFV-DP in DBS for F-TDF was 1676 (791-1895) fmol/punch consistent with daily dosing (TFV-DP in DBS for F-TAF was dependent on 33%, 67%, or 100% dosing). Table shows concentrations in fmol or pmol per 10^6 cells, per punch(es), and per µL in PBMC, DBS, RBC, neutrophils and platelets. The rank order of FTC-TP (pmol/µL) by cell type was PBMC>neutrophils>platelets>RBC and was the same for F-TAF versus F-TDF. The rank order for TFV-DP (fmol/µL) was PBMC>neutrophils>platelets>RBC for F-TAF versus RBC>PBMC~neutrophils>platelets for F-TDF.
Conclusion: FTC-TP was preferentially loaded in PBMC and neutrophils and was similar for F-TAF vs F-TDF. Despite the lower TFV dose, F-TAF produced higher TFV-DP in PBMC, neutrophils, and platelets whereas F-TDF produced higher TFV-DP in RBC. The presence (PBMC/neutrophils/platelets) or absence (RBC) of cathepsin A likely explains these findings. RBC loading with TDF is likely driven by the higher plasma TFV, as well as its disoproxil, tenofovir-monoester intermediates, in portal blood. These findings show that tenofovir prodrug moieties influence cell loading in vivo, providing insights into cell type differences important for using drug concentrations to monitor adherence and characterizing cell-specific drug effects.

Table 1. TFV-DP and FTC-TP concentrations across cell types

		Tenofovir-diphosphate (TFV-DP)				
		PBMC	DBS	RBC	Neutrophil	Platelet [b]
fmol/10^6 cells or fmol/punch(es) [a]	F-TAF Median (IQR)	329 (198-543)	1191 (676-1872)	8.86 (5.03-13.9)	180 (71.7-273)	3.76 (2.37-6.11)
	F-TDF Median (range)	66.6 (41.8-99.6)	1676 (791-1895)	140 (66-158)	83.2 (38.9-184)	0.238 (0.073-0.35)
fmol/µL	F-TAF Median (IQR)	1167 (702-1926)	-	98.5 (55.9-155)	600 (239-910)	345 (217-431)
	F-TDF Median (range)	236 (148-353)	-	1552 (732-1755)	277 (130-613)	21.8 (6.66-32.1)
		Emtricitabine-triphosphate (FTC-TP)				
		PBMC	DBS	RBC	Neutrophil	Platelet [b]
pmol/10^6 cells or pmol/punch(es) [a]	F-TAF Median (IQR)	4.47 (2.27-5.65)	2.38 (1.07-4.12)	0.018 (0.008-0.03)	2.78 (1.08-5.78)	0.057 (0.022-0.091)
	F-TDF Median (range)	6.92 (2.64-10.0)	0.35 (0.24-0.50)	0.029 (0.02-0.041)	4.22 (2.32-9.48)	0.07 (0.041-0.12)
pmol/µL	F-TAF Median (IQR)	15.9 (8.05-20.0)	-	0.197 (0.089-0.341)	9.27 (3.6-19.3)	5.23 (2.02-8.35)
	F-TDF Median (range)	24.5 (9.36-35.5)	-	0.324 (0.22-0.458)	14.1 (7.73-31.6)	6.42 (3.76-11.4)

[a] DBS expressed as fmol or pmol/punch for F-TDF and fmol or pmol/punches for F-TAF. All other cell types expressed as fmol or pmol/10^6 cells. A 3mm DBS punch was considered equivalent to 12 million RBC and two 7mm punches were considered equivalent to 134.4 million RBC.
[b] Two platelet TFV-DP concentrations were below the limit of quantification. These were calculated as the lower limit of quantification/2.

446 UTILITY OF MINIMALLY INVASIVE SPECIMENS TO INFORM ARV ADHERENCE TEST DEVELOPMENT

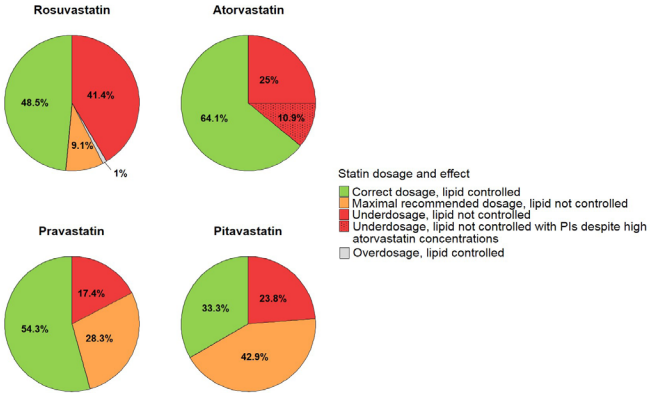
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Background: Antiretroviral drug (ARV) efficacy in treatment and prevention of HIV infection is currently dependent on high levels of adherence to daily oral dosing regimens. Rapid point of care (POC) tests to measure ARV levels could be used to track and improve individual adherence. This study sought to define the utility of urine, dried blood spots, and buccal swabs as minimally invasive specimens amenable to development of POC tests for ARVs.
Methods: Urine, buccal swabs, and peripheral blood were collected from 35 HIV-negative men who have sex with men aged 18-49 years enrolled in a clinical trial examining the pharmacokinetics of a single dose of 4 ARVs with a pharmacologic booster. Specimens were collected up to 96 hours following a single oral dose of tenofovir alafenamide (TAF)/emtricitabine (FTC)/elvitegravir (EVG)/cobicistat (COBI)/ and darunavir (DRV). Drug concentrations were measured by high performance liquid chromatography-mass spectrometry with a lower limit of quantification of 10 ng/mL for urine, plasma and blood spots and 2 ng/mL for buccal swabs.
Results: FTC was detectable in all urine specimens collected 48 hours following a single dose and TFV and DRV were detectable in all urine specimens collected 24 hours post dose. TFV, FTC and DRV remained detectable in most urine specimens collected at least 72 hours post dose. EVG was not detectable in urine, and COBI was only measurable up to 8 hours post dose. Urine ARV concentrations showed modest correlation with those in plasma for FTC ($r=0.510$, $p<0.001$), DRV ($r=0.555$, $p<0.001$), and COBI ($r=0.431$, $p<0.001$). FTC, EVG and DRV were detectable in all DBS collected up to 24 hours post dose, and FTC and DRV remained detectable in most DBS collected up to 48 hours post dose. COBI was only detectable in DBS up to 8 hours post dose. ARV concentrations in DBS correlated with plasma concentrations for FTC ($r=0.941$, $p<0.001$), EVG ($r=0.867$, $p<0.001$) and DRV ($r=0.917$, $p<0.001$), but not COBI. FTC and COBI were detectable up to 8 hours post dose in buccal swabs, while DRV was detectable in most buccal swab specimens up to 24 hours post dose. TFV was not detectable in plasma, DBS or buccal swabs.
Conclusion: Development of POC tests to detect ARV drugs from minimally invasive specimens may be attractive to assess adherence. Our results suggest that POC assays targeting TFV, FTC or DRV in urine or FTC, EVG or DRV in whole blood may provide the most reliable indicators of ARV adherence.

447 REAL-LIFE MANAGEMENT OF DRUG-DRUG INTERACTIONS BETWEEN ANTIRETROVIRALS AND STATINS

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Background: Protease inhibitors (PIs) cause drug-drug interactions (DDIs) with statins due to inhibition of drug metabolizing enzymes and/or the hepatic uptake transporter OATP1B1, which may alter the pharmacodynamic (PD) response to statins. There is a lack of data on real-life management of DDIs between antiretrovirals (ARVs) and statins.
Methods: Patients of the Swiss HIV Cohort Study followed-up in the centres of Lausanne and Basel were eligible if they received a statin concomitantly to ARVs. Low-density lipoprotein (LDL), total cholesterol (TC) and plasma concentration of the statin were measured during a follow-up visit. Individual LDL target values were set using the Framingham score whereas TC target values were set according to the 2018 European AIDS Clinical Society recommendations. Statins concentrations were interpreted using published plasma concentration time curves. DDIs management was evaluated based on the statin dose adjustment considering coadministered ARVs and the PD response on the lipid profile.
Results: Data were collected for 99 rosuvastatin, 93 atorvastatin, 46 pravastatin and 21 pitavastatin. DDIs management and PD response varied according to the statin (figure 1). Statin underdosing leading to suboptimal PD response was frequent with rosuvastatin and atorvastatin. However, the lipid target values were not always achieved in presence of PIs despite using the maximal recommended rosuvastatin dose. Similarly, suboptimal lipid control was observed with PIs despite high atorvastatin concentrations likely explained by inhibition of OATP1B1 resulting in less statin uptake in the liver, the site of action. Target lipid values were more often achieved with unboosted integrase inhibitors due to both their favourable DDIs profiles and neutral effect on lipids. Underdosing was less frequent with pravastatin and pitavastatin, nevertheless suboptimal lipid control was common regardless of coadministered ARVs and despite using maximal recommended pravastatin and pitavastatin doses. This is likely due to their lower efficacy compared to rosuvastatin or atorvastatin.
Conclusion: Suboptimal management of DDIs with statins underdosing was observed in overall 30% of cases. Management of dyslipidemia in patients on PIs is challenging due to this ARVs class negative impact on lipid profile and DDIs potentially impairing the effect of statins. Integrase inhibitors based regimens and/or treatment with rosuvastatin or atorvastatin should be favoured in patients with refractory dyslipidemia.



448 AGING DOES NOT IMPACT DRUG-DRUG INTERACTION MAGNITUDES INVOLVING ANTIRETROVIRAL DRUGS

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Background: The risk of drug-drug interactions (DDIs) is elevated in aging people living with HIV (PLWH) because their increased prevalence of comorbidities leads to a higher use of comedications. Currently, the impact of aging on the magnitude and subsequently the management of DDIs in aging PLWH is unknown. As it is neither feasible nor ethically possible to study every drug combination in aging PLWH, we used physiologically based pharmacokinetic (PBPK) modelling in combination with limited clinical data to investigate the impact of aging on DDI magnitudes involving antiretrovirals (ARVs).
Methods: A whole-body PBPK model was built in the mathematical programming language Matlab® including age-dependent physiological changes for the simulation of elderly subjects. The ability of the model to predict DDIs in young (20-50 years) adults and aging PLWH (55-80 years) was verified against clinical data for amlodipine (AML, 10mg QD) and rosuvastatin (ROS, 10mg QD) both being administered with darunavir/ritonavir (DRV/r, 800/100 mg QD). The clinical data were obtained in the framework of a Swiss HIV Cohort Study project enrolling PLWH older than 55 years or from publications. The verified PBPK model was used to conduct virtual clinical trials for 15 DDIs involving ARVs in virtual individuals aged 20 to 99 years. DDI magnitudes were normalized to the youngest investigated age group. Pearson's correlation was performed to analyse age-related changes of DDI magnitudes.
Results: Clinical data for AML and ROS in combination with DRV/r were within the 95% confidence interval (CI) of the predictions for young individuals (20-50 years) and aging PLWH (55-80 years). DDI magnitudes were always predicted within 1.25-fold of clinical data (Tab. 1).
Predicted magnitudes of the 15 investigated DDIs (10 inhibitions and 5 inductions) using the verified PBPK model did not change with age. The calculated correlation coefficient of the AUC-ratio [95% CI] was -0.23 [-0.65 0.30] with a p-value of 0.40.
Conclusion: PBPK modelling in combination with limited clinical data demonstrated that DDI magnitudes with ARVs appear not to be impacted by aging. Thus, in the absence of severe comorbidities, management of DDIs can be similar in elderly compared to young PLWH.

Tab. 1: Observed vs predicted mean DDI magnitudes between amlodipine (AML), rosuvastatin (ROS) and darunavir/ritonavir (DRV/r).

Age [years]	AUC-ratio – AML + DRV/r		AUC-ratio – ROS + DRV/r	
	observed	predicted	observed	predicted
20-50	2.11	2.23	1.57	1.68
55-80	2.06	2.09	1.77	1.78

449 PLASMA & INTRACELLULAR PK AND RENAL SAFETY OF TAF 25MG WITH BOOSTED PI AND LDV/SOF

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Background: Ledipasvir/sofosbuvir (LDV/SOF) is a recommended therapy for Hepatitis C virus (HCV). LDV/SOF increases tenofovir (TFV) exposures by 40-98% with TFV disoproxil fumarate (TDF) due in part to inhibition of TDF hydrolysis by SOF. This increase is greater with boosted HIV protease inhibitors (b/PI), resulting in renal toxicity concerns. There are no PK or renal safety data for TFV alafenamide (TAF) 25mg with b/PI and LDV/SOF. Our study objectives were to compare the plasma/intracellular PK and renal safety of b/PI with TDF, TAF, and TAF+LDV/SOF in persons living with HIV (PLWH).
Methods: PLWH 18-70 yrs on TDF with ritonavir (RTV)- or cobicistat (COBI)-b/PI were eligible. The study had 3 phases (Ph): (1) TDF 300mg + b/PI x 12 wks, (2) TAF 25mg + b/PI x 12 wks, and (3) TAF 25mg + b/PI + LDV/SOF x 4 wks. Adherence was electronically monitored using Wisepill®. Visits occurred at the end of each phase to collect PK (time 0 [pre-dose], 1 and 4 hrs post-dose) and renal biomarkers. PBMC were isolated pre-dose and plasma at every time point. TAF, TFV, and TFV-DP were quantified via LC-MS/MS. Plasma TFV exposure was calculated using non-compartmental methods. PK and renal biomarkers were log-transformed prior to analysis with mixed models. Results were back-transformed and Ph comparisons were reported as GMR (95% CI). $P<0.05$ was considered statistically significant with no adjustment for multiple comparisons.
Results: Ten participants (1 black female; 9 males [5 Hispanic, 4 white]) were enrolled; 9 were on darunavir (5 RTV, 4 COBI) and 1 on atazanavir/RTV. Plasma TFV exposures were 76-79% lower for Ph 2 and 3 vs. 1 (Table 1). TFV-DP in PBMC were 11.1-fold higher for Ph 2 vs. 1 and 13.5-fold higher for Ph 3 vs. 1. Plasma TAF/TFV and TFV-DP in PBMC did not significantly differ for Ph 3 vs. 2, but TFV-DP trended towards a ~20% increase. PBMC findings were similar after controlling for adherence. eGFR did not differ between phases. Renal biomarkers either trended toward or showed improvements following TDF to TAF switch, and did not worsen with LDV/SOF.
Conclusion: TFV-DP in PBMC increased 11-fold with TAF 25mg relative to TDF with b/PI. This increase is within the range of TFV-DP observed historically with higher TAF doses. Unlike prior findings with TDF, adding LDV/SOF with TAF did not significantly increase plasma TFV or TFV-DP in PBMC. This is likely due to

differences in hydrolysis pathways between TDF and TAF, and reassures on the safety of TAF + b/PI + LDV/SOF in HIV/HCV-coinfected patients.

Table 1. PK and Renal Safety Outcomes for TDF, TAF, TAF+LDV/SOF with b/PIs

Outcome	TDF + b/PI (Phase 1)	TAF + b/PI (Phase 2)	TAF + b/PI + LDV/SOF (Phase 3)	Ph 2 vs. 1	Ph 3 vs. 1	Ph 3 vs. 2
PK Results[a]						
TFV Plasma AUC_{24h} (ng*h/mL)	2075 (77.3%)	432 (63.5%)	500 (59.9%)	0.21 (0.13, 0.34) P<0.0001	0.24 (0.16, 0.36) P<0.0001	1.16 (0.97, 1.39) P=0.10
TAF C_{1h} (ng/mL)	n/a	58.7 (68.2%)	48.1 (78.5%)	n/a	n/a	0.83 (0.45, 1.55) P=0.53
TAF C_{4h} (ng/mL)	n/a	1.6 (133%)	2.0 (201%)	n/a	n/a	1.31 (0.59, 2.87) P=0.47
TFV-DP in PBMC (fmol/10^6 cells)	83.0 (66.6%)	926 (23.4%)	1129 (34.9%)	11.1 (5.9, 21.1) p<0.0001	13.5 (7.6, 24.1) p<0.0001	1.22 (0.99, 1.50) p=0.058
Renal Safety Outcomes[a]						
eGFR (mL/min/1.73 m^2)	86.7 (27.6%)	91.0 (23.0%)	88.1 (24.9%)	1.05 (0.92, 1.20) p=0.43	1.02 (0.93, 1.11) p=0.71	0.97 (0.89, 1.05) p=0.40
UPCR (mg/g)	134 (65.7%)	118 (50.2%)	97.3 (41.0%)	0.89 (0.69, 1.14) p=0.31	0.73 (0.47, 1.12) p=0.14	0.82 (0.54, 1.26) p=0.34
β2-microglobulin: Cr ratio (ug/g)	419 (176%)	224 (167%)	178 (156%)	0.53 (0.30, 0.96) p=0.039	0.42 (0.21, 0.83) p=0.018	0.79 (0.52, 1.22) p=0.25
RBP:Cr ratio (ug/g)	436 (174%)	242 (180%)	146 (91.6%)	0.56 (0.27, 1.12) p=0.092	0.34 (0.15, 0.75) p=0.012	0.60 (0.37, 0.99) p=0.047

Key: AUC_{24h} = area under the concentration-vs-time curve over a 24-hour period; b/PI = boosted protease inhibitor; C_{1h} = concentration at 1 hour post-dose; C_{4h} = concentration at 4 hours post-dose; Cr = creatinine; eGFR = estimated glomerular filtration rate; LDV/SOF = ledipasvir/sofosbuvir; PBMC = peripheral blood mononuclear cell; Ph = phase; RBP = retinol binding protein; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV-DP = tenofovir-diphosphate; UPCR = urine protein-to-creatinine ratio
[a]PK and renal safety outcomes summarized as geometric mean (CV%) and GMR (95% CI)

450 HIGH-DOSE RIFAMPICIN FOR THE TREATMENT OF LEPROSY IN HIV PATIENTS TAKING DOLUTEGRAVIR

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Background: High dose rifampicin is being investigated for shortening TB therapy as well as in other indications such as leprosy. Strategies to manage the risk of drug-drug interactions (DDIs) with co-administered antiretroviral drugs may therefore be needed. The current study used physiologically-based pharmacokinetic (PBPK) modelling to predict the magnitude of DDI between once monthly (QMT) high dose rifampicin (RIF) and multiple dolutegravir (DTG) regimens for the treatment of leprosy in HIV coinfected patients.

Methods: A whole-body PBPK model was designed in Simbiology v. 9.4.0 (MATLAB R2018a) and used to simulate 100 adult individuals. The DTG model was qualified against reported clinical data for DTG 50mg once daily (QD) and twice daily (BID). The RIF model describing the induction of DTG's major metabolic pathways, UGT1A1 and CYP3A4, was qualified using in vitro and oral clinical data for midazolam, nifedipine, raltegravir, DTG and RIF. As per convention, PBPK models were assumed to be qualified if the simulated values were within 2-fold of the mean reported clinical values and if the absolute average-fold error (AAFE) was below 2. The verified DTG and RIF models were used to simulate the magnitude of DDI between RIF 600mg QMT co-administered with DTG 50mg BID as well as RIF 1200mg QMT co-administered with DTG 50mg BID, DTG 50mg three times daily (TID) and DTG 100mg BID.

Results: The PBPK models were successfully qualified according to the criteria. There was a tendency to overpredict the magnitude of RIF induction for DTG 50mg BID, with simulated versus observed area under the curve (AUC), maximum plasma concentration (C_{max}) and minimum plasma concentration (C_{min}) ratios of 0.63, 0.58 and 0.74, respectively. The simulated C_{min} of DTG after the administration of RIF are summarised in the table. For DTG 50mg BID co-administered with RIF 1200mg QMT, the C_{min} minus one standard deviation (SD) fell below DTG's protein adjusted (PA)-IC_{90} 1 day post RIF dose and recovered within 24 hours.

Conclusion: The PBPK model predicted marked reductions in the C_{min} of several DTG dosing regimens when co-administered with 600mg and 1200mg RIF QMT. Importantly, the return of DTG plasma concentrations to steady state C_{min} was predicted to be considerably delayed after coadministration of both 600mg and 1200mg RIF QMT. These simulations could inform development of effective high-dose RIF strategies for special HIV populations with comorbidities such as Leprosy.

Table 1: Pharmacokinetic summary of the simulated drug-drug interactions between various doses of rifampicin and dolutegravir.

Days Post RIF Dose	DTG 50mg BID with RIF 600mg QMT C_{min} Ratio	DTG 50mg BID with RIF 1200mg QMT C_{min} Ratio	DTG 100mg BID with RIF 1200mg QMT C_{min} Ratio	DTG 50mg TID with RIF 1200mg QMT C_{min} Ratio
0	0.49	0.43	0.40	0.46
1	0.23	0.17	0.16	0.23
2	0.23	0.16	0.15	0.22
3	0.27	0.18	0.18	0.25
4	0.32	0.23	0.23	0.30
5	0.39	0.29	0.28	0.35
6	0.45	0.35	0.34	0.41
7	0.52	0.41	0.41	0.47
10	0.70	0.61	0.60	0.64
14	0.86	0.80	0.79	0.82
20	0.95	0.93	0.92	0.94
30	1.00	1.00	1.00	1.00

Values are presented as a ratio of DTG versus the DTG RIF DDI for each respective regimen, with no effect = 1. No shading - mean C_{min} ± 1 SD is above PA-IC_{90}, Grey shading - mean C_{min} ± 1 SD is below PA-IC_{90}. Note: C_{min} of DTG are higher with DTG 100 mg BID and DTG 50mg TID dosing so the ratios are always >1 SD above PA-IC_{90}.

451 TOTAL DOLUTEGRAVIR LEVELS DECREASED BUT FREE FRACTION INCREASED BY VALPROIC ACID

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Background: Dolutegravir-containing regimens are used worldwide to treat people living with HIV-1. A previous report on two patients suggested a drug-drug interaction (DDI) between dolutegravir (DTG) and valproic acid (VPA) causing >80% decreased DTG plasma concentrations. The underlying mechanism is unclear. In this pharmacokinetic (PK) sub study, we evaluated the DTG-VPA DDI in HIV-1 patients on DTG-containing regimens and identified a potential mechanism.

Methods: HIV-1 patients participating in a RCT investigating VPA as a latency reversing agent (LUNA: clinicaltrials.gov NCT: 03525730) were recruited in a pre-defined PK sub study if they were on DTG-containing regimens for >6 months with a plasma HIV-RNA of <50 c/mL. Patients all received 50 mg DTG QD and were randomized to receive either VPA 30 mg/kg BID from day 0 to 14 or not. Total DTG, unbound DTG, and DTG-glucuronide trough plasma concentrations were measured on day 0 (pre-dose and 6 hours post-dose VPA and DTG), and on day 1, 7, 14, and 42. Intra subject DTG concentrations were evaluated and compared to DTG controls without VPA.

Results: Nine HIV-1 patients on DTG were included in total. Of the six who were randomized to receive VPA, total DTG trough levels (geometric mean (GM)) were 1.35 mg/L on day 0 (before VPA) and 1.11 mg/L on day 42. During 14 days of VPA treatment, total GM DTG concentrations decreased sharply to 0.85, 0.31 and 0.14 mg/L on Day 1, 7 and 14, respectively, while total DTG concentration in the controls remained comparable: 1.49, 1.74 and 1.51 mg/L on days 1, 7, and 14 respectively. We observed a parallel increase in the unbound fraction of DTG: 0.28-0.26% without VPA compared to 0.46-0.58% during VPA administration (figure 1) without relevant alterations in the controls (median 0.25%). Unbound DTG concentrations were above the established in vitro EC_{90} value for unbound DTG of 0.9 µg/L in >90% of the participants.

Conclusion: This study shows that total DTG plasma concentrations decrease sharply after the addition of VPA, thus confirming the DDI. The decrease can be explained, at least partly, by displacement of DTG by VPA via competitive protein binding. Since unbound DTG levels remained sufficient this DDI should not be a reason to withhold DTG treatment to people living with HIV-1 who are also receiving VPA.

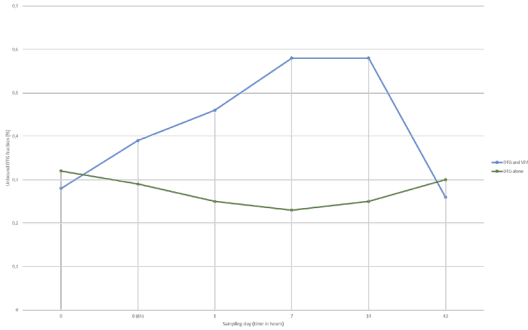


Figure 1: Dolutegravir (DTG) unbound fraction (%) of pre-dose plasma concentrations within the LUNA RCT (clinicaltrials.gov NCT: 03525730). Data points represent geometric means. The green line depicts data of patients treated with DTG alone (n=3). The blue line depicts data of patients treated with DTG who were randomized to receive a 14 day course of valproic acid 30mg/kg BID starting on day 0 (n=9).

452 PHARMACOKINETICS OF RUXOLITINIB WITH ART IN HIV-SUPPRESSED INDIVIDUALS (ACTG # A5336)

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Background: Ruxolitinib is an FDA-approved Janus kinase (JAK 1/2) inhibitor (myelofibrosis, polycythemia vera) that blocks key cytokines involved in HIV persistence including IL1, 6, 7 and 15. In A5336, low dose ruxolitinib (10 mg bid) was administered to healthy people living with HIV (PLWH) on antiretroviral therapy (ART) for 5 wk to investigate safety and to reduce ongoing inflammation that persists even with virologic suppression. Because ruxolitinib is metabolized via the cytochrome P450 system. Analysis sought to model variability of ruxolitinib pharmacokinetics (PK) between participants (inter individual variability, IIV) and assess PK interactions between ruxolitinib and ART.

Methods: Steady-state plasma concentrations of ruxolitinib and coadministered ART were drawn on wk 1 and 4/5 and assayed by liquid chromatography and tandem mass spectrometry (LC-MS/MS). Population PK models were fitted using NONMEMÔ 7.4. Parameter distributions were assumed log-normal, and residuals having an additive and residual component. IIV of Parameter and the variations in fraction of oral dose absorbed (between occasion variability of F) were estimated. Models converged to >3 decimals using the FOCE (first-order conditional estimation) with interaction method and were evaluated using statistical and graphical methods.

Results: No clinically relevant adverse events were observed across participants (33 male, 7 female), and HIV suppression was maintained. Ruxolitinib plasma concentrations versus time profiles from 39 and 38 participants on wk 1 and wk 4/5, respectively, were modeled. The PK profiles were adequately described using an open 2-compartment model with first-order absorption and elimination, and parameters were similar to reports in healthy volunteers and other indications: Distribution volumes V1/F = 61.83 L, 30.9% and V2/F = 2.36 L, 70.1% (normalized by body weight, mean 91.5 kg, IQ range 76.75-91.5 kg); Compartment clearance values were CL10/F = 14.47, 33.8% and CL12/F =4.84 L/hr; Absorption rate constant Ka = 4.96, 70.1%, and there was a 23% BOV in F. Area under the curve (AUC, dose/CL12) distributions were similar on wk 1 and wk 4/5. Overall, concentrations of ART were consistent with those reported in population PK studies without ruxolitinib.

Conclusion: These data suggest that ruxolitinib can be safely administered to ART suppressed PLWH without adverse consequences regarding ruxolitinib or ART plasma levels, and variability of ruxolitinib plasma concentrations is similar to other populations.

453 INFILTRATION OF bNAb VRC01 INTO THE CEREBROSPINAL FLUID IN HUMANS IN THE RV397 STUDY

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Background: HIV may persist in the central nervous system (CNS) despite antiretroviral therapy (ART), creating a barrier to HIV eradication. Novel strategies to reduce the latent HIV reservoir may need to cross the blood brain barrier (BBB) into the cerebrospinal fluid (CSF). Targeting the CD4 binding site, VRC01 is a broadly neutralizing antibody (bNab) capable of potently neutralizing over 90% of HIV-1 strains.

Methods: The RV397 study conducted in Bangkok, Thailand was a randomized, double-blind, placebo-controlled trial that randomized participants who initiated suppressive ART during acute HIV infection to receive VRC01 40mg/kg or placebo intravenously every 3 weeks during analytic interruption of ART (ATI). CSF samples were collected at two time points from 3 participants who received VRC01: pre-infusion and 2-4 days after first detectable plasma viral load. VRC01 levels were quantified using a standardized sensitive Singulex single molecule counting technology with a lower limit of quantitation (LLOQ) of 50pg/ml for VRC01. CSF VRC01 concentration was compared to concurrent plasma level for each participant.

Results: Three males, aged 18-47 years, initiated ART during acute HIV (Fiebig stages 1 or 2) and were on ART for at least 28 months before ATI. Pre-infusion, pre-ATI, CSF HIV RNA was <80 copies/ml, CSF WBC <2 cells/µl, CSF protein <38 mg/dL, blood HIV RNA <20 copies/ml and CD4 >400 cells/µL. Post ATI, post-VRC01 infusion CSF HIV RNA was <80 copies/ml, CSF WBC <2 cells/µl, CSF protein <43 mg/dL, blood HIV RNA 418-1789 copies/ml and CD4 T >400 cells/µl. VRC01 levels in CSF were below LLOQ preinfusion and ranged between 0.35 – 0.75ug/ml post-infusion (see Table). Concurrent VRC01 levels in plasma were 200-600ug/ml, indicating a 100-1000 fold lower penetration into the CNS compartment.

Conclusion: We report here the successful quantification of the bNab VRC01 in the CSF from 3 persons living with HIV. The bioavailability of this potent and broad HIV monoclonal antibody in the CNS is critical considering that the CNS can facilitate the generation of resistant HIV quasi-species that are distinct from virus in systemic circulation. These results thus serve to inform the design of immunotherapies to target HIV infection in the CNS.

Donor ID	VRC01 level (µg/mL)				Days between ATI and CSF draw post first viral rebound	Days between last VRC01 Infusion and CSF draw post first viral rebound
	Cerebrospinal Fluid		Serum			
	Before VRC01 Infusion	After first viral rebound	Before VRC01 Infusion	After first viral rebound		
3799	Not quantifiable	0.411	Not quantifiable	251.8	16	16
5040	Not quantifiable	0.383	Not quantifiable	528.8	25	4
3500	Not quantifiable	0.733	Not quantifiable	202.8	45	2

454 BICTEGRAVIR/FTC/TAF CSF DIFFUSION IN HIV-INFECTED PATIENTS WITH CNS IMPAIRMENT

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Background: The penetration of antiretroviral drugs in deep compartments, like the central nervous system (CNS), is a crucial part of strategies towards HIV cure. This study aimed to estimate cerebrospinal fluid (CSF) diffusion of bictegravir (BIC), that has high protein binding which could limit diffusion, emtricitabine (FTC) and tenofovir alafenamide (TAF) in patients with HIV-related CNS impairment (HCI) enrolled in a real-life observational study.

Methods: Patients (pts) with HCI on treatment by an optimized antiretroviral therapy including BIC since at least 1 month were enrolled between 2019 January and February (NeuroHIV Rehabilitation Care Unit, AP-HP, Bicêtre Hospital, France). Blood and CSF samples were collected simultaneously in the setting of routine care. Plasma and CSF HIV RNA were quantified by PCR (Abbott Realtime®, threshold=40 copies/mL). Total plasma (Tot) and CSF BIC/FTC/tenofovir (TNF) concentrations and unbound plasma (U) BIC concentrations, separated by ultrafiltration (Centrifree devices, cutoff, 30 kDa; Millipore), were measured by quality controls validated assays (LC-MS/MS). The albumin quotient (QA), calculated as the ratio of CSF to plasma albumin, was used to evaluate the blood-brain barrier (BBB) function. All numerical variables were expressed as median (IQR).

Results: Twelve pts (6 females) were enrolled. Age was 44 (12) years. HCI were: progressive multifocal leukoencephalopathy (PML, n=7), cerebral toxoplasmosis (CT) (n=3), CT combined with HIV encephalitis (n=1) and VZV meningoencephalitis (n=1). Backbone therapy co-administered to BIC was: TAF+FTC (n=10) or TAF+FTC+Maraviroc (n=2). Plasma HIV RNA was undetectable in 10 (83%) pts and <3 $\log_{10}$ copies/mL in others. Two (17%) pts had a detectable CSF viral load (1.7 and 1.9 $\log_{10}$ copies/mL). All concentrations and ratios are shown in table below. There are correlations between CSF and Tot concentrations for BIC and FTC (p=.008 for BIC and p=0.002 for FTC) and between CSF and U concentrations for BIC (p=.049). The median QA was 5.5 (1.8); 1 (8%) patient had a damaged BBB, but not related with a higher CSF BIC/FTC/TNF diffusion.

Conclusion: Total plasma concentrations remained as previously reported. Almost all CSF concentrations were above the in vitro 50% inhibitory concentration (IC_{50}). BIC with FTC/TAF backbone should be effective to target

HIV replication in the CNS, which is a deep reservoir, even though BBB is undamaged.

	BIC	TNF	FTC
Total plasma – *ng/mL*	2748 (2374)	17.6 (7.6)	219 (200)
Unbound plasma – *ng/mL*	10.7 (12.2)	/	/
Total CSF – *ng/mL*	12.5 (5.8)	33.2 (7.4)	70.9 (35.6)
CSF IC50 – *ng/mL*	3.5	11.5	70
> CSF IC50 – *n (%)*	11 (92)	12 (100)	8 (67)
Inhibitory quotient = Total CSF / CSF IC50	3.6 (1.6)	2.9 (0.6)	1 (0.5)

455 A CROSS-SECTIONAL ANALYSIS OF ANTIRETROVIRAL REGIMEN ACTIVITY IN CEREBROSPINAL FLUID

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Background: ACTG A5321 is a prospective cohort study of changes in HIV-1 reservoirs among participants with HIV on antiretroviral therapy (ART). We designed a single cross-sectional analysis of antiretroviral (ARV) pharmacokinetics (PK) in cerebrospinal fluid (CSF) and investigated relationships among a novel putative measure of ART regimen CSF activity and concurrent biomarkers of HIV persistence and inflammation.
Methods: Participants were on ART for ≥2 years with well-documented sustained plasma viral suppression at time of lumbar puncture (LP). CSF ARV concentrations, cell-associated HIV DNA and inflammatory biomarkers were measured at LP. ARV levels were quantified by LC/MS/MS. CSF inhibitory quotients (IQ) were calculated for each drug in ART regimen as ratio of measured CSF concentration to literature values for in vitro inhibitory concentration. Participants were ranked (low to high) by IQs for TFV, FTC, and third ARV, then drug ranks were averaged to give an overall rank for the ART regimen; a participant with highest IQ for all individual components would have the highest regimen IQ score. Rank-based analyses were used to evaluate associations among regimen IQ ranks and biomarkers.
Results: CSF ARV concentrations were available on 55 participants on TDF/FTC-based regimens: 52 males (95%); 40 (73%) white non-Hispanic, 10 (18%) black non-Hispanic; median age, 48 yrs; median yrs on ART, 8.1 yrs; median CD4 count, 651 cells/μL; 54 (98%) with plasma HIV-RNA <40 copies/mL. Third drugs in ART regimens included: EFV (n=17), ATV/r (8), EVG/c (8), RAL (8), DRV/r (4) and DTG (2). RPV and NVP (n=8) were not analyzed as CSF levels were unavailable. Figure shows CSF IQ values for ARV drugs, which were consistent with CNS Penetration Effectiveness (CPE) scores. Associations among ART CSF IQ and HIV-1 persistence measures were restricted to participants treated during chronic infection (n=44). Average regimen IQ rank was slightly higher in those with undetectable CSF HIV DNA vs detectable (median [Q1, Q3]: 25 [19.7, 34.3] for TND vs. 21.2 [15.7, 28.7] for detected); p=0.25. CSF neopterin was positively associated with average IQ rank (Spearman r = 0.28, p = 0.07 adjusting for age and pre-ART CD4:8 ratio).
Conclusion: The ART regimen IQ rank is a new approach to assess regimen vs individual drug activity. This tool provides a basis for continued work to expand regimen IQ data and investigate longitudinal relationships with biomarkers of HIV CSF persistence and inflammation.

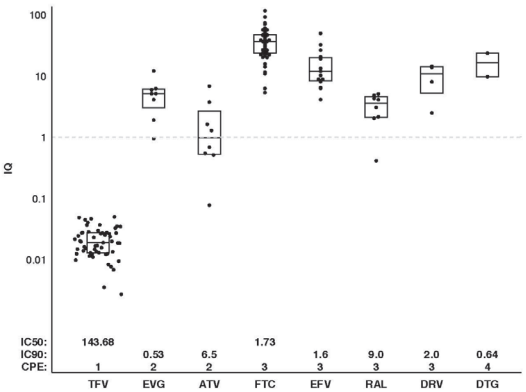
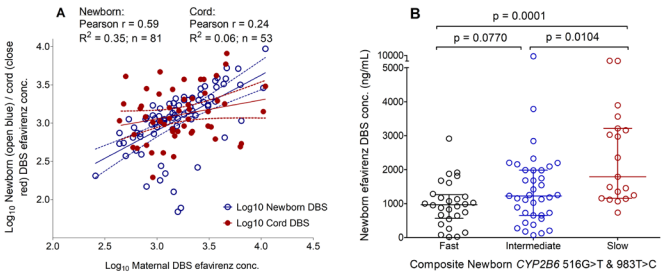


Figure. CSF 50% and 90% inhibitory quotients (IQ) by analyte. Boxes represent median (Q1, Q3). IQ_{50}s were used for TFV and FTC; IC_{90}s for other ARVs.

456 PRENATAL EFAVIRENZ EXPOSURE INDEPENDENTLY ASSOCIATED WITH FOETAL CYP2B6 GENOTYPE

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Background: Understanding the influence of foetal and maternal genetics on prenatal drug exposure could play an important role in assessing observed risk-benefit differentials during pregnancy. In this sub-study of VADICT (NCT03284645), the influence of functional CYP2B6 polymorphisms on prenatal exposure to efavirenz was investigated.
Methods: VADICT is a cohort study that started recruiting in June 2017 in four Nigerian hospitals investigating viral and antiretroviral dynamics in fluids important for mother-to-child transmission. Women commencing efavirenz-based regimens before/early/late in pregnancy or postpartum are being recruited with followed-up until breastfeeding ends. For this sub-study, maternal and newborn samples were collected immediately after delivery before breastfeeding started. Genomic DNA was extracted and genotyped by real-time PCR using TaqMan 5' nuclease assays for CYP2B6 516G>T and 983T>C single nucleotide polymorphisms (SNPs). Efavirenz was quantified using a validated LC-MS/MS method. Linear regression was used to explore association of genetic and non-genetic factors with newborn efavirenz concentrations.
Results: A total of 171 samples were available for this analysis (including 81 paired samples) from 86 women and 85 newborns. Mean (SD) maternal age at delivery was 30 (5.2) years, gestational age 40 (3.3) weeks, birth weight 2.9 (0.5) kg and APGAR score 7.6 (1.4). Samples were collected 18.5 (10.1) h after last maternal dose. A strong correlation was observed between maternal and newborn efavirenz concentrations (Figure A). Median (range) newborn efavirenz concentrations were 1180 (69.0-9230) ng/mL in unstratified newborns, 969 (15.9-2910), 1230 (69.2-9230) and 1790 (735-5230) ng/mL in fast (n = 28), intermediate (n = 37) and slow (19) metabolisers, respectively (Figure B). Newborn-to-mother concentration ratio was 0.88 (0.04-2.07). Newborn CYP2B6 516G>T, APGAR score, maternal CYP2B6 516G>T and body weight at delivery were independently associated with newborn efavirenz concentrations.
Conclusion: Both maternal and foetal genetics influence prenatal drug exposure. This can help progress assessment of the possible role of drug exposure in adverse foetal outcomes. These data are now being used to further qualify our previously described mechanistic model of prenatal drug exposure.



457 ASSOCIATION BETWEEN INTEGRASE INHIBITOR HAIR CONCENTRATIONS AND WEIGHT GAIN IN WOMEN

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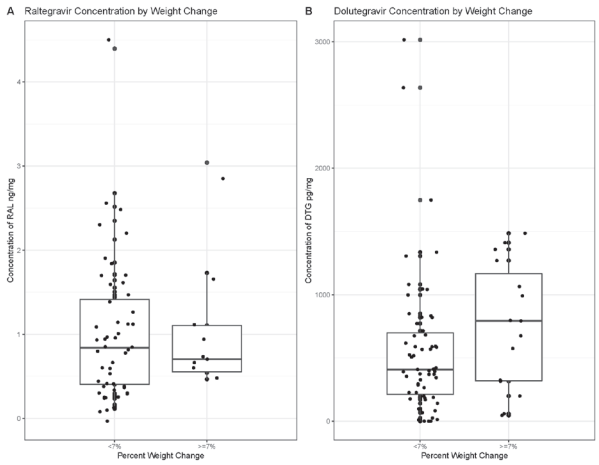
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Background: Integrase strand-transfer inhibitors (INSTIs) were associated with body weight gain among women living with HIV (WLH) in the Women's Interagency HIV Study (WIHS). Hair drug concentrations measure cumulative exposure and are associated with toxicity in other antiretroviral therapy (ART) medications. For the first time, we report the relationship between INSTI hair concentrations and weight change in WLH.

Methods: Data from 2006-2017 were analyzed from virally-suppressed (<1000 cop/mL) WLH in WIHS who switched/added raltegravir (RAL) or dolutegravir (DTG) to ART with quantifiable hair concentrations. Body weights were measured 6-12 months pre- and 6-18 months post INSTI switch/add. Hair concentrations were measured with validated liquid chromatography/tandem mass spectrometry assays 6-18 months post INSTI switch/add and dichotomized at the median. Linear models assessed the association between dichotomized INSTI hair concentration and weight change from pre-switch/add. The association between clinically significant weight gain (≥7%) and INSTI hair concentrations was assessed through Wilcoxon Rank Sum Tests and chi-square tests.

Results: 136 WLH contributed 231 hair samples with mean 1.9 years (±0.12) follow up. Mean age was 49.6(±9.2), 73(54%) Black, baseline BMI 30.4 kg/m$_2$(±9.5), 75(55%) were on DTG, and 61(45%) on RAL. Mean body weight change was +0.7 kg (±3.8) for RAL and +0.8 kg (±5.4) for DTG. No significant associations were seen between body weight change as a continuous variable with either RAL or DTG hair concentrations (p=0.2554 and p=0.2826, respectively). Median RAL and DTG hair concentrations were not significantly different in WLH with ≥7% weight gain compared to <7%: 0.71 ng/mg (Q1:0.55, Q3:1.10) vs 0.84 ng/mg (Q1:0.40, Q3:1.44), p=0.4735 and 793.0 pg/mg (Q1:316, Q3:1270) vs 409.0 pg/mg (Q1:198, Q3:714), p=0.1037 respectively (Figure). With combined INSTI groups, 14 of 24(58%) WLH with ≥7% weight gain had hair concentrations above the median vs 51 of 109(47%) with <7% weight gain, p=0.3057.

Conclusion: In virally-suppressed WLH, the effect of RAL and DTG cumulative drug exposure on body weight change over the short term appears to be limited. In addition to further pharmacologic assessments, other mechanisms to explain INSTI-associated weight gain should be explored.



458 CLINICAL TRIAL SIMULATION TO IMPROVE HIV PREEXPOSURE PROPHYLAXIS DOSING IN PREGNANCY

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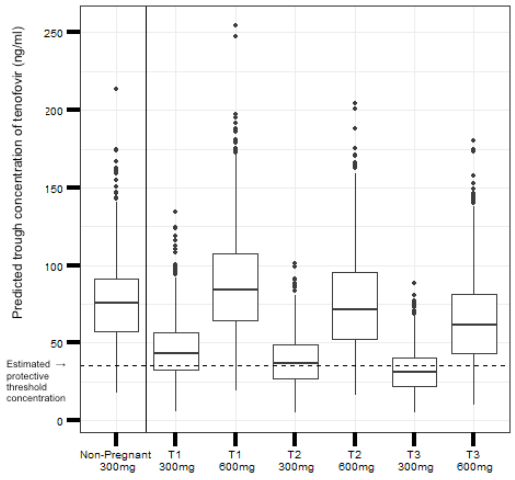
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Background: Several studies of pregnant women on TDF/FTC report lower TFV exposures in the 2nd and 3rd trimesters due to pregnancy-related increased volume of distribution and renal clearance. The Partners Demonstration Project showed the largest decline during pregnancy compared to non-pregnant women – 45% to 58% in TFV and active TFV diphosphate concentrations, respectively. We hypothesized that doubling the PrEP dose in pregnancy maintains the target plasma, PBMC, and tissue concentrations of TDF/FTC associated with high levels of HIV protection.

Methods: To estimate the TDF/FTC exposure associated with a 2-fold dose increase, we began with a prior population PK model of plasma TFV based on data from MTN-001, updated the model based on Partners Demonstration Project pregnancy cohort PK data, and performed an in silico simulation. We updated our prior model (NONMEM with FOCEI method for parameter estimation) by replacing creatinine clearance with trimester of pregnancy as a time-dependent covariate on clearance as the optimized final model. As the revised model fit the data well, we used it for further simulation. We simulated 1,000 women starting with a "standard" oral 300 mg daily oral TDF dose prior to pregnancy. Upon becoming pregnant, the simulated patients were split into 2 study arms through the 3 trimesters of pregnancy: 1 arm continuing on a "standard" dose and the other arm receiving "double" the standard dose. The estimated protective trough TFV concentration benchmark (35.5 ng/mL) was based on 90% sensitivity threshold for daily dosing in non-pregnant women in HPTN 066.

Results: In the non-pregnant population, our simulation showed 3.7% of women on a standard regimen would have trough levels below the protective threshold. In contrast, we found that 31.5%, 47.2%, and 62.6% of trough concentrations in the 1st, 2nd, and 3rd trimesters, respectively, were below the protective threshold (Figure). By comparison, in the simulated double dose group, only 4.4%, 7.9%, and 14.4% of troughs fell below protective levels in the 1st, 2nd, and 3rd trimesters, respectively.

Conclusion: Our simulation shows >50% of research participants on standard dosing will have 3rd trimester trough plasma TFV concentrations below levels associated with protection. The double dose arm median TFV concentration in pregnancy is very similar to non-pregnant standard dose median TFV. The simulation provides the quantitative basis for a prospective study to evaluate a double dose to adjust for TFV PK changes in pregnancy.



Simulated plasma trough concentrations of tenofovir during pregnancy at different dose levels (T1- 1st trimester, T2- 2nd trimester, T3- 3rd trimester)

459 GENITAL INFLAMMATION DOES NOT DECREASE VAGINAL TFV LEVELS IN WOMEN TAKING ORAL PrEP

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Background: African studies demonstrate that genital inflammation decreases tenofovir (TFV) gel's efficacy. We evaluated the impact of inflammation and

dysbiosis on cervicovaginal fluid (CVF) TFV concentrations in US women taking oral TDF/FTC for PrEP.

Methods: Southern Californian women on oral TDF/FTC in the Adherence Enhancement Guided by Individualized Texting and Drug Levels (AEGiS) study had CVF collected at week 24 to evaluate (i) sexually transmitted bacterial (gonorrhea, chlamydia, gardnerella and trichomonas), viral (HPV, CMV and HSV-1/2) and fungal (Candida) infections, (ii) microbiome composition by 16S sequencing (V3-V4 region) and (iii) cytokine profiles by ELISA (IL-8, MIP-1a, MIP-1b, and IP-10). Microbiome Community State Types (CSTs) were assigned based on described characteristics (i.e. CST I, II, III, V dominated by lactobacilli and CST IV containing mostly non-lactobacilli species). TFV in CVF and tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) were also measured at week 24. CVF TFV of 100-1000ng/mL benchmarked typical genital concentrations; DBS TVF-DP ≥700fmol/punch suggested long-term adherence. Univariate statistical analysis was used to determine factors associated with low and high CVF TFV.

Results: 34 women had CVF specimens collected at week 24. Median age was 43 (IQR 35-47) years. 15% (5/34) had discordant tenofovir concentrations (i.e. DBS TFV-DP≥700 and CVF TFV<100). No inflammatory process was associated with lower CVF TFV concentrations or tenofovir discordance. Notably, among the 26 participants assessed for vaginitis (Candida, Gardnerella or Trichomonas), women with possible vaginitis (n=13) were more likely to have high (>1000 ng/mL) CVF TFV concentrations compared to those without vaginitis (77% versus 31%, p<0.05). No difference was seen in CVF TFV concentrations by vaginal microbiome type. 3 of the 5 women with discordance had non-lactobacillus dominant microbiomes; however, they were dominated by non-vaginitis organisms (2 E. *cloacae*, 1 E. *coli*).

Conclusion: Presence of genital viruses, cytokines or *Gardnerella* spp. were not associated with low CVF TFV levels in women taking oral PrEP. Women with vaginitis may actually have higher CVF TFV levels, perhaps due to inflammatory processes augmenting blood flow and TFV penetration into the vaginal compartment.

460 ARV PENETRATION INTO FEMALE GENITAL TRACT DURING PREGNANCY: EFAVIRENZ AS A CASE STUDY

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Background: Proper characterisation of antiretroviral pharmacokinetics in the female genital tract is crucial in developing effective pre-exposure prophylaxis and prevention of intrapartum mother-to-child transmission interventions. Progress in this area has been limited by sampling constraints.

Methods: A novel assay to quantify efavirenz in cervicovaginal fluid from flocked swabs using LC-MS/MS was developed and validated as per FDA guidance. Efavirenz was quantified from cervicovaginal swabs (CVS) collected from HIV infected pregnant women enrolled in the VADICT study (NCT03284645) receiving 600 mg daily. To further characterise efavirenz penetration into the female genital tract, we extended a previously described pregnancy PBPK model constructed and implemented in SimBiology® (MATLAB® version 2018b) to include a multi-compartmental cervicovaginal unit (vagina fluid, epithelium, stroma blood and tissues). Variables representing drug and system characteristics were obtained from the literature for model parametrization. Efavirenz movement within the cervicovaginal compartments was by passive diffusion. The model was qualified by comparing predictions with data from the VADICT study.

Results: Mean CVS efavirenz concentration with the new method in this cohort (n = 39, mean gestational age 33.8 weeks) at 14.8 h post-dose was 1.237 µg/mL (95% CI: 0.138, 6.397), giving CVS:plasma concentration ratio of 0.64, more than previous reports. This was adequately predicted by the model, predicted CVF concentration being 1.190 µg/mL (0.542, 2.430) in a virtual cohort (n = 100, 29.5 weeks' gestation). Trough (C_{trough}), maximum (C_{max}) efavirenz concentration and area under the concentration-time curve (AUC0-24h) were 0.62 µg/mL (0.29-1.33), 1.67 µg/mL (1.05-2.67), and 28.4 (µg.hr/mL) (16.89-41.41) respectively. The corresponding parameters in vaginal epithelium, stroma blood and tissue were 7-22% higher. Importantly, both observed and predicted efavirenz C_{trough} were above reported protein-binding adjusted IC_{95} of 126 ng/mL for wild-type HIV-1 in all patients.

Conclusion: Our novel method indicates significantly higher penetration of efavirenz in the female genital tract than previously reported. This provided data for successful qualification of a PBPK model of efavirenz in pregnant women genitalia.

461 PK/PD STUDY OF RALTEGRAVIR ALONE OR COMBINED WITH LAMIVUDINE AS PrEP: AN RCT

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Background: Neither the added value of lamivudine or the effect of raltegravir as PrEP are well known. We evaluated raltegravir +/- lamivudine (RGV/3TC) pharmacokinetics and pharmacodynamics (PK/PD) using a tissue explant model.

Methods: Open label trial of 36 HIV- females and males (1:1) randomised to 7d raltegravir 400mg bd followed by 7d raltegravir 400mg/lamivudine 150mg bd (after washout), in 6 sampling blocks to capture different times post-dose. Blood, saliva, rectal fluid (RF)/tissue (RT), vaginal fluid (VF)/tissue (VT) sampled at baseline, on PrEP (day2, 4 or 6) and off PrEP (day8, 10 or 12) for PK (RGV, 3TC, 3TC-triphosphate) and antiviral activity (ex vivo challenge R5-tropic HIV-1BaL virus ;p24 levels at 15d). Protection was defined as >50% reduction in p24 compared to baseline.

Results: RGV and 3TC were detectable in all tissue samples at day 2 PrEP. On day 6, GM RGV levels were 247.9 ng/g in VT and 589.2 ng/g in RT; GM tissue-to-plasma accumulation ratios 0.75 (VT) and 2.6 (RT). After PrEP cessation, 50/7% of VT and 86/58% of RT samples remained above RGV IC_{95} (15 ng/mL) day 10. Extensive 3TC VT (1397 ng/g) and RT (2662 ng/g) accumulation: GM Tissue-to-plasma accumulation ratios were 7.3 (VT) and 17.1 (RT) day 6. Off PrEP, 3TC persisted in VT (102 ng/g) and RT (275 ng/g) until day12. G. Plasma explained a greater variability in VT level (r2 >0.759; P<0.001) compared with VF. Whereas RF explained more of the variability for 3TC RT levels (r2 =0.591; p<0.001), than plasma. Raltegravir provided maximum ex vivo protection at day 2-8 (83% of rectal; 100% of vaginal samples) Raltegravir/Lamivudine provided 100% protection in rectal tissue from day 2-10, and in vaginal tissue from day 8-12.

Conclusion: Following discontinuation, high concentrations of RGV remained in RT (but rapid decline in plasma and VT concentrations) with persistent inhibitory activity in RT up to 4 days later. Addition of lamivudine increased inhibitory activity in RT and VT, with similar persistent inhibition associated with high 3TC RT concentrations 4 days after discontinuation.

462 MODELING-SUPPORTED ISLATRAVIR DOSE SELECTION FOR PHASE III

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Background: Islatravir (ISL) is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI) in development for the treatment and prevention of HIV-1 infection. Single doses of ISL as low as 0.5 mg showed robust efficacy in a proof-of-concept (POC) clinical trial and established an IQ (ratio of drug exposure to potency) of 5 for ISL for wild-type HIV-1. In a Ph2 clinical trial (NCT03272347), participants who initiated ISL+doravirine (DOR) in combination with 3TC and switched to ISL+DOR no earlier than Wk 24 had high efficacy at Wk 48 as measured by HIV-1 RNA <50 c/mL. Data through Wk 48 showed that exposure-response was flat, indicating an achievement of maximal efficacy at the ISL doses examined (0.25, 0.75, and 2.25 mg). Modeling and simulation, along with in vitro potency data, were used to select the dose for further clinical development of ISL most appropriate for HIV-1 treatment-naïve, virologically suppressed, and highly-treatment experienced (HTE) populations.

Methods: A population pharmacokinetic model for ISL and its active moiety, ISL-triphosphate (ISL-TP), has been developed based on Ph1 and Ph2 data in healthy participants and people living with HIV-1 (PLWH) and used to examine the Ph2 exposure-response relationship. The population pharmacokinetic model was also used to predict the percentage of participants expected to have ISL-TP concentrations sufficient to have antiviral activity against common NRTI-resistant viruses (e.g., M184V, etc.).

Results: Based on an analysis of in vitro potency data, Ph1b POC efficacy, and Ph2 data, a dose of ISL 0.75 mg QD is expected to provide maximal efficacy in treatment-naïve PLWH, and also be highly efficacious in virologically suppressed and HTE participants. Based on the in vitro potency and supported by the POC data for ISL, the expected concentrations of ISL-TP after a single 0.75 mg dose are sufficient to suppress both wild-type virus and HIV-RT resistant variants. ISL-TP accumulates after multiple dosing resulting in higher IQ at steady state. Simulations show that most patients would rapidly surpass the IQ threshold for all common HIV-RT resistant variants.
Conclusion: ISL 0.75 mg QD, in combination with DOR 100 mg QD, is appropriate for further evaluation in a development program consisting of treatment-naïve, virologically-suppressed, and HTE PLWH.

463 FOSTEMSAVIR EXPOSURE-RESPONSE RELATIONSHIPS IN TREATMENT-EXPERIENCED HIV PATIENTS

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Background: Fostemsavir (FTR) is an oral prodrug of its active moiety, temsavir (TMR), an investigational HIV-1 attachment inhibitor. Phase 3 efficacy exposure-response (ER) relationships in heavily treatment-experienced (HTE; multi-drug resistant) HIV-1 patients with FTR 600 mg BID, and safety ER relationships from Phase 2b (TE) and P-3 (HTE) with FTR 400, 600, 800 mg BID and 600, 1200 mg QD were evaluated.
Methods: Individual PK parameters estimated from a population PK model were used to evaluate ER relationships. Efficacy endpoints: change in plasma HIV-1 RNA from Day 1 to 8 (functional monotherapy), >0.5 and >1.0 $\log_{10}$ decrease in HIV-1 RNA on Day 8 and at Week 24, proportion of subjects with HIV-1 RNA <40, <200 and <400 copies/mL. In addition, covariates of virologic (TMR IC_{50} and gp120 substitutions), immunologic (CD4+ T-cell count), and demographic factors as predictors of virologic response were investigated. Simulations were conducted to predict virologic responses on Day 8 under different extrinsic and intrinsic factors. Safety endpoints included: change from baseline in AST, ALT, CPK, SCr, QTcF up to Week 24, and occurrence of rash. Following graphical exploration, linear, inhibitory Emax and logistic regression models were explored.
Results: ER relationship was established between TMR C_{tau} and change in plasma HIV-1 RNA from Day 1 to 8, however, relationship was shallow and highly variable. Baseline HIV-1 RNA and CD4+ count were covariates; the higher the baseline value, the greater the reduction. Addition of IC_{50} (as $C_{tau}/PBIC_{50}$) did not improve the relationship. Model predicted probability of >0.5 and >1 $\log_{10}$ decrease in HIV-1 RNA on Day 8 was 80% and 58%, at plasma TMR C_{tau} of 500 ng/mL with median baseline HIV-1 RNA (4.65 $\log_{10}$ copies/mL) and CD4+ (>20 cells/mm_3). At Week 24, no relationship could be established between plasma TMR C_{tau} and HIV-1 RNA or CD4+ counts. Simulations showed no clinically relevant changes in Day 8 virologic response (Table 1). There was no clear correlation seen between TMR exposure and the safety endpoints explored.
Conclusion: Higher reduction in plasma HIV-1 RNA from Day 1 to 8 with increase in TMR C_{tau} in HTE HIV-1 patients on FTR 600 mg BID was observed. Simulations showed the impact of food, co-medications, and body weight were not clinically relevant.



464LB BICTEGRAVIR DISTRIBUTION AND BICTEGRAVIR/FTC/TAF ACTIVITY IN GENITAL TRACT AND RECTUM

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Background: Antiretroviral distribution in the genital tract (GT) and rectum is required to suppress HIV replication within these compartments. Pharmacokinetics and HIV decay in the GT and rectum have not yet been described for the new integrase inhibitor bictegravir (BIC).
Methods: Prospective study of HIV-1–infected, ART–naive males (n=15) and females (n=8) initiating BIC/F/TAF 50/200/25 mg. HIV-1 RNA was measured (Abbott RealTime HIV-1; quantification limit 40 c/mL) in blood plasma(BP) as well as in seminal plasma (SP) and rectal fluid (RF) in men, and cervicovaginal fluid (CVF) in women, at baseline (BL), days 3, 7, 14 and 28, and weeks 12 and 24. HIV-1 RNA decline between timepoints in SF and RF were compared to BP. Total BIC concentrations were quantified in BP, SP, RF, rectal tissue (RT) and CVF at 24 hours post dose (C_{24h}) on day 28 and week 12 using a validated LC-MS/MS assay.
Results: Median (range) BL characteristics were: age 30 (20-57) yrs; CD4 419 (9-1165) cells/µL; BP HIV-1 RNA 4.89 (3.17-6.10) $\log_{10}$ c/mL. HIV-1 RNA was >40 c/mL at BL in SP, RF and CVF in 12/15, 13/15 and 4/8 individuals, with a median(range) of 3.74 (2.29-4.74), 4.29 (2.75-5.22) and 2.56 (1.61-3.56) $\log_{10}$ c/mL. HIV-1 RNA decrease was significantly lower in SP compared to BP up to day 14 with no statistically significant differences thereafter, whereas no differences were observed between RF and BP. Of those with HIV-1 RNA >40 c/mL in SP, RF and CVF at BL, 42%, 77% and 100% had undetectable HIV-1 RNA at day 14, and 92%, 92% and 100%, respectively, at day 28, whereas 47% of men and 37% of women had HIV-1 RNA >40 c/mL in BP at day 28. In men, median(range) BIC C_{24h} in BP, SP, RF and RT were 2640 (424-10300) ng/mL; 65.5 (20.1-923) ng/mL; 23.4 (4.5-336.9) ng/swab; and 74.1 (6.0-478.5) ng/g, respectively. In women, BIC C_{24h} in BP and CFV were 2320 (834-5770) ng/mL and 61.6 (14.4-1760.2) ng/mL. On average BIC C_{24h} in SP,CVF and RT (assuming tissue density=1g/ml) were 2.7%, 2.8% and 2.6% of BP C_{24h}. Total BIC concentrations exceeded the EC_{50} for wild type HIV-1 (1.1 ng/mL) in all compartments.
Conclusion: BIC/F/TAF resulted in rapid HIV-1 RNA decay in GT and rectum. Total BIC concentrations in these compartments exceed the EC_{50} for wild-type HIV-1.

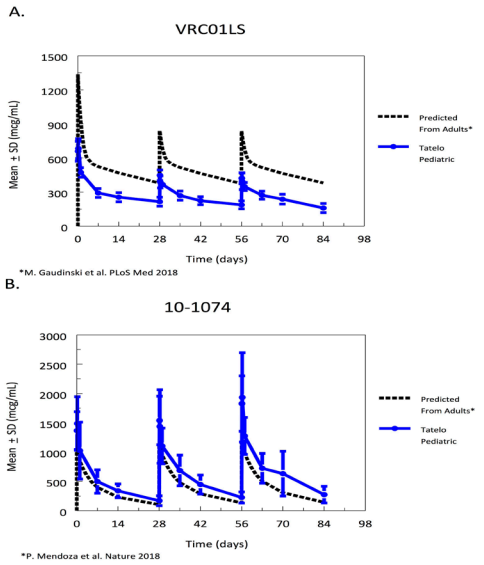
465LB SAFETY AND PHARMACOKINETICS OF INTRAVENOUS VRC01LS AND 10-1074 IN YOUNG CHILDREN

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Background: Early-treated HIV+ children may be ideal candidates for use of broadly neutralizing monoclonal antibodies (bNAbs) as an alternative to antiretroviral treatment (ART), but pediatric bNAb data to date has been limited to subcutaneous administration of VRC01/LS during infancy. In preparation for a trial of dual bNAb use as a treatment alternative, we evaluated the safety and pharmacokinetics (PK) of monthly VRC01LS or 10-1074 dosed intravenously among HIV+ children on suppressive ART.
Methods: The PK phase of the Tatelo Study in Botswana enrolled 12 children who had received ART continuously from < 7 days through at least 96 weeks of life, and had HIV-1 RNA < 40 copies/mL for at least 24 weeks prior to entry. While continuing ART, 6 participants received VRC01LS (30 mg/kg load at day 0, then 10mg/kg at days 28 and 56) and 6 participants received 10-1074 (30 mg/kg on days 0, 28 and 56). bNAb concentrations were tested 18 times over 12 weeks using murine anti-VRC01 and anti-10-1074 antibodies.

Results: Among the 12 children enrolled, the median age was 38 months (range 26 to 50 months), 75% were female, the median CD4 cell count was 1211 cells/mm_3 and CD4% was 34%. All children were receiving lopinavir/ritonavir, zidovudine, lamivudine (and one was also on abacavir). All but one infusion occurred on schedule and to completion, and infusions were well tolerated. No infusion reactions occurred, and no grade 3 or 4 events were related to either bNAb. For VRC01LS, median (range) first dose peak concentrations (C_{max}) and Day 84 trough concentrations (C84D) were 726 (559-799) mcg/mL and 157 (126-201) mcg/mL respectively, both about half of predicted values based on PK in uninfected adults (Figure 1A). For 10-1074, median (range) first dose C_{max} and C84D concentrations were 1633 (1174-1999) mcg/mL and 258 (122-467) mcg/mL respectively, both somewhat greater than predicted values from HIV-infected adults on suppressive ART (Figure 1B).
Conclusion: Intravenous VRC01LS and 10-1074 were safe and well tolerated among HIV+ children receiving ART.Pediatric PK of these two bNAbs differed from PK in adults. For VRC01LS, an increased maintenance dose of at least 15mg/kg may be needed to achieve concentrations similar to adults when dosed monthly. For 10-1074, predicted adult concentrations were slightly exceeded with 30mg/kg monthly.

Figure 1: VRC01LS (A) and 10-1074 (B) pharmacokinetic profiles after intravenous administration in HIV+ children

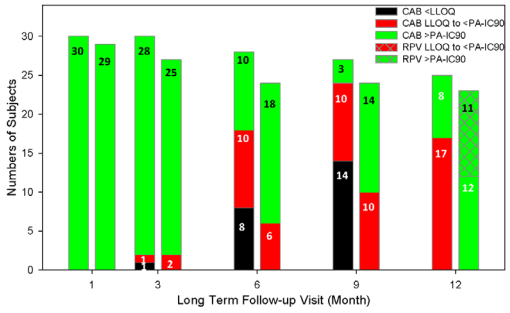


466 CABOTEGRAVIR AND RILPIVIRINE PK FOLLOWING LONG-ACTING HIV TREATMENT DISCONTINUATION

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Background: Long-acting (LA) regimens of cabotegravir (CAB) + rilpivirine (RPV) given monthly and every 2-months are in development for maintenance of HIV suppression. Both products exhibit absorption-rate limited PK following intramuscular (IM) administration, with apparent half-life ($t_{1/2}$) estimates of 5.6 -11 weeks (CAB) and 28 weeks (RPV). Following LA treatment discontinuation, CAB and RPV may remain measurable in plasma for a year or longer. Available long-term follow up (LTFU) pharmacokinetic (PK) data from discontinued subjects in Phase 2b/3 studies (LATTE-2/ATLAS) are presented.
Methods: HIV-infected subjects who received CAB LA + RPV LA every 4 (Q4W, n=33) or every 8 weeks (Q8W, n=5) and withdrew for any reason were required to switch to alternative antiretroviral therapy (ART) and enter LTFU (1 year), with PK sampling at 1, 3, 6, 9 and 12 months after final injections. Plasma CAB and RPV concentrations were determined by validated LC-MS/MS assays. RPV concentrations in subjects receiving oral RPV in LTFU were excluded from the results (n=6).
Results: Figure 1 represents CAB and RPV plasma concentrations for subjects entering LTFU after having been on CAB LA+RPV LA from 4 to 72 weeks. Plasma CAB was > 0.166µg/mL (protein adjusted (PA)-IC_{90}) in 30/30 subjects at the 1-month LTFU visit, and ranged between 0.034 to 0.152µg/mL (< PA-IC_{90}) in 8 subjects and was nonquantifiable (<lower limit of quantification (LLOQ, 0.025µg/mL)) in 17 subjects at the 12-month LTFU visit. At the 1-month LTFU visit, plasma RPV was >12 ng/mL (PA-IC_{90}) in all subjects (29/29); at 12-month LTFU visit, plasma RPV was >LLOQ (1ng/mL) in all subjects (23/23), ranging up to 63.8 ng/mL and >PA-IC_{90} in 11/23. Adverse events were uncommonly reported, and no patients met CVF criteria during LTFU on alternative ART, which included dolutegravir and elvitegravir integrase inhibitor based regimens, darunavir protease inhibitor based regimens, and RPV non-nucleoside reverse transcriptase based regimens.
Conclusion: The CAB and RPV plasma concentrations observed during LTFU are consistent with the apparent absorption-rate limited $t_{1/2}$ for each LA formulation. Both CAB and RPV have a low drug interaction potential as perpetrators. Alternative ART selection after discontinuing CAB LA + RPV LA may include CYP3A and/or UGT1A1 inducers or inhibitors, without efficacy or safety concerns despite potential for transient increases in CAB and RPV concentrations by inhibitors.

Figure 1 Range of CAB (left) and RPV (right) Concentrations by LTFU Visit



467 WITHDRAWN

468 MK-8504 AND MK-8583 (TENOFOVIR PRODRUGS) SINGLE-DOSE PK AND ANTIVIRAL ACTIVITY IN HIV

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Background: There is a need for Human Immunodeficiency Virus (HIV-1) treatments with improved safety profiles and increased ease of administration. MK-8504 and MK-8583 are nucleoside reverse transcriptase inhibitors (NRTIs) that are novel tenofovir (TFV) prodrugs, with a potential for weekly dosing due to the long $t_{1/2}$ of the active diphosphate (TFV-DP). Single-dose pharmacokinetics (PK) and antivirologic activity of these compounds were assessed in two Phase 1 programs.
Methods: Single doses of 2-240 mg MK-8504 were tested in healthy adults, and single doses up to 240 mg were tested in ART-naïve persons living with HIV (PLWH). Single doses of MK-8583 2-150 mg were tested in healthy adults, and a single dose of 100 mg was tested in ART-naïve PLWH. Plasma and peripheral blood mononuclear cells (PBMCs) were collected up to 10 days after dosing for PK and viral load (VL).
Results: Oral MK-8504 and MK-8583 were rapidly absorbed (T_{max} ~ 0.5 hour); MK-8583 was rapidly eliminated from plasma ($t_{1/2}$ 0.2-0.4 hours), while MK-8504 had slower elimination ($t_{1/2}$ 6-8 hours). As expected, plasma TFV concentrations were generally similar, with a median T_{max} of 1-4 hours after both MK-8504 and MK-8583 administration, and a $t_{1/2}$ of 20-38 hours for MK-8504 and 19-30 hours for MK-8583. The levels of TFV-DP in PBMCs exhibited a median T_{max} of 4-24 hr for both compounds, with a $t_{1/2}$ of 48-115 hours for MK-8504 and 65-192 hours for MK-8504. The PK in PLWH and healthy participants were similar. Despite PBMC TFV-DP concentrations consistently above the efficacious trough concentration for marketed TFV prodrugs (100 nM), HIV-1 VL reduction was suboptimal for both compounds. The mean VL reduction at 7 days was 0.6 log_{10} copies/mL for MK-8583 and 0.9 log_{10} copies/mL at the top dose of MK-8504, and several participants failed to achieve consistent VL reduction. There was

no relationship observed between Day 7 PBMC TFV-DP concentrations and VL reduction for either compound. No genetic resistant variants were identified.
Conclusion: Single doses of MK-8504 and MK-8583 were generally well-tolerated. These TFV prodrugs were rapidly converted to the active form and maintained target concentrations in PBMCs through 7 days. Unlike other TFV prodrugs administered daily in monotherapy trials, the antiretroviral activity of MK-8504 and MK-8583 was modest and transient. The persistent adequate concentrations of TFV-DP belie the poor VL response; it is possible, though, that VL responses could improve with daily administration of MK-8504 or MK-8583. Collectively, these data raise questions about the feasibility of TFV prodrugs in extended-interval dosing regimens.

469 DOSE-RESPONSE RELATIONSHIP OF SUBCUTANEOUS LONG-ACTING HIV CAPSID INHIBITOR GS-6207

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Background: GS-6207, a potent, selective, first-in-class, multi-stage inhibitor of HIV-1 capsid function that inhibits HIV at picomolar concentrations and is in development as a long-acting agent for treatment of HIV-1 infection. The safety, antiviral activity and pharmacokinetics (PK) of GS-6207 were evaluated in people living with HIV (PLWH) in this Phase 1b study.
Methods: This is an ongoing, Phase 1b, randomized, double-blinded, placebo-controlled dose-ranging study of GS-6207 in HIV capsid-inhibitor naive PLWH who are not taking antiretroviral therapy. A single subcutaneous (SC) dose of GS-6207 (20, 50, 150, 450, or 750 mg; N=6/cohort) or placebo (N=2/cohort) was administered. The primary endpoint was maximum reduction of plasma HIV-1 RNA through post dose day 10 (D10). Safety was assessed using laboratory tests and adverse event (AE) reporting. We present antiviral activity, blinded safety, and dose-response relationship for the 20 to 450 mg dose cohorts; enrollment of the 750 mg cohort is ongoing.
Results: Demographics and baseline characteristics were similar across groups (N=32, n=8 per group). All PLWH who received active drug had significantly greater reductions in HIV-1 RNA by D10 than the placebo (all $p<0.0001$). The 50 to 450 mg groups had a numerically greater mean reductions in HIV-1 RNA through D10 (range: 1.8 to 2.2 $\log_{10}$copies/mL) than the 20 mg group (1.4 $\log_{10}$copies/mL). At these doses, the inhibitory quotients (mean GS-6207 concentrations for each group/protein adjusted 95% maximal effective concentration in MT-4 cells for wild type HIV-1) on D10 ranged from 0.7 to 9.9. Using a maximum effect (Emax) model for GS-6207 (SC 20 to 450 mg) and antiviral activity, Emax was ~2.1 $\log_{10}$copies/mL decline in HIV-1 RNA, and a dose inhibiting viral replication by 50% (ED50) was ~10 mg. One participant experienced a serious AE (Grade 3) of atrial fibrillation after using methamphetamine; no other SAEs, Grade 3 or 4 AEs, AEs leading to discontinuation, or clinically relevant Grade 3 or 4 laboratory abnormalities were reported. The most common AEs were injection site reactions that were mostly mild and transient (50%).
Conclusion: In PLWH, GS-6207 demonstrated potent antiviral activity, with up to a 2.2 $\log_{10}$ copies/mL decline at Day 10, and was generally safe and well tolerated. These results support further clinical evaluation of GS-6207 as a long-acting antiretroviral agent.

470 PK, FOOD EFFECT, AND SAFETY OF ORAL GS-6207, A NOVEL HIV-1 CAPSID INHIBITOR

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Background: GS-6207, a potent, selective, first-in-class, multi-stage inhibitor of HIV-1 capsid function is in development for treatment of HIV-1 infection as a long acting agent. In people living with HIV (PWH), GS-6207 administered subcutaneously (SC) has shown potent antiviral activity, and is generally well tolerated. In addition to GS-6207 SC formulations, an oral tablet formulation is also in development. The safety, single ascending dose (SAD) pharmacokinetics (PK) and effect of food (FE) on GS-6207 oral tablets were evaluated in HIV negative participants.
Methods: This is an ongoing, blinded, placebo-controlled Phase 1 study with staggered SAD and open label FE cohorts. In each SAD cohort subjects were randomized (4:1) to receive single doses of GS 6207 (n=8/cohort) or placebo (n=2/cohort), at 50, 300, 900 or 1800 mg. In the FE cohorts (n=8/cohort), subjects received GS-6207 300 mg following a high fat (~1000 kcal; ~50% fat) or low fat (~400 kcal; ~25% fat) meal. Intensive PK sampling will be performed for 64 days post-dose. Single dose PK parameters were estimated using noncompartmental methods using available data; dose proportionality and FE were assessed. Safety was evaluated throughout the study.
Results: Interim safety and PK data are available through 35 (300 and 900 mg fasted) or 8 days post dose (50 and 1800 mg fasted, 300 mg high and low fat). 56 of 56 participants completed dosing. GS-6207 oral tablets were generally well tolerated. No serious adverse events (AEs), Grade 3 or 4 AEs, or discontinuations due to AEs were reported. The most common AEs were back pain (n=2) and headache (n=3); all Grade 1.
Based on the available data, GS-6207 exposures increased in a less than dose-proportional manner over the dose range of 50 to 1800 mg. Maximal concentrations (C_{max}) of GS-6207 were achieved ~4 to 8 h post dose (T_{max}), and GS-6207 $t_{1/2}$ was ~12 days. Exposure (C_{max} and AUC0-D8) and time to maximal exposure (T_{max}) were not affected by administration following a high or low fat meal, supporting dosing of GS-6207 tablets without regard to food (Table 1).
Conclusion: The preliminary PK and safety data suggest GS-6207 oral tablets are well tolerated following single oral doses up to 1800 mg, and can be dosed without regards to food. These data support ongoing clinical development of oral GS-6207 for use in PWH.

Table 1. Preliminary PK data for GS-6207 oral tablets:

Dose; meal type N=8/cohort	$AUC_{0\text{-}D8}$ (ng* hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (days)*
50 mg, fasted	694 (56.0)	8.24 (48.3)	4.00 (4.00, 5.50)	NC
300 mg, fasted	2790 (81.5)	33.7 (96.3)	4.00 (4.00, 6.00)	11.0 (9.3, 14.5)
900 mg, fasted	3900 (67.2)	43.9 (73.3)	4.00 (2.50, 20.0)	13.4 (9.88, 13.9)
1800 mg, fasted	5080 (56.3)	53.8 (48.0)	8.00 (5.00, 8.00)	NC
300 mg, high-fat meal	2540 (33.6)	35.0 (33.0)	5.00 (4.00, 6.00)	NC
300 mg, low-fat meal	2060 (55.7)	28.1 (60.6)	6.00 (4.00, 8.00)	NC

Preliminary pharmacokinetic parameters are presented to 3 significant figures as mean (%CV) for AUC and C_{max}, and median (Q1, Q3) for T_{max} and $T_{1/2}$.
**PK data through 35 days post dose available for 300 and 900 mg fasted used to estimate $T_{1/2}$. NC: not calculated due to insufficient data*

471 ANTIRETROVIRAL & RIFAMPICIN COTREATMENT AFFECTS DMPA EXPOSURE: DOSING IMPLICATIONS

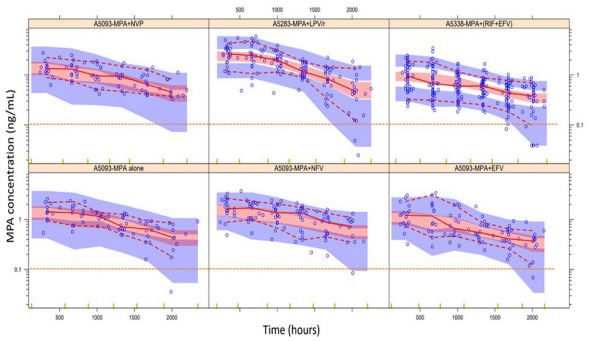
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Background: Depot medroxyprogesterone acetate (DMPA) is an intermediate-acting hormonal contraceptive, administered as 150-mg intramuscular injection every 3 months and is commonly used by women with HIV and TB. As MPA is a CYP3A4 substrate, drug-drug interactions (DDI) with drugs used for HIV or TB may lead to subtherapeutic MPA concentrations (<0.1 ng/mL) before the next injection, resulting in unwanted pregnancies.
Methods: Pharmacokinetic data from DMPA studies ACTG A5093 (DMPA alone, or with nelfinavir, efavirenz or nevirapine), A5283 (with lopinavir/ritonavir), and A5338 (with rifampicin+efavirenz), were pooled and interpreted with a population PK model. MPA concentrations were measured at week 2, 4, 6, 8, 10 and 12 after injection. Allometric body weight was used to scale the clearance and volume of distribution parameters and the effect of DDI were investigated. Monte Carlo simulations were used to identify percentage of participants at risk of subtherapeutic MPA exposures and derive alternative dosing strategies.
Results: A total of 138 women with HIV, contributing 744 MPA concentration observations were included. Median (range) weight and age were 62.5 kg (41-125) and 34 years (15-47), respectively. A one-compartment model with first-order elimination characterized DMPA disposition, while the release of MPA from the micro-crystalline suspension was characterized using two-way absorption pathway. A fraction of the dose is readily available in the systemic circulation, while the rest is released more slowly. RIF+EFV and EFV co-treatment increased clearance of MPA by 52.4% and 24.7%, respectively;

whereas LPV/r and NFV decreased clearance by 28.7% and 15.8%, respectively. LPV/r co-treatment was also found to accelerate the rate of slow release of MPA into systemic circulation, thus shortening the terminal half-life. The model predicted that, at week 12, a typical 60-kg woman on RIF+EFV and EFV has a higher risk of having a subtherapeutic concentration (3.4% and 2.6%) compared to MPA-alone (1.6%). This risk increased with body weight. Simulations demonstrated that re-dosing every 8-10 weeks can overcome the risk of contraceptive failure associated with these DDI.

Conclusion: Co-treatment with RIF+EFV, and to a lesser extent EFV alone, decreases systemic exposure of MPA, thus increasing the risk of subtherapeutic exposure and contraception failure. Dosing DMPA every 10 or even 8 weeks when prescribing RIF+EFV should eliminate this risk.

Visual predictive check of the final model (log scale) stratified by different study arms. The solid and dashed lines are the 5th, 50th, and 95th percentiles of the observed data, while the shaded areas represent the 90% confidence intervals for the same percentiles, as predicted by the model. An appropriate model is expected to have all observed percentiles within the simulated confidence intervals



472 A LONG-ACTING NANOFORMULATED TENOFOVIR PRODRUG

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Background: Despite the success of existing antiretroviral therapy (ART) in controlling human immunodeficiency virus type 1 (HIV-1) infection, treatment requires life-long adherence to medicines. ART compliance can be compromised by frequency of dosing, and long acting formulations could potentially improve patient adherence. However, the hydrophilic nature of nucleoside reverse transcriptase inhibitors (NRTI) limits their transformation into long acting formulations. To this end, tenofovir (TFV), a NRTI, was modified into two different lipophilic prodrugs (M1TFV and M2TFV) to extend the apparent drug half-life, improve potency and facilitate access to viral replication sites.

Methods: TFV was modified and formulated into long acting lipid nanocrystals by high-pressure homogenization. The created TFV prodrugs were purified by silica column chromatography and characterized by NMR and FTIR. Nanoparticles were produced by high-pressure homogenization (NM1TFV, NM2TFV). Human monocyte derived macrophages (MDM) and CEM-ss T-cells were used as a biological platform to measure drug uptake and retention. Drug levels were quantitated in cell lysates by UPLC-TUV. After MDM treatment with 100 µM NM1TFV cells were challenged with HIV-ADA at a MOI of 0.1 at five day intervals for one month. Culture fluids were assayed for reverse transcriptase activity and cell-based HIV-p24 antigens recorded by immunohistochemistry. To assess the pharmacokinetic (PK) profile of these TFV prodrug formulations, male Sprague Dawley rats were injected with 75 mg/kg TFV equivalents of NM1TFV, NM2TFV, or TAF. Plasma, blood and peripheral blood mononuclear cells were collected weekly after injection. At the end of the four-week study, organs and tissues were collected for analysis of prodrug, parent drug, and triphosphate levels.

Results: Prodrug modifications enhanced drug uptake compared to tenofovir alefenimde fumarate (TAF) in both MDM and CEM-ss T-cells. M1TFV and M2TFV nanoparticles showed sustained prodrug levels in MDM for 30 and 15 days respectively; whereas TAF was eliminated within a day. In cellular efficacy studies, single treatment of ND1TFV restricted viral replication for 30 days. Analysis of the preliminary rat PK study is currently ongoing.

Conclusion: Long acting TFV formulations were developed and preliminary studies showed enhanced cellular uptake and sustained anti-HIV activity in vitro single dosing when compared against TAF. These results are promising for development of a long-acting TFV for HIV treatment and prevention.

473LB SAFETY AND PK STUDY OF VM-1500A-LAI, A NOVEL LONG-ACTING INJECTABLE THERAPY FOR HIV

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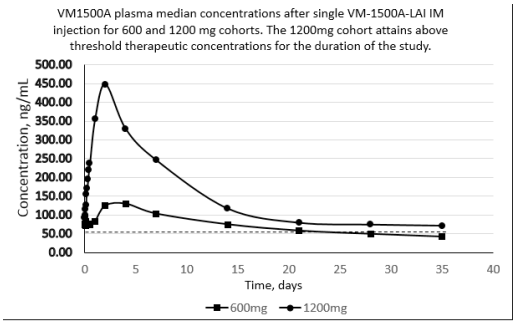
Background: VM1500A is a novel, potent NNRTI with unique clinical PK profile and broad-spectrum activity across HIV-1 variants. An oral dosage form of elsulfavirine, a pro-drug of VM1500A, has been approved in 2017 in Russia for treatment of HIV-infected patients in combination with standard antiretroviral therapy, under the brand name Elpida®. A long-acting injectable (LAI) form of VM1500A has been developed to expand the dosing options of VM1500A.

Methods: This Phase 1 trial is an ongoing open-label, single-center study to evaluate safety, tolerability and pharmacokinetics of single and multiple ascending intramuscular (IM) doses of the LAI nano-formulation of VM-1500A (VM1500A-LAI) in HIV-uninfected volunteers.

Results: 30 HIV-uninfected volunteers were enrolled and received single ascending doses (SAD) of VM-1500A of 150, 300, 600, and 1200 mg, after a 2-week dosing of 20 mg Elpida® capsules qd. The subjects were evaluated for 35 days post-injection and during that period provided serial blood samples for PK assessments. In the SAD cohorts, the main PK parameter was the sustained median plasma concentration of VM1500A above the target trough level (associated with efficacy of daily oral dose of 20 mg of Elpida® during 96 weeks treatment in HIV-infected patients) C_{trough} of 61 ng/ml. Upon completion of the 1200 mg, enrollment of subjects to receive multiple IM injections (once per month) was recommended by the SRC and is currently ongoing. In the SAD part of the study, a total of 21 male (5 Asians, 16 Caucasians) volunteers with a mean age of 26 y.o. and mean BMI of 23.9 kg/m_2 were enrolled. There were no significant baseline differences between the groups. The observed PK profile of IM VM-1500A-LAI is consistent with sustained delivery. Median (range) plasma concentrations of VM1500A at 35 days post-injection were 71 (52, 190), 42 (29, 44), 25 (17, 28) and 19 (12, 19) ng/ml for the 1200, 600, 300 and 150 mg dose levels, respectively. All doses were well tolerated and no-dose limiting toxicities were reported. Injection site related pain was notable at the highest dose tested. There have been no death or serious adverse event. Most AEs were mild (Grade 1) and resolved.

Conclusion: VM-1500A-LAI IM qm of 600 mg achieved median plasma C_{trough} above target trough level for at least 3 weeks. VM-1500A-LAI IM qm of 1200 mg achieved median plasma C_{trough} above target for 35 days and above. VM1500A LAI was tolerated and had an acceptable PK profile in healthy volunteers following single IM dosing in a range of 150mg to 1200mg.

VM1500A plasma median concentrations after single VM-1500A-LAI IM injection for 600 and 1200 mg cohorts. The 1200mg cohort attains above threshold therapeutic concentrations for the duration of the study.



474 CD4/CD8 RECOVERY AND FIRST-LINE ART: GREATEST IMPROVEMENT WITH INTEGRASE INHIBITORS

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Background: A low CD4/CD8 ratio during ART identifies subjects with heightened immunosenescence and increased risk of mortality. We aimed to assess the effects of the INSTI, PI or NNRTI-based first-line ART on long-term CD4/CD8 ratio recovery in a large prospective cohort.

Methods: Prospective cohort study in 13,026 HIV-infected individuals registered in the Spanish HIV Research Network (CoRIS) cohort. We included subjects who started triple ART and achieved HIV RNA suppression at 48 weeks. We used multilevel mixed models with linear splines to compare longitudinal changes in the CD4/CD8 ratio and Cox proportional-hazard models to compare the times to CD4/CD8 normalization by treatment groups (NNRTI, PI, INSTI) at 0.4, 1 and 1.5 cut-offs. Analyses were adjusted for sex, country of origin, mode of transmission, calendar year, educational level, baseline HIV RNA, presence of AIDS, pre-ART nadir CD4, acme CD8 count and backbone NRTI and censored at virologic failure.

Results: A total of 6,804 individuals contributing to 37,149 persons/years and 37,680 observations were analyzed. Median follow-up was 49 months (IQR 22-89). As compared to NNRTI and PI treatment, INSTI treatment was associated with greater CD4/CD8 gain. Differences were observed since the first year of therapy and were driven by changes in both CD4 and CD8 counts. At year 4, the adjusted mean CD4 count for INSTI, NNRTI and PI was 904, 718 and 696 cells/uL ($p<0.0001$) and the adjusted mean CD8 count was 832, 875 and 996 cells/ul, respectively ($p<0.0001$). Within INSTI, the greatest CD4/CD8 ratio gain was observed with elvitegravir, followed by dolutegravir, and was largely due to higher CD8 count declines. Compared to INSTI, the NNRTI and PI groups showed lower rates of CD4/CD8 ratio normalization ≥1 (NNRTI, aHR 0.80 [0.72–0.89]; PI, aHR 0.79 [0.69–0.89] and ≥1.5 (NNRTI, aHR 0.79 [0.65–0.95]; PI, aHR 0.78 [0.64–0.97]. Subanalyses adjusted for backbone NRTIs or allowing observations after virologic failure yielded similar results.

Conclusion: INSTI-based first line ART is associated with a greater CD4/CD8 ratio gain compared to NNRTI and PI-based ART. This study in real life indicates that ART initiation with INSTI improves immune recovery with respect to other ART classes, which could affect long-term mortality.

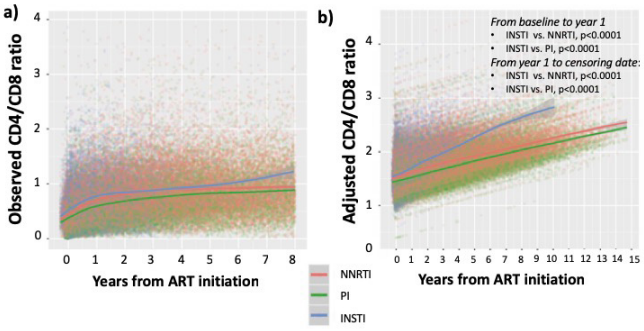


Figure 1. a) Observed CD4/CD8 ratio trajectories. b) Predicted CD4/CD8 ratio trajectories in linear mixed models.

475 CLINICAL AND LABORATORY OUTCOMES 24 WEEKS AFTER STARTING DTG VERSUS EFV IN ACUTE HIV

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Background: This study compared clinical and laboratory parameters before and after initiating Efavirenz(EFV)- and Dolutegravir(DTG)-based antiretroviral therapy (ART), the prior and current 1st line ART, during acute HIV infection (AHI).

Methods: Individuals with AHI (Fiebig I-V) enrolled in the RV254 cohort in Thailand initiated ART within days (median=0; IQR 0-1) after diagnosis (EFV+2 NRTI: 2009-Jan2017; DTG+2 NRTI: Feb2017 onwards). Plasma HIV-1 RNA, blood CD4 and CD8 T-cell counts, and mood parameters, measured by the 9-item Patient Health Questionnaire (PHQ-9, score 0-27) for depression symptoms and the Distress Thermometer (DT) for anxiety/stress (score 0-10) were measured before and 24 weeks after ART. Participants who received other ART regimens were excluded.

Results: From 2009-2019, 415 participants (98% male, median age 26 years) initiated ART at AHI (EFV-based=325; DTG-based=90). By week 24, 15 (5%) EFV users reduced their daily EFV dose from 600mg to 300mg due to side effects and super-therapeutic plasma EFV levels. Another 23 (7%) discontinued EFV due to EFV-associated adverse events (AEs) and/or resistance; 2 (2%) DTG users discontinued DTG, both for acute hepatitis C with liver enzyme elevations ($p=0.130$). At baseline, both groups (EFV=302; DTG=88) were similar in age, sex composition, CD4/CD8 ratio, plasma HIV-1 RNA, PHQ-9 and DT scores ($p>0.05$); 167 (43%) had moderate depression symptoms (PHQ-9>9). The DTG group had lower CD4 and CD8 T-cells and higher rates of Fiebig III and CRF01 AE/B recombinant subtype than the EFV group ($p<0.05$). HIV suppression (<50 copies/ml) rates were 98% and 93% in the DTG and EFV group respectively ($p=0.124$). Comparing the change of parameters (i.e. difference between week 24 and baseline) by ART regimen showed greater gain in CD4 and CD8 T-cells in DTG users (Table). DTG-based ART remained independently associated with greater CD4 recovery (mean diff +78.0, 95%CI [40.2 to 115.8], $p<0.001$) in multivariable analysis. At week 24, the rate of PHQ-9>9 in the DTG and EFV groups were 15% vs 13% respectively ($p=0.644$). Both groups had lower PHQ-9 and DT scores than at baseline ($p<0.001$) but both scores were similar across the groups ($p>0.05$).

Conclusion: Compared to EFV, initiating DTG-based ART at AHI was associated with a greater gain in CD4 T-cells and a higher absolute CD4 count at week 24. There were no DTG related AEs leading to discontinuation. Self-reported depression symptoms observed at AHI improved with ART regardless of the regimen.

Table. Interval Change of Various Parameters by ART Regimen

	EFV-based	DTG-based	p-value
Δ CD4	+205 (105 to 314)	+286 (174 to 435)	<0.001
Δ CD8	+19 (-333 to 241)	+169 (-42 to 331)	<0.001
Δ CD4/CD8	+0.29 (0.03 to 0.61)	+0.19 (0 to 0.46)	0.106
Δ PHQ-9	-4 (-1 to -8)	-3 (0 to -7)	0.122
Δ Affective	-3 (0 to -5)	-2 (0 to -5)	0.252
Δ Somatic	-1 (0 to -3)	-1 (0 to -2)	0.086
Δ Distress Thermometer Score	-1.8 (0 to -4)	-1.4 (0 to -3.4)	0.392

Median (IQR) and, n (%) are shown accordingly
Δparameter = W24 parameter – W0 parameter

476 RAPID ART IN BLOOD DONORS WITH ACUTE AND RECENT HIV CLADE C INFECTION IN SOUTH AFRICA

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Background: Blood donations in South Africa are tested in parallel for HIV antibody (Ab) and RNA using individual-donation nucleic acid testing (ID-NAT), allowing annual detection of ~60 Acute (RNA+/ Ab-; Fiebig stages I-III) and >400 Recent (RNA+/Ab+; Fiebig stages IV to VI) HIV infections. We hypothesized that initiation of antiretroviral therapy (ART) in earlier Fiebig stages would correlate with smaller HIV reservoir size.

Methods: A prospective cohort study enrolled Acute and Recent HIV clade C infected blood donors. HIV Ab (Abbott Prism) and RNA (Grifols ID-NAT) were measured on samples taken at index donation and enrolment. Recency (< 195 days) was detected by limiting-antigen avidity assay (Sedia). Enrolled donors were referred rapidly for ART with RAL/TDF/FTC X 6 months followed by EFV/TDF/FTC. We measured plasma RNA using the Aptima HIV-1 Quant Assay (Hologic) with 5 replicates. Cell-associated (CA) HIV RNA and total DNA were measured by qRT-PCR and real-time nested PCR, respectively. After median treatment duration of 20 months, we compared HIV reservoir size between

treatment initiated in Fiebig I-III vs. IV-VI using repeated measures analysis adjusting for baseline RNA or DNA.

Results: From 2015 to 2017 we enrolled 49 donors with Acute and 34 with Recent HIV. Cohort enrolment/ART initiation occurred at medians of 13/15 days after index donations. Longitudinal HIV reservoir data were available for 18 Fiebig I-III and 42 Fiebig IV-VI subjects. Median plasma RNA was 5.4 log_{10} copies/mL at enrolment, declined to 0.23 log_{10} copies/mL, did not differ by Fiebig stage (p=0.56) but was 0.31 log_{10} lower in females (p=0.02). Median CA RNA was 3.7 log_{10} copies/10^6 PBMC at enrolment, falling to 2.2 log_{10} copies/10^6 PBMC, and was 0.64 log_{10} higher in Fiebig IV-VI than Fiebig I-III treated-subjects (p=0.002). Median CA total DNA was 1.8 log_{10} copies/10^6 PBMC at enrolment, falling to 0.85 log_{10} copies/10^6 PBMC with no difference by Fiebig stage (p=0.95).

Conclusion: Among clade C HIV-infected donors initiated on ART within 195 days of infection, we observed lower CA HIV RNA in Fiebig I-III vs. Fiebig IV-VI groups, demonstrating a small impact of earlier treatment on long-term reservoir expression, and lower post-ART plasma HIV-1 (single copy assay) in women vs. men. This study demonstrated that a partnership between a national blood service and a treatment NGO can establish early treatment cohorts for subsequent entry into HIV Cure research initiatives.

477 144-WEEK EFFICACY AND SAFETY OF B/F/TAF IN TREATMENT-NAIVE ADULTS ≥50 YRS

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Background: As people living with HIV age, identifying effective and safe regimens for older individuals is of heightened importance. The single-tablet regimen bictegravir, emtricitabine, tenofovir alafenamide (B/F/TAF) may benefit older adults due to its favorable adverse event (AE) profile and few drug interactions.

Methods: We conducted two randomized, double blind, phase 3 studies of B/F/TAF in treatment-naïve adults, Study 1489: B/F/TAF vs dolutegravir, abacavir, and lamivudine (DTG/ABC/3TC) and Study 1490: B/F/TAF vs DTG + F/TAF. A pooled analysis assessed efficacy as the proportion with HIV-1 RNA <50 c/mL (FDA Snapshot) and safety at Week (W) 144 in adults ≥50 and <50 yrs at baseline. Proteinuria and bone mineral density (BMD) were measured in Study 1489 only.

Results: 1274 were randomized and treated (634 B/F/TAF, 315 DTG/ABC/3TC, 325 DTG + F/TAF); 196 were age ≥50 yrs (96 B/F/TAF, 41 DTG/ABC/3TC, 59 DTG + F/TAF) of whom 17% were women, 27% Black, and 15% Latino/Hispanic. Efficacy was high for all treatments (Table). The most common AEs in adults ≥50 were nasopharyngitis (20%, 22%, 25%), diarrhea (19%, 22%, 8%), and upper respiratory tract infection (16%, 17%, 12%). The most common AEs in adults <50 were diarrhea (19%, 18%, 18%), headache (17%, 18%, 19%), and nausea (11%, 26%, 15%). Treatment-related AEs occurred in 24%, 37%, and 29% of participants ≥50; the frequency was 26%, 43% and 29% in participants <50 yrs (p<0.001 for B/F/TAF vs DTG/ABC/3TC). Most treatment related AEs were grade 1. AEs leading to study drug discontinuation for participants ≥50 occurred in 2% on B/F/TAF, 5% on DTG/ABC/3TC and 7% on DTG + F/TAF compared to 1% in each treatment group for participants <50 yrs. For those ≥50 with AEs leading to discontinuation, 1 on B/F/TAF, 1 on DTG/ABC/3TC and 3 on DTG+F/TAF were treatment-related. In Study 1489, mean % changes in hip and spine BMD, proteinuria, and renal biomarkers were similar between B/F/TAF to DTG/ABC/3TC. There were small changes from baseline in all treatment groups in fasting lipids. Median weight increased from baseline at W144 with no significant difference between treatment groups (Table).

Conclusion: Through three years of treatment, B/F/TAF was highly effective, safe and well tolerated in adults ≥50 yrs with no clinically significant impact on bone or renal safety, fasting lipids or weight. B/F/TAF provides a safe and effective treatment option for older adults with a low potential for drug-drug interactions.

Table. Efficacy and safety for adults age ≥50 and <50 years in Studies 1489 and 1490 at Week 144

	Age ≥50 years			Age <50 years		
	B/F/TAF (n=96)	DTG/ABC/3TC (n=41)	DTG + F/TAF (n=59)	B/F/TAF (n=538)	DTG/ABC/3TC (n=274)	DTG + F/TAF (n=266)
HIV-1 RNA < 50 c/mL, % (Snapshot)	81	83	88	82	84	83
HIV-1 RNA < 50 c/mL, % (Per Protocol)	100	100	100	100	99	99
Any AE, %	93	93	90	93	97	93
Any grade 3 or 4 AEs, %	25	20	15	15	15	13
AEs related to study drug, %	24	37	29	26	43	29
AEs leading to study drug discontinuation, %	2	5	7	1	1	1
Deaths, n	5	0	2	1	1	2
eGFR, median change, mL/min (Q1, Q3)	-9 (-19, -1)	-11 (-20, 2)	-9 (-20, -2)	-9 (-20, 0)	-12 (-24, -1)	-12 (-22, 1)
Median weight change, kg	4.3	4.7	3.4	4.2	3.3	5.3

478 CD4:CD8 NORMALIZATION BY INTEGRASE INHIBITORS AMONG TREATMENT-NAIVE PATIENTS

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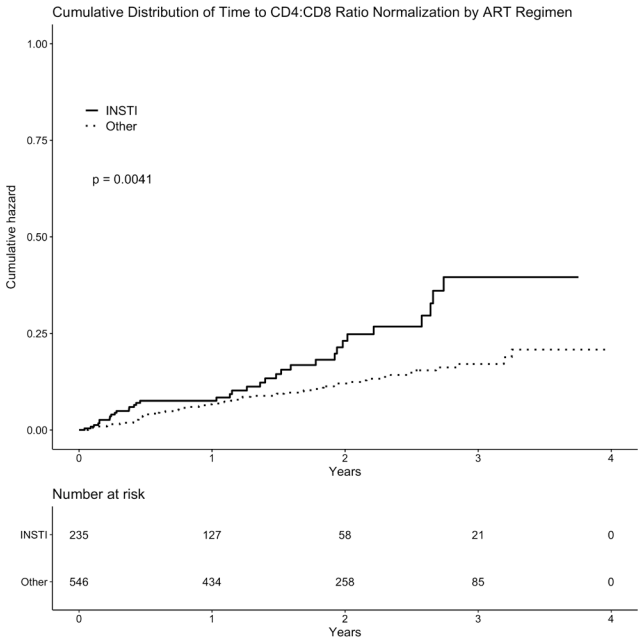
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Background: HIV infection leads to selective depletion of CD4+ T cells and an increase in CD8+ T cells resulting in an inverted CD4:CD8 ratio which often persists despite antiretroviral therapy (ART). A low CD4:CD8 ratio is associated with AIDS and non-AIDS related morbidities. A positive association between CD4:CD8 ratio normalization and initiation of raltegravir containing regimens has been observed. We hypothesize that Integrase Strand Transfer Inhibitor (INSTI)-containing regimens are associated with shorter time to CD4:CD8 normalization relative to other ART regimens among treatment naïve patients.

Methods: Retrospective analysis of the Canadian Observational Cohort (CANOC), a collaboration of HIV-infected individuals initiating combination ART between 2000 and 2014. Participants starting on 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)/1 INSTI or a non-INSTI regimen on or after January 1, 2011 with a pre-treatment CD4:CD8 ratio <1.2 and ≥2 follow-up ratios within 6 months of treatment initiation were included. Kaplan Meier estimates were used to describe time to CD4:CD8 ratio normalization (CD4:CD8 ratio ≥1.2 on 2 consecutive measures ≥ 30 days apart). Multivariable proportional hazards models were used to estimate the association between ART class and time to CD4:CD8 normalization.

Results: 781 participants were included and followed for a median [IQR] 1.9 [1.0, 2.7] years. Median [IQR] age was 38 [31, 47] and 699 (90%) were men. 235 participants starting on INSTI-containing regimens were more likely to have a higher median [IQR] pre-treatment CD4 count (370 [225, 480] vs. 330 [210, 440], p=0.04) compared to those starting non-INSTI regimens. 35 (15%) participants on INSTI-containing regimens normalized their CD4:CD8 ratio with a 0.21 (95%CI 0.13, 0.28) probability of achieving normalization within 2 years. 63 (12%) of those on non-INSTI regimens normalized with a 0.11 (95%CI 0.08, 0.14) probability of achieving so within 2 years (p<0.01). After adjusting for pre-treatment CD4, viral load, risk factor, hepatitis B and C, those starting INSTI-containing regimens compared to other ART were more likely to achieve normalization (HR=1.75, 95%CI 1.10, 2.77).

Conclusion: Our results provide further evidence that initiation of INSTI-containing regimens results in a higher rate of normalization of the CD4:CD8 ratio in ART naïve subjects. Whether this is associated with lower rates of comorbidity or improved survival requires further study.



479 PERSISTENT POOR CLINICAL OUTCOMES FOR AIDS PRESENTATION IN ITALY OVER THE LAST DECADE

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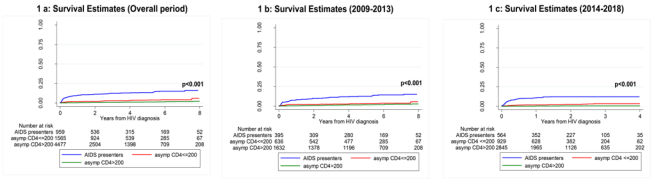
Background: The aim of this study was to evaluate survival and treatment outcomes of AIDS presenters compared to the remaining portion of antiretroviral therapy (ART)-naive patients (pts) in a large Italian cohort.

Methods: All consecutive ART-naïve HIV+ pts, enrolled in Icona Foundation Study Cohort from January 2009 to December 2018, with HIV diagnosis within 3 months from enrolment, were included and divided into 3 groups: pts with an AIDS diagnosis at/within 3 months from HIV diagnosis [(1):AIDS presenters], asymptomatic pts with CD4 count at the enrolment ≤200 cell/mL [(2):asympt CD4≤200] or >200 cell/mL [(3):asympt CD4>200]. Survival probability was estimated by Kaplan Meier curves in both the overall period and separately, analyzing two 5-year periods (2009-2013; 2014-2018). Independent risk of survival and, in the subgroup of patients starting ART, virological failure (VF) (2 consecutive HIV-RNA >200 cp/ml after 6 months of ART) and treatment discontinuation (TD) for drug toxicity were identified by fitting a Cox regression model.

Results: Overall, 7001 pts included: 959 AIDS presenters, 1,565 asympt CD4≤200 and 4,477 asympt CD4>200. ART was started in 6440 pts of whom 95%, 97% and 90% in group 1, 2 and 3 respectively. From 2009 to 2013, pts with advanced HIV presentation were significantly more likely to start PI/b-based regimen compared to asympt CD4>200 (63% and 68% vs 41%,p=0.001) whereas in the last five years INSTIs were the main third-drug started in all groups (60% for both group 1 and 2 and 52% for group3). At survival analysis, AIDS presenters showed the lowest probability of survival among the treatment groups [Fig1a]. 4-year survival estimates remained substantially stable over the two time periods [Fig1b,1c]. After adjusting for the main confounders, both the groups with advanced HIV presentation were associated to a higher risk of death compared to asympt CD4>200. This data was confirmed also restricting the analysis to those who started ART [Fig1d]. By multivariable analysis, AIDS presenters were associated with a greater risk of VF and of TD for toxicity compared to asympt CD4>200 [Fig1d].

Conclusion: Over the last decade, pts presenting with advanced HIV disease, particularly AIDS presenters, remained at consistently higher risk of death and poor response to ART. Public health strategies for emerging unknown infections and early treatment access are urgent to constrain the mortality gap of this vulnerable population.

Figure 1: Estimated probabilities of survival in the overall period (a) and in the two consecutive time periods (2009-2013; 2014-2018) (b,c) and relative hazard ratios of death, VF and TD for toxicity from fitting Cox regression models according to ART history (d).



Survival Estimates (95% CI)	AIDS presenters	Asymp CD4 ≤ 200	Asymp CD4>200
1-year	90.3 % (88.1-92.1)	98.0 % (97.2-98.6)	99.7 % (99.4-99.8)
2-year	88.7 % (86.3-90.6)	97.8 % (96.9-98.5)	99.4 % (99.1-99.6)
4-year	86.6 % (83.8-88.9)	96.4% (94.9-97.4)	98.8 % (98.2-99.1)

Survival Estimates (95% CI)	AIDS presenters	Asymp CD4 ≤ 200	Asymp CD4>200
1-year	91.8 % (88.6-94.2)	97.9 % (96.4-98.8)	99.5 % (99.0-99.8)
2-year	90.1 % (86.6-92.7)	97.9 % (96.4-98.8)	99.1 % (98.5-99.5)
4-year	88.0 % (84.2-90.9)	97.1 % (95.4-98.2)	98.4 % (97.6-98.9)

Survival Estimates (95% CI)	AIDS presenters	Asymp CD4 ≤ 200	Asymp CD4>200
1-year	89.2 % (86.1-91.6)	98.1 % (96.6-98.9)	99.8 % (99.5-99.9)
2-year	87.8 % (84.4-89.4)	97.7 % (96.3-98.6)	99.7% (99.2-99.8)
4-year	87.8 % (84.4-89.4)	96.7% (94.7-98.0)	99.7 % (99.2-99.8)

1d

	aRH* (95% CI) of VF^ (n=5,204)	p	aRH* (95% CI) of TD for toxicity (n=6,440)	p	aRH* (95% CI) of death (n=7,001)	p	aRH* (95% CI) of death# (n=6,440)	p
Asymptomatic with CD4 count >200 cells/mm³	1.00		1.00		1.00			
Asymptomatic with CD4 count <200 cells/mm³	0.96 (0.66-1.40)	0.821	1.10 (0.93, 1.30)	0.261	3.04 (1.88, 4.91)	<0.001	1.91 (1.16-3.14)	0.011
AIDS presenters	1.52 (1.03-2.26)	0.037	1.39 (1.14, 1.68)	0.001	11.79 (7.69, 18.09)	<0.001	7.48 (4.78-11.71)	<0.001

* Adjusted for: age, gender, mode of HIV transmission, nationality, days between HIV diagnosis and enrolment, days from HIV diagnosis and ART initiation (only in the model restricted to patients who started ART), n. of comorbidities, educational level, CD4 count and VL at baseline, HCV and HBV co-infection, NRTI backbone, third ARV drug class, calendar year of HIV diagnosis.
^ Virological failure (VF) definition: 2 consecutive HIV-RNA >200 copies/mL after 6 months of ART.
# Sensitivity analysis including only patients who started ART

480 EMULATION OF AN RCT OF DOLUTEGRAVIR VS BOOSTED-DARUNAVIR IN ADVANCED ART NAIVE

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Background: Second generation INSTIs currently represent the most highly recommended option for first-line ART but superiority to boosted-PI regimens in people with advanced HIV disease (CD4 count <200 cells/mm_3 or AIDS), generally underrepresented or excluded from RCTs, has not been demonstrated.

Methods: We included ART-naïve patients with CD4 count <200 cells/mm_3 or AIDS diagnosis in the Icona Foundation Cohort between 2014-2018, who started a dolutegravir [DTG] or boosted-darunavir [DRV/b (ritonavir or cobicistat)] based ART. We estimated the effect of the difference in risk of a composite endpoint (death, AIDS, serious non-AIDS events - SNAE - viral failure >200 copies/mL, anchor drug discontinuation not followed by a restart of a drug in the same class) between the two strategies using a marginal structural model. We accounted for differences in prognostic factors measured at time of ART initiation. We also accounted for differences in censoring by these same prognostic factors, and time-varying CD4, HIV-RNA and ALT.

Results: Characteristics of the 685 ART-naïve patients were (DTG=416; DRV/b=269; 224 DRV/r and 45 DRV/cobi): male 87%; heterosexual contacts 50%, MSM 37%; born outside Italy 48%; AIDS presenting 36%; median CD4 count 78 cell/mm_3 (IQR 30-140); median HIV-RNA 5.25 log_{10} copies/mL (IQR 4.64, 5.73). All these variables were comparable between the two groups, except for higher proportion of migrant in DTG (51% vs 43%; p <0.001) and higher HIV-RNA values in DRV/b (5.35 vs 5.18 log_{10}/mL; p=0.019). NRTI backbone was TDF/FTC in 58% (80% in DRV/b and 44% in DTG), TAF/FTC in 11% (10% in DRV/b and 12% in DTG), and ABC/3TC in 30% (10% in DRV/b and 44% in DTG) (p <0.001). 116 patients receiving DTG and 145 receiving DRV/b experienced the composite endpoint. The 1-year weighted probability of the composite endpoint was 37% for DRV/b and 21% for DTG (Figure 1a). Patients who initiated DTG were at lower risk of experiencing the composite endpoint compared to those who started DRV/b [aHR 0.50 (95%CI 0.32, 0.79)] (Figure 1b). Calendar year of starting was a key factor but results were consistent across periods of ART initiation.

Conclusion: Under the assumptions of no unmeasured confounding and correct model specification, our analysis suggests that a RCT conducted in the

target population of ART-naïve patients with CD4 count<200 or AIDS is likely to show a notable reduction in risk of treatment failure in people initiated with dolutegravir vs. boosted-darunavir based therapies.

Figure 1a. Kaplan-Meier curves of reaching treatment failure combined endpoint by anchor drug (DRV/b, by ritonavir or cobicistat, and DTG); a) unweighted; b) weighted

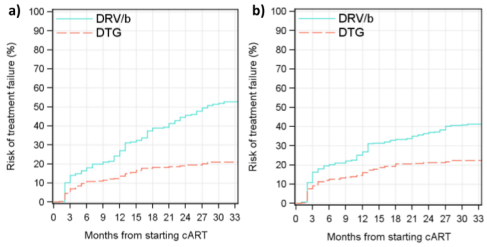


Figure 1b. HR ratio of the estimated causal effect from fitting a weighted Cox regression model

	Unadjusted and adjusted relative hazards of treatment failure[&]			
	Unadjusted RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
All years				
DRV/b	1.00		1.00	
DTG	0.36 (0.27, 0.48)	<.001	0.50 (0.32, 0.79)	0.003
2014-2015				
DRV/b	1.00		1.00	
DTG	0.19 (0.09, 0.40)	<.001	0.34 (0.12, 0.97)	0.043
2016-2018				
DRV/b	1.00		1.00	
DTG	0.49 (0.33, 0.74)	<.001	0.62 (0.37, 1.03)	0.063

*adjusted for age, gender, mode of HIV transmission, nationality, calendar year of starting ART, AIDS/SNAE at baseline, time from HIV diagnosis, NRTI used, and current ALT, CD4 and HIV-RNA values.
[&]newly developed AIDS and SNAE events, virologic failure >200 copies/mL, stop of DRV/b or DTG without restarting a drug within the same class of anchor, death.

481 FLOW CYTOMETRIC SCREENING OF HLA-B17 IN HIV+ PATIENTS UNDERGOING ABACAVIR THERAPY

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Background: The Abacavir Hypersensitivity Syndrome (AHS) is a life-threatening side effect that can occur in HLA-B*5701+ HIV+ patients treated with Abacavir. Every HIV+ patient eligible for Abacavir therapy must be therefore screened for the presence of the HLA-B*5701 allele and treated only if negative. The B*5701 allele is a member of the HLA-B17 family. HLA-B *5701 typing is mostly based on molecular methods, that are expensive and require a median of 21 days for processing. In this study we have developed a rapid dual-color Flow Cytometric (FC) assay, including anti-B17monoclonal antibody that provides a cheap and sensitive screening for putative HLA-B*5701+ patients

Methods: 21 HIV+ patients already SSO-typed for HLA-B*5701 served as positive (6) or negative (15) controls, respectively. Other 437 HIV+ patients were prospectively evaluated for HLA-B17 by FC and their outcome during Abacavir treatment was monitored.Briefly, 50 mL of EDTA blood were stained with 10 mL of unconjugated IgM monoclonal anti-B17 antigen (OneLambda) in a stain-lyse-and-wash procedure. A secondary PE- anti-mouse IgM was used for indirect immunofluorescence, with anti-CD3 FITC counterstaining. Isotype cold IgM and secondary PE conjugate were used as negative controls. The staining intensity of anti-B17 PE expression on T cells was considered to calculate the reaction cutoff, which was used to discriminate positive and negative cases

Results: The agreement between SSO typing and FC assay in the controls was 6/6 for double-positives; one false-positive FC case was due to the cross-reacting antigen B*5702; whereas 14/14 cases were double negatives. Of the prospective 437 cases, 43 (10%) resulted positive for anti-B17, as expected. In 28/43 cases a confirmatory molecular test for HLA-B*5701 allele was performed, which disclosed the B*5701 in 11 patients. In the other 17 cases different alleles of the B17 family were detected, that did not prevent Abacavir therapy. None of the 394 FC B17-negative patients developed AHS during Abacavir administration.

Conclusion: In conclusion, the rapid FC assay to evaluate the HLA-B17 phenotype in HIV+ subjects eligible to Abacavir therapy proved reliable to safely screen out HLAB*5701-negative subjects, that represent the majority of cases. Its prospective use allows significant saving of time and money, since it can restrict the confirmative molecular HLA B*5701 typing to the small group of FC positive individuals.

482 LONG-ACTING CABOTEGRAVIR + RILPIVIRINE FOR HIV TREATMENT: FLAIR WEEK 96 RESULTS

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Background: Chronic daily oral ART can be lifesaving but also inconvenient, increasing the risks of non-adherence and treatment failure. To address these issues, long-acting (LA) injectable regimens of the INSTI cabotegravir (CAB) and the NNRTI rilpivirine (RPV) are under evaluation. FLAIR (NCT02938520) is a randomized, Phase 3, open-label, multicenter study investigating whether switching to monthly CAB+RPV LA is non-inferior to daily dolutegravir/abacavir/lamivudine (DTG/ABC/3TC [CAR]) in virologically suppressed adults infected with HIV-1.

Methods: ART-naive participants received induction therapy with oral CAR for 20 weeks. After 16 weeks, participants with HIV-1 RNA <50c/mL were eligible to enter the maintenance phase (MP) and were randomized (1:1) to either switch to LA or continue CAR. Those randomized to the LA arm received an oral lead-in of CAB 30mg + RPV 25mg once daily for 4 weeks before receiving monthly injectable CAB+RPV LA. The primary endpoint was viral load ≥50c/mL at MP Week 48 (W48) by FDA snapshot algorithm (NI margin 6%). Endpoints assessed at MP Week 96 (W96) included viral loads ≥50c/mL and <50c/mL, confirmed virologic failure (CVF; two consecutive viral loads ≥200c/mL), safety, tolerability, and patient satisfaction.

Results: From 629 participants who initiated induction therapy, 566 were randomized to either the LA or CAR arm (283/arm). Median age was 34y (11% ≥50y); 22% were female and 74% were white. At W96, 9 (3.2%) participants in each arm had HIV-1 RNA ≥50c/mL, underscoring the non-inferiority established at W48 (Table). For the LA arm, the rate of CVF was unchanged from W48 at W96 (4 participants [1.4%]); 3 had mutations in the NNRTI + INSTI domains and 1 had no mutations). The CAR arm had 4 CVFs through W96 (vs. 3 through W48); none had mutations. Across both treatment arms, AEs leading to withdrawal were infrequent. Injection site reactions (ISRs) were the most common drug-related AE (86% of participants in the LA arm); their frequency decreased over time. Median ISR duration was 3 days and 99% were Grade 1 or 2. At W96, the LA regimen was associated with a greater treatment satisfaction vs. oral CAR as measured by HIVTSQs.

Conclusion: CAB+RPV LA maintained viral suppression with no further CVFs between W48 and W96 and was non-inferior to oral standard of care ART. Although ISRs were frequently reported with CAB+RPV LA, they seldom led to withdrawal, and overall treatment satisfaction was higher than with ART. These results attest to the durability of CAB+RPV LA.

483 DTG+3TC VS DTG+TDF/FTC (GEMINI 1&2): CONFIRMED VIROLOGIC WITHDRAWALS THROUGH WEEK 96

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Background: In GEMINI-1&2, the dolutegravir (DTG) + lamivudine (3TC) 2-drug regimen (2DR) is non-inferior to the DTG + tenofovir/emtricitabine (TDF/FTC) 3-drug regimen (3DR) in HIV-1 ART-naïve participants at Weeks 48/96. Eleven participants on 2DR and seven on 3DR met protocol-defined Confirmed Virologic Withdrawal (CVW) criteria through Week 96. We present a detailed description of these CVWs.

Methods: Patients were stratified by viral load (VL) ≤/>100,000c/mL and CD4+ ≤/>200cells/mm$_3$. Patients were not eligible if screening HIV-1

genotype showed major RT/PR resistance mutations. CVW was defined as two consecutive VLs meeting virologic non-response (VL ≥200c/mL after Week 24 or <1.0 log decline in VL by Week 12 unless HIV-1 RNA is <200c/mL) or virologic rebound criteria (≥200c/mL after prior suppression to <200c/mL). Monogram Bioscience performed integrase and RT/PR genotypic and phenotypic resistance testing on Day 1 and Virologic Withdrawal timepoint samples. We evaluated CVW patient baseline (BL) VL and CD4 characteristics, adherence, study drug interruption, resistance, and VL progression through the study course.

Results: In GEMINI-1&2, 3 participants screen failed due to M184I/V resistance. Overall, 11 participants on DTG+3TC and 7 on DTG+TDF/FTC met CVW criteria through Week 96. Of these, 5 vs 2 CVWs occurred after Week 48. All CVWs experienced virologic rebound; none had VL blips (VLs between 50-<200c/mL with adjacent values <50c/mL) that preceded CVW. One DTG+3TC participant never suppressed to <50c/ml. Table 1 summarizes key information for CVWs in the DTG+3TC arm. Among the 11 and 7 participants on DTG+3TC vs DTG+TDF/FTC respectively: 9 vs 7 were infected with HIV-1 subtype B; 3 vs 2 had Baseline CD4 <200cells/mm_3; 5 vs 3 had Baseline HIV-1 VLs >100,000c/mL; and HIV-1 VL decreased from CVW time point to the withdrawal (WD) visit ≥2 fold for 7 of 9 vs 4 of 5 cases with WD visit VLs. Resistance data were available for all samples except 2 cases on DTG+TDF/FTC where testing failed with HIV-1 VL below the assay cut-off; no treatment-emergent genotypic or phenotypic resistance in IN or RT was observed in any CVWs.

Conclusion: In GEMINI1&2, there were low and comparable numbers of participants meeting CVW through 96 weeks in the DTG+3TC and DTG+TDF/FTC arms without apparent predisposition by BL VL or CD4; no emergent genotypic/phenotypic resistance to INSTI/NRTIs was observed. These data further support the potency and durability of DTG+3TC.

Table. DTG+3TC arm CVW summary: Baseline (BL) Viral Load and CD4 Values, SVW, CVW, and Withdrawal (WD) Viral Loads, and Non-Virologic Characteristics.

Sub#	BL VL (c/mL)	BL CD4 (cells/mm^3)	CVW Visit	SVW VL	CVW VL	WD VL	Non-adherence/Treatment interruption
1	368439	19	W24	212	376	362	Adherent
2	341818	317	W108	396	726	280	Non-adherence
3	124492	212	W16	6648	56435	95	Unknown
4	112812	74	W72	61076	87794	671	Non-adherence
5	101671	347	WK60	703	85556	ND	Treatment interruption
6	96277	213	W24	451	9602	67	Treatment interruption
7	63817	50	W72	422	2154	115	Non-adherence
8	50263	284	W24	348	206	96	Adherent
9	37701	414	W48	43908	38457	ND	Unknown; had concurrent SAE of psychosis
10	17232	529	W24	461	251	59	Unknown
11	7654	567	W60	3972	3131	1513	Non-adherence

484 HIV-1 REPLICATION AT <50 C/ML TO 148 WEEKS FOR SWORD-1/SWORD-2 STUDIES WITH DTG+RPV

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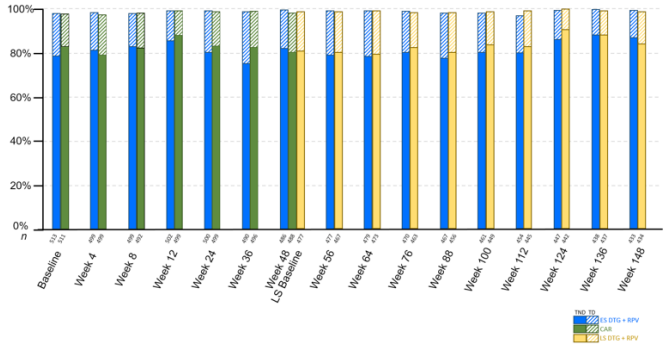
Background: The SWORD studies demonstrated non-inferiority on switch to dolutegravir (DTG) + rilpivirine (RPV) vs continuing a 3- to 4-drug Current Antiretroviral Regimen (CAR) for 48 weeks, and also showed long term suppression to HIV-1 RNA <50 c/mL. The clinical significance of low-level viral load (VL) <50c/mL remains unclear. We present here low level qualitative VL data from the Phase 3 SWORD studies up to Week 148.

Methods: Adults with VL<50 c/mL for ≥6 months were randomized to switch to DTG+RPV (Early Switch (ES) group) for 148 weeks or continue CAR. CAR participants <50c/mL at Week 48 switched at Week 52 (Late Switch (LS) group) to receive DTG+RPV for 96 weeks. The Abbott Realtime assay measures VL quantitatively from 40c/mL to 10,000,000c/mL; when VL<40c/mL it returns qualitative Target Detected (TD) or Target Not Detected (TND) results. We explored participants' TND and TD status over time, overall and by Baseline TD or TND status.

Results: 1024 participants were randomized and exposed (ES DTG+RPV 513; CAR 511) across both studies; 477 CAR participants switched to DTG+RPV at Week 52. The proportions of participants with TND at all visit weeks were similar and did not decline over time (Figure); TND ranges across visits were 75%-88% in the ES group, 79%-90% in the LS group and 79%-88% in the CAR group. Participant proportions with BL TND and TND at all visits through 48 Weeks exposure in comparator ES DTG+RPV, LS DTG+RPV, and CAR groups were respectively 47% (180/383), 52% (189/367), and 53% (215/408), and for participants with BL TD the proportions with TND at all visits were respectively 19% (18/94), 33% (25/76), and 19% (13/70). Among participants in the ES DTG+RPV group with pre-switch TND vs TD, the proportions with TND at all visits through Week 148 were respectively 23% (79/341) vs 10% (8/84), and among LS DTG+RPV group the proportions with TND through Week 148 (96 weeks of DTG+RPV) were 40% (142/352) vs 20% (15/76). In the ES DTG+RPV group, 20% of the 433 participants who reached Week 148 had TND at all visits, and in the LS DTG+RPV group, 36% of the 434 participants who reached Week 148 (with 96 weeks of DTG+RPV exposure) had TND at all visits.

Conclusion: The frequency of participants with TND status under DTG+RPV remained high across all visits with no decline observed through 148 weeks. This is supportive evidence that long term treatment with DTG+RPV is efficacious in virologic suppression to <50c/mL.

Figure: Progression of TND and TD for DTG+RPV ES, CAR, and DTG+RPV LS group through Week 148



485 LONG-TERM DTG-3TC SWITCH EFFICACY IN PATIENTS WITH ARCHIVED 3TC RESISTANCE

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Background: ART-PRO pilot trial showed that at 48 weeks DTG+3TC was effective in maintaining virologic control despite history of lamivudine resistance and persistence of archived 3TC mutations detected by NGS. Here we present resistance analysis and virologic outcomes after 80 weeks of DTG+3TC treatment.

Methods: Open, single-arm, pilot trial including HIV-1 infected adults, INSTI-naïve, CD4 count >350 cell/µL, VL< 50 copies/mL for 1 year prior to study entry. Participants were excluded if baseline proviral DNA population genotyping detected M184V/I or K65R/E/N. Baseline proviral DNA NGS genotype was retrospectively performed to detect resistance minority variants. All participants were switched to DTG+3TC.

Results: 41 participants (78% male) switched to DTG+3TC: 21 participants had M184V/I or K65R/E/N in historical plasma genotyping and 20 had not. At baseline: median CD4 661, ART duration 18 years, duration of suppressed plasma HIV RNA 7.7 years, number of prior ART regimens 6. Participants with historical 3TC resistance were significantly less likely to receive a regimen including 3TC before the switch (p<0.001). NGS of baseline proviral DNA detected M184V/I at >5%/>20% thresholds in 67%/29% of participants with and 15%/5% of participants without history of 3TC resistance. K65R was detected in proviral DNA by NGS only in participants with historical resistance to 3TC (9.5%/5% at the >5%/>20% cut-off respectively). At week 80, 87.8% of participants (37/41) remained with VL< 50 copies/mL (Table 1). There were no virologic failures through week 80. Of the 21 participants with historical 3TC resistance, 3 prematurely discontinued with suppressed viremia (2 protocol violations, one AE [insomnia, W8]). One participant without historical 3TC resistance declined to participate in the 144w study extension. There were 12 blips, 6 in the group with historical resistance. There were 30 related AE, 4/30 were severe and only 1 led to discontinuation.

Conclusion: In this pilot trial, DTG+3TC was effective maintaining long-term virologic control after 80 weeks of follow up despite history of 3TC resistance

and presence of archived 3TC mutations detected by NGS. 144-week study

Snapshot at W80, Intention to treat-exposed (ITT-e) analysis population

	All participants (n=41)	Historical resistance to 3TC (n=21)	No historical resistance to 3TC (n=20)
HIV-1 RNA ≤50 copies/mL	37 (87.8)	18 (85.7)	19 (95%)
HIV-1 RNA ≥50 copies/mL	0 (0)	0 (0)	0 (0)
- HIV-1 RNA ≥50 copies/mL in W80 window	0 (0)	0 (0)	0 (0)
- Discontinuation Study Drug due to Lack of Efficacy	0 (0)	0 (0)	0 (0)
- Discontinuation Study Drug due to other reasons and last available HIV-1 RNA ≥50 copies/mL	0 (0)	0 (0)	0 (0)
No virologic data at W80	4 (9.7)	3 (14.3)	1* (5)
- Discontinuation Study Drug Due to AE	1 (2.4)	1 (4.8)	0 (0)
- Discontinuation Study Drug due to other reasons and Last available HIV-1 RNA <50 copies/mL	3 (7.3)	2 (9.5)	1 (5)

* 1 patient after week 48 declined to participate in the 144-week study extension

486 EFFECT OF PAST VIROLOGICAL FAILURE ON DOLUTEGRAVIR+LAMIVUDINE AS MAINTENANCE REGIMEN

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Background: Dolutegravir (DTG)+lamivudine (3TC) was shown to be as effective as triple therapy in RCT on patients (pts) switching during virological suppression, but limited data are available about the use of this regimen in pts with previous virological failures (VF), since RCT excluded these pts.

Methods: The analysis included data of HIV+ pts with HIV-RNA<=50 c/ml enrolled in a retrospective multi-cohort study across Italian infectious disease clinics switching for the first time to DTG+3TC from any other regimen (baseline). Primary endpoint was viral rebound (VR, confirmed HIV-RNA >=50 c/mL). Kaplan-Meier curves were used to estimate probabilities of VR according to history of previous VF (single HIV-RNA >=1000 or confirmed HIV-RNA >=50 c/mL). Weighted Cox regression model was fitted to estimate causal HR of VR, after controlling for confounding variables (time of viral suppression and nadir CD4). A further analysis with a different definition [Def 2] of previous VF (only at NRTI or INSTI regimens) and of VR (that included also a single HIV-RNA>=50 c/ml followed by change of therapy) and a sensitivity analysis excluding pts with incomplete history of viral load data (>1 year gap in measurements) were performed.

Results: 966 pts included: 74% males, median age 51 (IQR 44-57), 15% CDC-C stage, nadir CD4 246 (99-372), years of viral suppression 7 (3-12), 80% without previous VF, 12% with one previous VF, 8% with >=2 previous VF. VR was detected in 11 pts over 1555 person-year-follow-up (PYFU): total incidence ratio (IR) was 0.7 x 100 PYFU (95% CI 0.4-1.3), 0.5 x 100 PYFU (0.2-1.1) in pts without previous failures and 1.4 x 100 PYFU (0.6-3.4) in pts with >=1 previous VF, with an estimated 1-year probability of 0.4% (0.1-1.4) and 1.3% (0.3-5.3) respectively (log-rank p=0.071). With Def 2, VR was detected in 18 pts, IR 1.2 x 100 PYFU (0.7-1.9), 1.9 x 100 PYFU (0.6-1.8) in pts without previous failures and 1.9 x 100 PYFU (0.8-4.2) in pts with >=1 previous VF. By multivariate analysis, pts with 1 previous VF had higher risk of VR but not statistically significant throughout all the analyses (table), while having >=1 previous VF resulted to be associated to VR in the two sensitivity analyses.

Conclusion: Despite the increased risk of VR in pts with previous VF, especially in those with >=1 VF, the 1-year VR was very low. Although longer follow-up is needed to confirm this observation, current data suggest that DTG+3TC should be cautiously used in pts with current viral suppression but a history of VF

Table. Crude and adjusted hazard ratios (95%CI) of the risk of VR from fitting a weighted Cox regression model according to presence and number of previous virological failures and by standard and modified definitions [Def 2] of VR. Sensitivity analysis excluded pts with uncomplete data about past viral loads.

Viral Rebound	HR 95%CI	p-value	AHR 95%CI	p-value	AHR 95% CI (sensitivity analysis)	p-value
previous VF 1 vs 0	2.81 (0.70-11.25)	0.144	2.87 (0.65-12.74)	0.166	3.71 (0.53-25.75)	0.185
previous VF >=1 vs 0	2.88 (0.74-11.13)	0.125	3.39 (0.77-14.90)	0.106	5.39 (0.99-29.30)	0.051
Viral Rebound [Def 2]						
previous VF 1 vs 0	2.62 (0.93-7.42)	0.069	2.37 (0.75-7.51)	0.142	2.69 (0.53-13.60)	0.231
previous VF >=1 vs 0	1.88 (0.71-4.99)	0.204	2.36 (0.73-7.63)	0.152	4.32 (1.00-18.53)	0.049

487 CLINICAL OUTCOMES OF 2-DRUG REGIMENS (2DRS) VS 3-DRUG REGIMENS (3DRS) IN HIV

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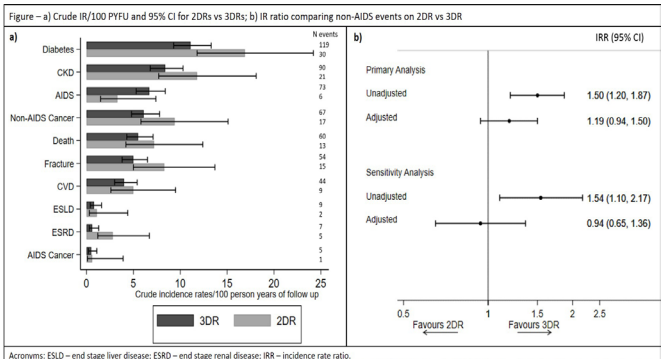
Background: While 2DRs have shown good efficacy in clinical trials, there are limited data comparing longer term clinical outcomes to 3DRs.

Methods: Antiretroviral treatment (ART) experienced persons in RESPOND starting a new 2DR or 3DR from 1/1/12-1/1/18 were included (figure). Poisson regression compared prospectively collected AIDS and non-AIDS events (non-AIDS-defining cancer, cardiovascular disease, end stage liver/renal disease, diabetes, chronic kidney disease [CKD], fractures, non-AIDS related death) between 2DRs vs 3DRs.

Results: Of 5211 persons included, 967 (18.6%) started 2DRs and 4244 (81.4%) started 3DRs. The most common 2DRs were dolutegravir plus lamivudine (18.7%) and boosted darunavir plus raltegravir (18.5%). The main reason for discontinuing the previous regimen before starting a 2DR/3DR was toxicity (33.3% and 36.3% 2DRs vs 3DRs respectively; p=0.14). Persons on 2DRs were older (median 52 years [interquartile range 46-59] 2DRs vs 46 [39-53] 3DRs), had been on ART longer (14 years [6-18] vs 9 [4-15]), had higher CD4 counts (611 cells/µL [394-822] vs 590 [411-797]), and a lower CD4 nadir (170 [68-282] vs 205 [96-310]). A similar proportion had ≥1 comorbidity (63.1% vs 60.7%) and were virally supressed at baseline (86.6% vs 84.5%). Overall, there were 99 AIDS and 548 non-AIDS events during 12717 person years of follow-up [PYFU] (1813 2DR, 10904 3DR). The most common events were diabetes (crude incidence rate [IR] 1.2/100 PYFU [95% CI 1.0-1.4]) and CKD (0.9 [0.7-1.1]; figure). In unadjusted analyses, there was a lower IR of AIDS events on 2DRs (0.4 [0.2-0.9] 2DRs vs 0.8 [0.7-1.0] 3DRs) and a higher IR of non-AIDS events (6.1 [5.1-7.4] vs 4.0 [3.7-4.4]). After adjustment there was no significant difference between 2DRs and 3DRs for non-AIDS events (IR ratio 1.19 [0.94-1.50], p=0.15). The small number of AIDS events precluded adjusted analyses. Sensitivity analyses excluding diabetes, CKD, and fractures showed similar results.

Conclusion: This is the first large, international cohort to assess clinical outcomes on 2DRs. After accounting for demographic and clinical characteristics, there was a similar incidence of non-AIDS events on 2DRs and 3DRs, however confounding by indication cannot be excluded. With a median follow-up of 1.7 years, 2DRs appear to be a viable treatment option with regard to clinical outcomes, although further research on long-term durability and potential toxicities of 2DRs is needed.

Figure – a) Crude IR/100 PYFU and 95% CI for 2DRs vs 3DRs; b) IR ratio comparing non-AIDS events on 2DR vs 3DR



Acronyms: ESLD – end stage liver disease; ESRD – end stage renal disease; IRR – incidence rate ratio.
Eligible 2DRs (n): dolutegravir (DTG) and lamivudine (3TC) (181), raltegravir (RAL) and boosted darunavir (DRV/b) (179), 3TC and DRV/b (159), DTG and DRV/b (147), DTG and rilpivirine (RPV) (108), RAL and etravirine (ETV) (77), 3TC and boosted atazanavir (ATV/b) (50), RAL and nevirapine (NVP) (33), RPV and DRV/b (33); eligible 3DRs include exactly two nucleoside reverse transcriptase inhibitors and one of: RPV (1159), DTG (1112), DRV/b (760), RAL (515), NVP (316), ATV (308), ETV (74).
Adjusted analysis adjusted for year of regimen start, age, ethnicity, smoking status, HIV risk, CD4 nadir, CD4 at regimen start, hepatitis C antibody positive, hepatitis B surface antigenemia positive, hypertension, prior diagnosis of diabetes, AIDS, non-AIDS cancer, ESLD, CVD, fracture, CKD, chronic liver enzyme elevation, geographical region.

488 EFFICACY AND DURABILITY OF 2-DRUG VS 3-DRUG InSTI-BASED REGIMENS: DATA FROM REAL LIFE

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Background: Due to high efficacy and tolerability, the use of integrase strand transfer inhibitors (InSTI) is increasing not only in standard 3-drug regimens (3DR) but also in 2-drug regimens (2DR). However, few data are available about comparison of these strategies in a real-life setting.
Methods: Retrospective multicentre (8 clinical centers in Italy) observational study including HIV+ treatment-experienced patients with HIV-RNA (VL)<50copies/mL switching to InSTI-based 2DR or 3DR with at least one follow-up visit. Major outcomes were virological failure (VF, defined as 1 VL>1000copies/mL or 2 consecutive VL>50copies/mL) and regimen discontinuation due to any reason. Survival analyses were performed to estimate the probability of VF and discontinuation, and to evaluate their predictors.
Results: Overall, 1666 patients [73% males, median age 51 years, 26% previously exposed to InSTI, median time from last VL>50 copies/mL 55 months, current and nadir CD4+ 676 and 184 cells/mmc, respectively] were included, of which 1334(80%) treated with 3DR [n=265 elvitegravir(EVG), n=334 raltegravir(RAL), n=735 dolutegravir(DTG)] and 332(20%) with 2DR [n=263 lamivudine+DTG; n=69 rilpivirine+DTG]. Over a median follow-up of 100 weeks(IQR 52-150), 52(3.1%) patients experienced VF with an incidence of 1.5 per 100 PYFU; the estimated 48-week probability of VF was not different between 2DR and 3DR(1.4% vs 1.8%;p=0.53), but it was higher for EVG(3.5%) and RAL(3%) when compared to DTG(1%)(p=0.04). By multivariate analysis, previous VF (aHR 2.7;p<0.001) and shorter time from last VL>50copies/mL(aHR 0.9;p=0.04) predicted VF. Four-hundred(24%) patients discontinued InSTI-based regimen with an incidence of 11.3 per 100 PYFU. Main reasons for discontinuation were toxicity[n=159 (40%) of which 51(13%) CNS toxicity] and simplification(n=119, 30%). The estimated 48-week probability of discontinuation for any reason was 20% for RAL, 10% for DTG and 16% for EVG(p< 0.001), without differences comparing 2DR and 3DR DTG-based(9% vs 10%;p=0.21). By multivariate analysis, there was higher risk of discontinuation in 3DR(vs 2DR aHR= 2.1;p<0.001) and lower risk in MSM(vs heterosexuals aHR= 0.75;p=0.02) and regimens started for simplification(aHR 0.5;p<0.001).
Conclusion: In our real-life setting, both 2DR and 3DR InSTI-based regimens showed high efficacy and durability. Regimens including DTG were associated with a lower risk of VF and discontinuation

489 ASSESSING THE VIROLOGIC IMPACT OF ARCHIVED RESISTANCE IN AN HIV-1 SWITCH STUDY, TANGO

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Background: TANGO study demonstrated that switching to DTG/3TC fixed dose combination (FDC) 2-Drug Regimen (2DR) was non-inferior to continuing a TAF-based 3-drug regimen (TBR, 3DR) in maintaining virologic suppression in HIV-1 infected, ART-experienced adults through Week 48. The impact of pre-existing, HIV-1 drug resistance on virologic outcomes through Week 48 was assessed.
Methods: Participants with historical IAS major NRTI or INSTI resistance associated mutations (RAMs) were excluded from the study. Pro-viral DNA genotyping was conducted retrospectively on baseline samples from randomized participants by Monogram Bioscience using GenoSure Archive assay. Virologic outcomes based on IAS major NRTI, NNRTI, PI and INSTI RAMs were determined by last available on-treatment HIV-1 RNA through Week 48 in order to assess pure virologic responses by censoring discontinuations due to non-efficacy reasons. This was repeated on the FDA Snapshot Algorithm at Week 48 as a sensitivity analysis.
Results: 322 (87%) of participants in the DTG/3TC arm and 321 (86%) in the TBR arm had both pro-viral genotype data and at least one on-treatment HIV-1 RNA result. Archived major NRTI, NNRTI, PI and INSTI RAMs were observed in 42 (7%), 90 (14%), 43 (7%) and 6 (1%) participants, respectively across both arms (Table 1), and 474 (74%) participants were without any major RAMs at the baseline. The frequencies of NRTI RAMs M184V/I, K65E/N/R and thymidine analog mutations (TAMs) were low. Through Week 48, 322 (100%) of participants on DTG/3TC and 319 (>99%) on TBR were virologically suppressed (last on-treatment HIV-1 RNA <50 c/mL). For participants with any major NRTI, INSTI, NNRTI or PI RAMs, all were virologically suppressed. The results of a sensitivity analysis using the FDA Snapshot algorithm were consistent with those using last available on-treatment HIV-1 RNA. One participant in TBR arm without any archived RAMs met the protocol-defined, confirmed Virologic withdrawal criterion (CVW) with no emergent resistance. None in the DTG/3TC arm met CVW criteria through Week 48.
Conclusion: In TANGO, archived major NRTI (e.g., M184V/I, K65E/N/R and TAMs) and INSTI (e.g., Q148R, Y143C/H, R263K) RAMs were infrequent. High rates of virologic suppression were maintained in participants on both treatment arms through Week 48. The presence of pre-existing, archived RAMS did not appear to impact virologic outcomes through Week 48.

Table 1. Virologic Outcomes by Archived Resistance Category through Week 48

Resistance Class at Baseline	DTG/3TC FDC (N=322)		TBR (N=321)	
	With Mutation (%) / Suppressed (%)	Without Mutation[a] (%) / Suppressed[c] (%)	With Mutation[a] (%) / Suppressed[b] (%)	Without Mutation[a] (%) / Suppressed[c] (%)
Major NRTI[d]-associated	25 (8%) / 25 (100%)	297 (92%) / 297 (100%)	17 (5%) / 17 (100%)	304 (95%) / 302 (>99%)
M184V/I	4 (1%) / 4 (100%)	318 (99%) / 318 (100%)	3 (1%) / 3 (100%)	318 (>99%) / 316 (>99%)
K65R/N	0 / 0	322 (100%) / 322 (100%)	2 (<1%) / 2 (100%)	319 (>99%) / 317 (>99%)
TAM[e]	9 (3%) / 9 (100%)	313 (97%) / 313 (100%)	5 (2%) / 5 (100%)	316 (>99%) / 314 (>99%)
Major INSTI[d]-associated	3 (<1%) / 3 (100%)	319 (>99%) / 319 (100%)	3 (<1%) / 3 (100%)	318 (>99%) / 316 (>99%)
Q148R	2 (<1%) / 2 (100%)	320 (>99%) / 320 (100%)	1 (1%) / 1 (100%)	320 (>99%) / 318 (>99%)
Y143C/H	1 (<1%) / 1 (100%)	321 (>99%) / 321 (100%)	2 (<1%) / 2 (100%)	319 (>99%) / 317 (>99%)
R263K	0 / 0	322 (100%) / 322(100%)	2 (<1%) / 2 (100%)	319 (>99%) / 317 (>99%)
Major NNRTI[d]-associated	38 (12%) / 38 (100%)	284 (88%) / 284 (100%)	52 (16%) / 52 (100%)	269 (84%) / 267 (>99%)
Major PI[d]-associated	23 (7%) / 23 (100%)	299 (93%) / 299 (100%)	20 (6%) / 20 (100%)	301 (94%) / 299 (>99%)

Footnote: [a]Denominator is N. [b]Denominator is number of participants with mutation. [c]Denominator is number of participants without mutation. [d]Resistance mutations used in these analyses are based on 2019 IAS-USA guidelines. [e]TAMs: Thymidine Analogue Mutations (M41L, D67N, K70R, L210W, T215F/Y, K219E/N/R/Q), all of which are Major NRTI mutations except K219N/R.

490 VIROLOGIC FAILURE AND RESISTANCE IN DOLUTEGRAVIR-BASED MAINTENANCE DUAL REGIMENS

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Background: Maintenance ART with dolutegravir (DTG)-based dual regimens (2DR) have proved their efficacy among HIV-1 infected subjects in large and randomized trials. Real-life data are scarce with limited population and follow-up. In a large cohort (Dat'AIDS), we evaluated virologic failure (VF) and resistance-associated mutations (RAMs) on DTG maintenance regimens in combination with rilpivirine (RPV) or 3TC/FTC (xTC), and we analyzed the factors associated with VF.
Methods: Between 2014 and 2018, all HIV-1 adults starting DTG/RPV or DTG/xTC as a maintenance 2DR (i.e. with HIV RNA <50 c/mL) were enrolled in a retrospective analysis within the Dat'AIDS cohort (NCT02898987). VF was defined as 2 consecutive HIV RNA >50 c/mL or a single value >400 c/mL. We compared cumulative genotypes prior to 2DR and at VF (ANRS algorithm V29; 2018). Cox-models were used to analyze factors associated with VF.
Results: 1374 subjects were included (DTG/RPV: 799, DTG/xTC: 575) with a median follow-up of 587 days [IQR 334-934] and 562 days [IQR 326-938],

respectively. Baseline characteristics are shown in Table. VF occurred in 3.8% (n=30) of DTG/RPV and 2.6% (n=15) of DTG/xTC subjects (p=NS), with a median delay to VF of 232 days [IQR 100-507] and 301 days [IQR 188-427], respectively. Among VF subjects, 9/30 (33%) had history of VF on NNRTI-based regimen in DTG/RPV group and 5/15 (30%) had history of VF on NRTI-based regimen in DTG/xTC group. At DTG/RPV VF, 17/30 genotypes were available: 2 genotypes harbored NNRTI RAMs already detected on historical genotypes (E138A ; E138A+L100I) ; 2 genotypes harbored new RAMs, 1 genotype with E138K on NNRTI and 1 genotype with E138K+K101E on NNRTI and N155H on INSTI. At DTG/xTC VF, 6/15 genotypes were available: no new RAM was detected and 1 genotype harbored M184V already detected on historical genotypes. The only predictive factor of VF on DTG/RPV was history of VF to NNRTI-based ART (HR 2.82, CI95% 1.04-7.6), while gender, age, duration of HIV RNA <50 c/mL prior to 2DR, nadir CD4, zenith HIV RNA and CDC stage C were not. No factor was associated with VF under DTG/xTC.

Conclusion: In this large real-life cohort, DTG-2DR maintained sustain HIV RNA virologic suppression, and were associated with a low rate of VF. DTX/xTC was associated with slightly lower VF rate than DTG/RPV and the absence of RAM emergence at VF. ARV history are prior VF are key issues to consider before offering 2DR maintenance.

Table – Baseline characteristics

Median [IQR] or n(%)	DTG/RPV	DTG/xTC
n	799	575
Age, years	55 [49, 62]	53 [45, 61]
Male gender	552 (69.1)	402 (69.9)
CDC stage C	231 (28.9)	109 (19.0)
Nadir CD4 <200/mm^3	401 (50.2)	177 (30.8)
Zenith HIV RNA >5 log_{10} copies/mL	388 (48.6)	248 (43.1)
History of NRTI VF	333 (41.7)	108 (18.8)
History of NNRTI VF	90 (11.3)	38 (6.6)
History of INSTI VF	38 (4.8)	10 (1.7)
HIV RNA < 50 c/mL, months	90 [46, 137]	75 [41, 125]
<12 months	50 (6.3)	41 (7.1)

491 2-DRUG REGIMEN COMPARABLE TO 3-DRUG REGIMENS UP TO 18 MONTHS IN A REAL WORLD SETTING

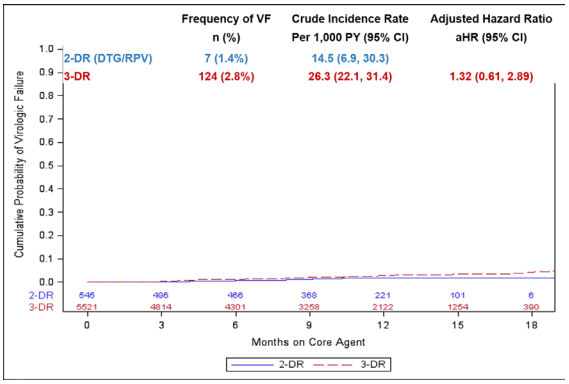
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Background: Dolutegravir/rilpivirine (DTG/RPV) was the first single tablet, once daily regimen, containing only two antiretrovirals to be approved. Our objective was to compare the effectiveness and durability of DTG/RPV to standard three-drug regimens (3-DR) in a real-world setting.

Methods: People living with HIV-1 (PLWH) who initiated a two drug regimen (2-DR) comprised of DTG/RPV or 3-DR, defined as one core agent and two NRTIs, were identified in the OPERA Database. Those who initiated therapy between 1/1/2018–12/31/2018, were ART experienced, age ≥13 years, and suppressed (<50 copies/mL) at start were analyzed. Discontinuation (d/c) was defined as cessation of 2- or 3-DR. Sustained suppression was defined as last viral load (VL) <200 copies. Virologic failure (VF) was defined as either 2 consecutive VL ≥ 200 copies/mL or 1 VL ≥ 200 copies/mL + d/c. The population was observed through 06/30/2019. Baseline characteristics were described using Pearson's chi-square, Fisher exact, or Wilcoxon rank-sum tests. Kaplan-Meier methods were used to describe d/c and VF. Cox Proportional Hazards modeling was used to assess the risk of VF adjusting for age, sex, race, ethnicity, risk of infection, region, baseline CD4 cell count, history of substance abuse, history of syphilis and VACS score at baseline.

Results: Among 545 PLWH who initiated DTG/RPV as a 2-DR and 5,524 PLWH who initiated 3-DR, DTG/RPV 2-DR users were significantly (p<.0001) older, more likely to be Hispanic, MSM, to have comorbidities and to receive care in the southern and western United States. They were less likely to be African American or to receive care in the Northeast or Midwest. PLWH initiating 3-DR were more likely to have a history of syphilis. Median (IQR) follow-up was similar between 2-DR and 3-DR initiators at 10.7 (6.8-14.6) months. DTG/RPV 2-DR users experienced fewer discontinuations compared to 3-DR users (15.0% vs. 28.0%, <.0001) and were more likely to sustain suppression (97.7% vs 95.5%, p=.02) compared to 3-DR users. VF rates per 100 person-years (95% CI) did not differ (DTG/RPV: 1.45 (0.69, 3.03) vs. 3-DR: 2.63 (2.21, 3.14)). Differences in the risk of VF between 3-DR, DTG/RPV initiators in adjusted Cox models were not significant (aHR 1.32, 95% CI 0.61,2.89) (Fig. 1).

Conclusion: Among ART-experienced, virologically suppressed PLWH initiating DTG/RPV as a 2-DR or standard 3-DR, there was no observed difference in the risk of virological failure in a real-world setting.



492 SHALL WE DANCE? EXTENDING TANGO'S RESULTS TO CLINICAL PRACTICE

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Background: Results from the TANGO study highlight the high efficacy and tolerability of lamivudine (3TC) and dolutegravir (DTG) as a switch strategy. However, trials' populations often differ from real-practice settings. We aimed to confirm the study's findings in our multicenter cohort.

Methods: This was an observational study enrolling HIV-infected, virologically suppressed patients switching to 3TC+DTG, divided into 2 groups based on their adherence to the TANGO inclusion criteria. We collected patients' history, virological, immunological assessment at baseline, 48, 96 and 144 weeks. We performed Kaplan-Meier survival analysis to evaluate time to virological failure (VF, defined by 2 consecutive HIV-RNA determinations≥50 cps/mL or a single HIV-RNA≥1000 cps/mL) and treatment discontinuation (TD), Cox-regression to find predictors of VF or TD and linear mixed model for repeated measures to identify significant changes in immunological parameters.

Results: We analyzed 557 patients: 145 (26.0%) met the TANGO inclusion criteria (TANGO group, TG). During 248 PYFU in the TG and 776 PYFU in the non-TG, 1 and 11 VF occurred in the 2 groups respectively. The estimated probability of maintaining virological suppression was 99.2% (SD±1.6) at 48, 96 and 144 weeks in the TG, and 98.5% (SD±1.4) at 48 weeks, 97.7 (SD±1.8) at 96 weeks and 95.7% (SD±2.6) at 144 weeks in the non-TG (log-rank p=0.189). Respecting TANGO's criteria did not affect the risk of VF (aHR 0.35, 95%CI 0.04-2.84; p=0.327), even after adjusting for age, anti-HCV serostatus and HIV duration. Estimated probabilities of remaining on 3TC+DTG were 86.6% (SD±5.9) at week 48 and 79.5% (SD±7.5) at weeks 96 and 144 in the TG, and 85.8% (SD±3.5), 78.9% (SD±4.3) and 73.9% (SD±5.1) at weeks 48, 96 and 144 in the non-TG (log-rank p=0.654), with no significant increase in the hazard of TD for the TG after adjustment for age, gender, HIV risk factor, CD4 nadir, HIV duration and time on ARV. A significant increase in CD4 cell count (mean change at 96 weeks, +87 cell/µL in TG and +40 cell/µL in the non-TG) and CD4/CD8 ratio (mean change at 96 weeks, +0.05 in the TG and +0.07 in the other) was observed over time in both groups.

Conclusion: Results from our multicenter study are in line with the results from the TANGO study and their applicability to everyday clinical practice.

Table 1. Patients' characteristics at baseline.

	TANGO group (n=145)	Non-TANGO group (412)	P value
Age (Years), Median (IQR)	49 (40-55)	53 (47-58)	<0.001
Male sex, n (%)	111 (76.6)	281 (68.2)	0.058
Risk factor for HIV, n (%):			<0.001
- Eterosexual	56 (38.6)	169 (41.0)	
- MSM	37 (25.5)	108 (26.2)	
- IDU	15 (10.4)	86 (20.9)	
- Other/Unknown	37 (25.5)	49 (11.9)	
CDC Stage C, n (%)	20 (13.8)	62 (15.0)	0.854
Anti HCV positive serostatus, n (%)	25 (17.2)	101 (24.5)	0.076
Zenith HIV-RNA (log10 copies/mL), media (IQR)	4.95 (4.45-5.35)	4.89 (4.37-5.43)	0.780
Nadir CD4+ cell count	278 (140-395)	212 (93-309)	0.001
Non-B viral subtype, n (%)	5 (3.4)	13 (3.2)	0.875
Years from HIV diagnosis, median (IQR)	9 (5-17)	18 (10-24)	<0.001
Years of cumulative ARV exposure, median (IQR)	7 (3-12)	13 (8-19)	<0.001
M184V resistance mutation detection at last genotipic resistance test	/	45 (10.9)	NA

493 VIROLOGIC OUTCOMES BY RESISTANCE CATEGORY AND PRETREATMENT IN THE DUALIS STUDY

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Background: Advances in potency and resistance barrier of antiretroviral drugs for HIV infection and evidence from recent randomized clinical trials (RCTs) support the use of dual therapy at least in specific patient populations. Both, Dolutegravir (DTG) and boosted darunavir (bDRV) are potent antiretroviral drugs with a high resistance barrier. DUALIS, a phase IIIb, open-label RCT demonstrated non-inferiority of a switch to DTG+bDRV (2DR) versus continuous 2NRTI+bDRV (3DR) in virologically suppressed people living with HIV (PLWH) with week 48 virologic response rates of 86% (2DR) and 88% (3DR).

Methods: Post-hoc analysis of virologic outcomes in DUALIS with respect to treatment history and HIV drug resistance. Among study inclusion criteria was an HIV-RNA level <50 cps/mL for ≥24 weeks (one blip accepted); any history/presence of drug resistance other than INSTI or bDRV was not exclusionary. Documentation of resistance-associated mutations (RAMs) was based on the Stanford HIVdb mutation list involving specific additional RAMs. Virologic outcomes in subgroups include the primary endpoint (PE, i.e. % with HIV-RNA<50cps/mL at week 48) and % of patients with ≥50 cps/mL (i.e. data in window and ≥50 cps/mL or discontinuation for lack of efficacy or discontinuation for other reason and ≥50 cps/mL).

Results: The ITTe set included 263 subjects (2DR n=131, 3DR n=132): 90.1% males, median age 48 years, CDC stage C 29.7%, CD4 nadir<200/µl 47.0%; median time on ART 5.3 years, 27.4% with ≥2 ART changes, 8.4% with prior INSTI use; 20.9% and 11.0% had a history of ≥2 NRTI and ≥2 PI changes, respectively. NRTI, NNRTI and (minor or major) PI RAMS were observed in 9.1, 12.9, and 26.6% (major PI RAMS 3.4%), respectively. Resistance categories and PE analyses within subgroups are shown in Table 1 with response rates ≥80% across groups. Response rates with major and/or minor RAMs were 88.9% on 2DR and 95.5% on 3DR versus 84.9% (2DR) and 84.1% (3DR) without documented RAMs. No patient with major/minor RAMs in either group had ≥50 HIV-RNA cps/mL at last follow-up. No emergence of RAMs during follow-up was observed.

Conclusion: As shown in the DUALIS study, dual therapy with DTG+bDRV tends to be an effective treatment option with no treatment-emergent resistance for PLWH on suppressive first- or further-line ART with or without evidence of pre-existing NRTI, NNRTI or PI RAMs.

Table 1		2DR (N=131)	Cont. 3DR (N=132)
Resistance-associated mutations (RAMs) prior to baseline (BL)	Any major or minor RAM; N (%)	45 (34.4)	44 (33.3)
	NRTI RAMs; N (%)	12 (9.2)	12 (9.1)
	NNRTI RAMs; N (%)	17 (13.0)	17 (12.9)
	Any PI RAM (major/minor); N (%)	35 (26.7)	35 (26.5)
	PI RAM, major (±minor); N (%)	5 (3.8)	4 (3.0)
	PI RAM, minor; N (%)	30 (22.9)	31 (23.5)
HIV-RNA<50 cps/mL at w48 (PE°); n/N (%)	ITTe set	113/131 (86%)	116/132 (88%)
PE in subgroups	ART prior to BL: 1st-line ART	64/75 (85.3)	49/57 (86.0)
	2nd-line ART	25/29 (86.2)	24/30 (80.0)
	≥3rd-line ART	24/27 (88.9)	43/45 (95.6)
	Any major or minor RAM	40/45 (88.9)	42/44 (95.5)
	No RAMs/no resistance testing*	73/86 (84.9)	74/88 (84.1)
	- no RAMs	30/35 (85.7)	27/33 (81.8)
	- no resistance testing*	43/51 (84.3)	47/55 (85.5)
	Any major or minor NRTI RAM	10/12 (83.3)	12/12 (100.0)
	No NRTI RAMs/no res. testing*	103/119 (86.6)	104/120 (86.7)
	Major PI RAMs (±minor)	5/5 (100.0)	4/4 (100.0)
	Minor PI RAMs	26/30 (86.7)	29/31 (93.6)
	No PI RAMs/no res. testing*	82/96 (85.4)	83/97 (85.6)
HIV-RNA≥50 cps/mL at w48/at disc.**; n/N (%)	Any major or minor RAM	0/45 (0.0)	1/44 (2.3)
	no RAMs/no resistance testing*	5/86 (5.8)	6/88 (6.8)

°primary endpoint, *historical resistance testing not available, **for definition see methods

494 ONCE-DAILY ETRAVIRINE/RALTEGRAVIR (400/800 MG) AS MAINTENANCE REGIMEN

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Background: The ANRS163-ETRAL study showed 99.4% of virological success rate for etravirine/raltegravir (200/400 mg) twice-daily (ETR/RAL BID) dual therapy in suppressed HIV-infected patients older than 45 years [Katlama C, et al., *J Antimicrob Chemother*, 2019]. To simplify this regimen, we aimed to assess the efficacy of etravirine/raltegravir (400/800 mg) given once-daily (ETR/RAL QD).

Methods: Patients with plasma viral load (pVL) <50 copies/mL under ETR/RAL BID for at least 96 weeks were switched to ETR/RAL QD in this prospective, multicenter, open-label, single arm study. Primary outcome consisted in the rate of virological failure (VF, defined as 2 consecutive pVL >50 copies/mL 2-4 weeks apart or a single value >400 copies/mL) at W48, estimated with the Kaplan-Meier method. Secondary outcomes included tolerance, treatment strategy success rate (defined as absence of VF with no treatment discontinuation), plasma drugs concentrations and resistance profile in case of VF. The objective of the study was to show a VF rate <10%.

Results: A total of 111 patients were included with a median (IQR) age: 57 years (52-62), CD4: 710 cells/mm$_3$ (501-919), CD4 nadir: 183 cells/mm$_3$ (90-269) and HIV suppression duration: 7.9 years (5.9- 10.7). Two VF occurred at W24 and W48 leading to a VF rate of 2.0% (95%CI [0.5-7.8]). One of both reported poor compliance and were virologically suppressed after ART resumption, with no acquired resistance. The second patient had low etravirine and raltegravir plasma concentrations (C_{24h}: 365 ng/mL and 71 ng/mL, respectively), with selection of INI associated resistance mutations L74I, G140A and Q148H. Overall 7 patients discontinued ETR/RAL QD for non VF reasons: adverse events (n=3, lethal myocardial infarction, nausea and death), investigator decision (n=2), pregnancy (n=1) and patient decision (n=1), leading to a strategy success rate of 91.7% (95%CI [84.6-95.6]) at W48. Median (IQR) C_{24h} values of etravirine 400 mg and raltegravir 800 mg QD were 401 ng/mL (286-591) and 51 ng/mL (26-93), respectively.

Conclusion: Switching from ETR/RAL BID to QD regimen is highly effective in maintaining virological suppression in HIV-infected patients. This once-daily combination is a good option to avoid protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) in aging patients.

495 PATTERNS OF ADHERENCE IN BICTEGRAVIR- AND DOLUTEGRAVIR-BASED REGIMENS

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Background: Regimen complexity can adversely affect adherence, leading to virologic failure. It is unknown whether this occurs with regimens that contain the second-generation integrase inhibitors (INSTIs), bictegravir and dolutegravir, both of which are recommended in the current DHHS Guidelines.
Methods: EMR, prescription and dispensing data for 2,217 patients initiating BIC/FTC/TAF, DTG/ABC/3TC, DTG+TDF/FTC, or DTG+TAF/FTC between Aug 2013 - Aug 2019 were collected from 5 practices across 17 US states. Only those without prior documented treatment with DTG or BIC, respectively, were included. Adherence was defined as proportion of days covered through the first 6 months of regimen treatment. To determine treatment effects on adherence, we (1) used multiple imputation with predictive posterior matching to account for incomplete baseline measures, (2) used mixed effects logistic regression, using BIC/FTC/TAF vs DTG-regimens with random intercept for practice, to adjust for heterogeneity between practices, (3) adjusted models using demographics and relevant baseline clinical data (CD4 count, viral load, AST, ALT, lipids, eGFR, hemoglobin A1C) and year of regimen initiation, and (4) employed propensity score matching using imputed baseline labs and demographics, allowing for squares and first order interactions between all included predictors. In addition to adherence, we assessed viral suppression (<200 copies/mL) in a subset of 655 patients at 6 months (measured within 1 week prior and up to two months after).
Results: In observed (unadjusted) data, adherence was significantly greater at 6 months to BIC/FTC/TAF compared to any dolutegravir-regimen and to DTG/ABC/3TC in comparison to DTG+TDF/FTC or DTG+TAF/FTC at the 80% level [TABLE]. After controlling for non-treatment effects, adherence was only significantly different for BIC/FTC/TAF compared to DTG+TDF/FTC or DTG+TAF/FTC ($p<0.01$). Assessment of viral suppression at 6 months for patients with measures (n=655) was favorably impacted by adherence ≥80% (OR 2.27 [1.26-4.07] $p<0.01$) and ≥95% (OR 2.63 [1.55-4.48] $p<0.01$).
Conclusion: This study of bictegravir and dolutegravir-based regimens supports the notion that simplifying treatment to a single tablet aids in adherence, and that adherence yields improved virologic outcomes in clinical settings.

Observed (unadjusted) adherence between groups (Observed) and estimated Treatment Effect (Adjusted odds ratios [AOR] with 95% CI) on adherence within first 6 months.

1. BIC/FTC/TAF v. DTG-containing regimens (DTG/ABC/3TC, DTG+TDF/FTC or DTG+TAF/FTC)		
Adherence	**Observed; n/N (%) [p]**	**AOR (95% CI) [p]; Matched Cohort, n=482**
>95%	BIC 853/1060 (80.5); DTG 808/1157 (69.8); [<0.01]	1.86 (1.06, 3.26) [0.03]
>80%	BIC 979/1060 (92.4); DTG 943/1157 (81.5); [<0.01]	2.38 (1.16, 4.89) [0.02]
2. STR BIC/FTC/TAF v. STR DTG/ABC/3TC		
Adherence	**Observed; n/N (%) [p]**	**AOR (95% CI) [p]; Matched Cohort, n=376**
>95%	BIC 853/1060 (80.5); STR DTG 394/542 (72.7); [<0.01]	1.61 (0.75, 3.46) [0.22]
>80%	BIC 979/1060 (92.4); STR DTG 457/542 (84.3); [<0.01]	1.11 (0.36, 3.44) [0.85]
3. STR BIC/FTC/TAF v. MTR DTG+TDF/FTC or DTG+TAF/FTC		
Adherence	**Observed; n/N (%) [p]**	**AOR (95% CI) [p]; Matched Cohort, n=384**
>95%	BIC 853/1060 (80.5); MTR DTG 414/615 (67.3); [<0.01]	2.18 (1.26, 3.77) [<0.01]
>80%	BIC 979/1060 (92.4); MTR DTG 486/615 (79.0); [<0.01]	4.15 (2.18, 7.88) [<0.01]
4. STR DTG/ABC/3TC v. MTR DTG+TDF/FTC or DTG+TAF/FTC		
Adherence	**Observed; n/N (%) [p]**	**AOR (95% CI) [p]; Matched Cohort, n=376**
>95%	STR DTG 394/542 (72.7); MTR DTG 414/615 (67.3); [0.06]	1.15 (0.82, 1.62) [0.41]
>80%	STR DTG 457/542 (84.3); MTR DTG 486/615 (79.0); [0.02]	1.24 (0.85, 1.82) [0.26]
5. STR (BIC/FTC/TAF or DTG/ABC/3TC) v. MTR (DTG+TDF/FTC or DTG+TAF/FTC)		
Adherence	**Observed; n/N (%) [p]**	**AOR (95% CI) [p]; Matched Cohort, n=384**
>95%	STR 1247/1602 (77.8); MTR 414/615 (67.3); [<0.01]	1.18 (0.8, 1.73) [0.41]
>80%	STR 1436/1602 (89.6); MTR 486/615 (79.0); [<0.01]	1.34 (0.87, 2.08) [0.18]

Observed Adherence tested with Fisher's Exact Test. Treatment effects (AOR) estimated using Mixed Effects Multiple Logistic Regression with propensity score-matched treatment groups. Reference is 2nd group in each comparison.

496 SOCIAL NORMS AND ART ADHERENCE: POPULATION-BASED STUDY OF PERSONS WITH HIV IN UGANDA

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Background: The extent to which certain health behaviors are perceived as normative is known to be an important determinant of one's own propensity to engage in such behaviors. It is unknown, however, whether people living with HIV (PLWH) accurately perceive norms around antiretroviral treatment (ART) adherence and whether these perceptions influence their own propensities to adhere to ART.
Methods: We recruited a population-based sample of PLWH on ART in Nyakabare Parish, a rural region of southwest Uganda. Self-reported ART non-adherence was defined as missing any ART doses in the past 7 days. We also elicited their perception about the extent to which most other adult PLWH in their community were non-adherent to ART. Actual ART non-adherence was calculated by aggregating responses across all PLWH. Non-adherence was classified as normative if reported non-adherence was present among more than 50% of PLWH in the village. We then compared individuals' perception of the adherence norm to the actual adherence norm, and also assessed the relationship between perception and personal adherence.
Results: Adherence was normative among 158 adult PLWH (response rate 95%): only 15% of HIV+ men and 9% of HIV+ women reported missing any doses in the past 7 days. However, approximately one-half of study participants (45% of men and 54% of women) incorrectly believed that most PLWH in their communities were non-adherent to ART. In addition, approximately one-quarter (22% of men and 25% of women) did not know whether most people had missed any doses. Only about one-quarter of this population (33% of HIV+ men and 21% of HIV+ women) accurately perceived that ART adherence was normative among PLWH. Overestimating the pervasiveness of ART non-adherence was not associated with age, education, time since diagnosis, or serostatus status disclosure. Finally, there were almost three times as many non-adherents among the participants who misperceived the norm as compared to non-adherents among the participants who accurately perceived the norm (14% vs. 5%), though this difference was not statistically significant.
Conclusion: Many PLWH on ART believe that non-adherence to ART is present among most PLWH on ART in their community, despite adherence actually being normative among PLWH in this population-based study from rural Uganda. Because those who are non-adherent appear to also perceive poor adherence as a normative behavior, altering those misperceptions might represent an opportunity for novel ART adherence intervention development.

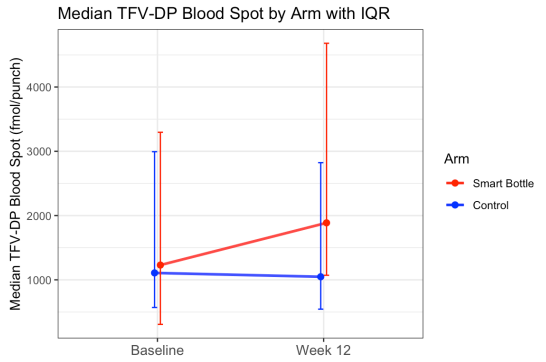
497 RANDOMIZED STUDY OF AN ART ADHERENCE INTERVENTION USING A SMART-PILL BOTTLE SERVICE

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Background: Adherence is critical to achieve the benefits of antiretroviral therapy (ART). Smart-pill bottles (AdhereTech) securely transmit real-time adherence information via cellular networks to a central service that sends prompts to non-adherent patients by phone call or text in addition to on-device visual and audio cues. The smart-pill bottle service may improve adherence to ART.
Methods: Adults with HIV taking a tenofovir disoproxil fumarate (TDF)-containing regimen with suboptimal adherence (2 detectable HIV RNA assays during the prior year) were randomized to receive adherence counseling with or without the smart-pill bottle service for 12 weeks. Tenofovir diphosphate (TFV-DP) levels by dried blood spot, HIV RNA, CD4 levels, and self-reported adherence (using the AIDS Clinical Trials Group [ACTG] Adherence Questionnaire) were collected.
Results: 63 participants (22% women; 48% black, 25% Latino) were randomized (30 bottle, 33 control). At baseline, 49% of participants had HIV RNA <20 copies/mL and 61% reported 100% adherence with antiretroviral medications over the prior 4 days. From baseline to week 12, median TFV-DP levels increased from 1230 to 1887 fmol/punch in the smart-bottle group compared to a decrease from 1108 to 1048 fmol/punch in controls (see figure; median change +252 versus -41 fmol/punch, respectively, $p=0.101$). Discontinuation rates were 5 of 30 (17%) in the smart-bottle group vs. 7 of 33 (22%) in the control group ($p=0.89$). The number of participants with HIV RNA >20 copies/mL at baseline who decreased to ≤20 copies/mL at 12 weeks was 3 of 24 in the smart-bottle group vs. 7 of 26 in the control group (OR for the intervention 0.4; 95% CI 0.1, 2.0). The median change in CD4 count from

baseline to week 12 was +14 cells/μL in the smart-bottle group and -16 cells/μL in the control group (p=0.36). At week 12, 75% of the smart-bottle group and 77% of the control group reported 100% adherence taking their antiretroviral medications over the prior 4 days.

Conclusion: This pilot study demonstrates that in patients with HIV infection on ART, the smart-pill bottle service was associated with higher tenofovir diphosphate levels (though this did not reach statistical significance); HIV RNA suppression rates, CD4 cell counts, and self-reported adherence rates (over the prior 4 days) were not different.



498 PHARMACIST-DRIVEN RAPID ART REDUCES TIME TO VIROLOGIC SUPPRESSION IN RHODE ISLAND

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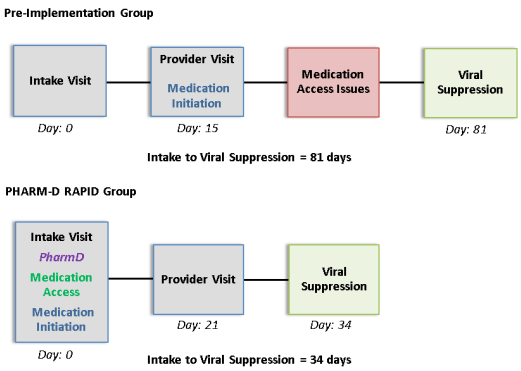
Background: Rapid start antiretroviral therapy (ART) protocols have emerged as an innovative care model for persons newly diagnosed with HIV (PNDWH). Shifting to a model where clinical pharmacists are at the forefront of rapid ART initiation may provide a sustainable solution for the logistical challenges that limit widespread implementation.

Methods: We conducted a preliminary retrospective analysis at Rhode Island's largest HIV clinic to compare clinical outcomes of PNDWH before (1/2017 – 12/2017) and after (1/2019 – 8/2019) implementation of a Pharmacist Driven Rapid ART (PHARM-D RAPID) protocol. Prior to implementation of the protocol at this Ryan White clinic, patients attended an intake visit with a nurse upon HIV diagnosis, which preceded their first provider appointment and ART initiation by approximately 2 weeks. Following implementation of the PHARM-D RAPID protocol, PNDWH are evaluated by a multidisciplinary team on intake and offered rapid ART initiation by clinical pharmacists prior to their first provider visit. During intake, clinical pharmacists provide education, assess readiness to initiate ART, evaluate drug-drug interactions, resolve medication access issues, and recommend patient-specific ART to the triage physician for initiation. Follow-up phone calls are conducted by pharmacists 2 weeks following ART initiation. Clinical and demographic data were extracted from the electronic medical record. The primary outcome was time from intake visit to viral suppression (HIV RNA <200 copies/mL).

Results: A total of 88 patients were included in the preliminary analysis; 55 and 33 in the pre-group and PHARM-D RAPID group, respectively. Baseline characteristics were similar between groups. Mean age was 37 with 85% male, 58% white, 25% black, 30% Hispanic, and 53% with MSM as their sole reported risk factor. 26% were uninsured, 25% presented with AIDS, and half had history of substance use (54%) and/or mental illness (50%). Pharmacists' recommendations for ART regimens were accepted in all PHARM-D RAPID patients. Medication access issues were preemptively resolved in 61% of PHARM-D RAPID patients. Time from intake to viral suppression (81 vs. 34 days, P=0.001) and time from intake to ART (16 vs. 0 days, P<0.001) significantly decreased in the PHARM-D RAPID group.

Conclusion: Our PHARM-D RAPID protocol demonstrates a novel pathway for decreasing time to viral suppression and HIV transmission, which are key for achieving 90-90-90 efforts in a complex patient population.

Figure 1. Flow Diagram



499 DO PRESCRIBING DATA REFLECT ACTUAL TREATMENT IN PEOPLE LIVING WITH HIV (PLWH)?

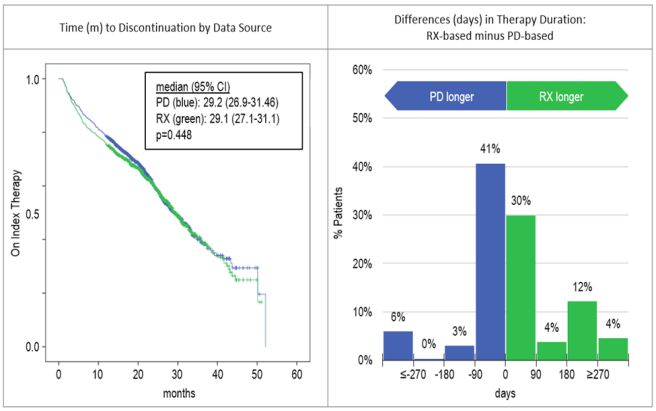
Joseph J. Eron[1], Dushyantha Jayaweera[2], Gregory D. Huhn[3], Kelsey Milligan[4], Scott Milligan[4], Paul E. Sax5, Keith Spitz[4], Richard A. Elion[6]
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Background: Data created during the care continuum are challenging to assemble, and disparate sources may account for varied results in observational studies. To assess the limitation of one source, we contrasted adherence, duration, and regimen composition between prescription (RX) and pharmacy dispense (PD) data generated during care of PLWH.

Methods: Antiretroviral (ARV) RX and PD data were obtained for 1270 treatment-experienced PLWH from the TRIO network, consisting of 11 HIV treatment centers servicing 39 US states. Follow up was ≥12 months (m) post index, defined as the first ARV regimen switch between 2014 to 2017 with final data collection Jun 2019. Adherence was based upon proportion of days (d) with all drugs. Regimen discontinuation was dated at exhaustion of all regimen components and/or upon addition of a new ARV drug. Time to discontinuation was assessed by Kaplan-Meier with log-rank. Univariate analyses were via chi-square, exact, or T-test.

Results: Discontinuation rates (46% RX v 43% PD, p=0.060) and median time to discontinuation (29 m RX v. 29 m PD, p=0.448) were not significantly different by data source, though time to discontinuation/censoring differed by >90 d (+/-) for 29% (374) of PLWH, with 20% (258) discontinuing therapy >90 d before the end of the RX-based regimen [FIGURE]. ≥80% adherence was calculated for 90% (1143) PLWH based on RX v 92% (1166) PD (p=0.129) and ≥95% adherence for 86% (1087) RX v 87% (1110) PD (p=0.202). Of PLWH with <80% adherence by PD, 28% (29/104) were classified with ≥80% adherence by RX. Conversely, 41% (52/127) patients classified with <80% adherence by RX had ≥80% adherence by PD. Changes in multi-tablet regimen (MTR) due to early discontinuation of a component (>90 d before discontinuation of remaining regimen drugs) were indicated in 16% (75/478) PLWH by RX and 13% (63/478) by PD (p=0.311). Of PLWH with a change in MTR by PD, 14% (9/63) were not reflected by RX as having any early drug discontinuation and an additional 37% (23/63) were indicated as having a change that differed in time >90 d from observed by PD. In total, 37% (473/1270) of study patients had one or more of these differences in duration, adherence, and/or MTR composition.

Conclusion: These data suggest a lack of concordance between what is prescribed and dispensed for over a third of PLWH. As dispensing data are more likely to reflect actual treatment, observational studies should include this information whenever possible.



500 INVESTIGATION OF A POTENTIAL COMPOSITE ENDPOINT FOR IMMUNOLOGIC NONRESPONDER TRIALS

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Background: Although most people with HIV (PWH) experience robust CD4 recovery after achieving virologic suppression on antiretroviral therapy (ART), immunologic non-responders (INR) have persistently low CD4 T cell counts. Studies suggest INRs have an increased risk of mortality and serious morbidity, but these events are uncommon in ART-treated PWH and may not be feasible trial endpoints. Patient advocates urged FDA to encourage drug development for INRs by providing guidance on acceptable endpoints for INR trials.Therefore, we investigated the feasibility of a composite endpoint designed to capture non-serious and serious adverse events associated with CD4 lymphopenia.

Methods: Among Phase 3 clinical trial datasets submitted to the FDA (2005-2016) in support of ART approval for ART-naïve adults, we identified datasets with 144 wks of HIV RNA, CD4, and safety data. We excluded subjects with virologic failure between Wks 24 and 144 and, based on the Week 96 CD4 value, categorized subjects as INR (CD4 <200 cells/μL), immunologic responders (IR, CD4 200 – 349 cells/μL) or optimal immunologic responders (OIR, CD4 ≥ 350 cells/μL). Using safety data between Wks 96 and 144 and descriptive statistics, we evaluated differences in our composite endpoint, which included 1993 CDC HIV Classification System events (Categories A, B and C [not limited by duration, response to tx, or recurrence]), non-AIDS related events included in the START study, HPV-related disease, skin and soft tissue infections, and neurocognitive events.

Results: 79 (1.7%) participants met criteria for INR, 481 (10.3%) for IRs, and 4110 (88%) for OIRs. INRs were older (41.8 yrs) compared to IRs (39.6 yrs) and OIRs (36.7 yrs). INRs had lower baseline CD4 (64 c/μL) compared to IRs (152 c/μL) and OIRs (381 c/μL) and were more likely to have enrolled in a trial that started before 2010 (63% of IRs) than IRs (52.2%) and OIRs (20.2%). The composite endpoint occurred in 17 (21.5%) INRs, 92 (19.1%) IRs, and 709 OIRs (17.2%).

Conclusion: INRs were uncommon among ART-naïve adults starting ART in the 2000s, and even more uncommon after 2010. Like previous studies, INRs were older with lower baseline CD4 counts. The proportion of INRs experiencing the composite endpoint was slightly higher compared to IRs and OIRs. Our results suggest our composite endpoint is not a feasible endpoint for clinical trials evaluating drugs to treat INRs.

Table 1: Study Results. Numbers of participants (percent) are shown for categorical data. For age, CD4, and HIV RNA, means are shown with standard deviations.

		INR (n=79)	IR (n=481)	OIR (n=4110)	Total (n=4670)
Baseline demographics and immune parameters					
Age (years)		41.8 (11.1)	39.6 (9.8)	36.7 (10.1)	37.1 (10.1)
Sex	Female	15 (19.0%)	91 (18.9%)	601 (14.6%)	707 (15.1%)
	Male	64 (81.0%)	390 (81.1%)	3509 (85.4%)	3963 (84.9%)
Baseline CD4+ T-cell Count (cells/μL)		64 (50)	152 (103)	381 (180)	352 (189)
Baseline HIV Viral Load (log copies/mL)		5.05 (0.57)	4.97 (0.63)	4.70 (0.64)	4.73 (0.64)
Start of Study	2003- 2010	50 (63.3%)	251 (52.2%)	830 (20.2%)	1131 (24.2%)
	2010 -2013	29 (36.7%)	230 (47.8%)	3280 (79.8%)	3539 (75.8%)
Adverse Events					
Subjects with AEs in the composite endpoint, n (%)		17 (21.5%)	92 (19.1%)	709 (17.3%)	818 (17.5%)
Subjects with AEs in the following event categories, n (%)					
Subjects with AEs by event categories, n (%)	Death	0	1 (0.2%)	1 (<0.1%)	2 (<0.1%)
	1993 CDC Category C Events (Not limited by duration, response to treatment, or recurrence)	9 (11.4%)	13 (2.7%)	144 (3.5%)	166 (3.6%)
	1993 CDC Categories A and B Events	6 (7.6%)	46 (9.6%)	355 (8.6%)	407 (8.7%)
	Serious Non-AIDS-related events	0	5 (1.0%)	18 (0.4%)	23 (0.5%)
	Neurocognitive, HPV-related, and skin/soft tissue events	5 (6.3%)	35 (7.3%)	263 (6.4%)	303 (6.5%)

501 TREATMENT INTERRUPTION STRATEGIES FOR NNRTI-BASED ART: DOES THE NRTI MATTER?

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Background: In the SMART trial, simultaneously stopping NRTIs and NNRTIs resulted in emergence of drug resistance mutations (DRMs) and lower HIV-RNA resuppression rates compared to either a PI-switch strategy or staggered discontinuation of the NNRTI before the NRTIs. This finding was proposed to be related to the longer half-life ($T_{1/2}$) of NNRTIs compared to NRTIs, resulting in short-term NNRTI monotherapy. We postulated that since TDF has a long intracellular $T_{1/2}$ (>60 hrs), stopping NNRTI-based ART containing TDF simultaneously may not result in lower resuppression rates or more resistance.

Methods: A reanalysis of the SMART study was undertaken in participants who interrupted NNRTI-based ART and later restarted an NNRTI regimen. Participants were included who had HIV-RNA<400 c/mL at ART discontinuation and had an HIV-RNA level drawn 4-8 months after restart to assess resuppression. For individuals who had HIV RNA >1000 c/mL at 2 months after ART interruption and had standard HIV genotypic testing (TRUGENE), presence of NNRTI or NRTI DRMs was assessed. Results are given according to stopping approach, separately for TDF vs. non-TDF use.

Results: Of the 513 participants who met the inclusion criteria, 319 (62.2%) received EFV, and 194 (37.8%) received NVP. Stopping was simultaneous in 100 (19.5%) participants, staggered in 302 (58.9%), and switched in 111 (21.6%). Overall, 124 (24.2%) received TDF and 389 (75.8%) received other NRTIs (AZT, D4T, or ddI); in both groups the most common second NRTI was 3TC or FTC. Irrespective of TDF use, resuppression was lowest with simultaneous stopping and highest with a switch strategy (Table). Among those who stopped simultaneously, there was no difference between TDF or non-TDF group for rate of resuppression (95% CI for difference: -26.3, 8.2; p=0.27) or percent with NNRTI DRM (95% CI for difference: -0.9, 34.3; p=0.20). Results were similar for those stopping EFV and NVP (data not shown).

Conclusion: Despite TDF having a longer intracellular $T_{1/2}$ than other NRTIs, the resuppression rate after simultaneously stopping all ARVs in an NNRTI-regimen was not different for TDF versus non-TDF regimens, nor did TDF prevent emergence of DRMs. Though limited by small number of subjects on TDF, these data support the current recommendation that if stoppage of an NNRTI-based regimen is planned, ARVs should not be stopped simultaneously. This is particularly crucial when stopping NNRTI regimens during analytical ART interruption trials.

	NNRTI Stopping Method / Baseline TDF or non-TDF Use					
	Simultaneous		Staggered		Switched	
	TDF	non-TDF	TDF	non-TDF	TDF	non-TDF
Restarted NNRTI with HIV-RNA available 4-8 months after restart, n	30	70	64	238	30	81
HIV-RNA resuppression at 4-8 months after restart, n (%)	23 (76.7)	60 (85.7)	56 (87.5)	217 (91.2)	28 (93.3)	78 (96.3)
Median (IQR) log_{10} HIV RNA before ART restart	4.7 (4.1, 5.1)	4.8 (4.2, 5.1)	5.0 (4.3, 5.2)	4.8 (4.2, 5.1)	4.9 (4.6, 5.1)	5.0 (4.4, 5.3)
Mean (SD) months off ART prior to restart	6.9 (6.1)	7.2 (6.5)	6.2 (4.3)	6.9 (4.9)	6.6 (5.4)	6.4 (5.0)
Genotypic Resistance Testing 2 months after NNRTI-Regimen Discontinuation (n=141)						
Resistance testing, n	20	41	24	32	8	16
NNRTI DRMs, n (%)	5 (25.0)	5 (12.2)	1 (4.2)	6 (18.8)	0 (0.0)	1 (6.3)
NRTI DRM, n (%)	2 (10.0)	7 (17.1)	5 (20.8)	6 (18.8)	1 (12.5)	2 (12.5)

502 NO SIGNIFICANT CHANGE ON RESERVOIR IN QUATUOR: A 4/7 DAYS A WEEK MAINTENANCE STRATEGY

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Background: ANRS 170 QUATUOR study demonstrated the non-inferiority of a 4/7 days maintenance strategy vs a 7/7 days regimen in patients with controlled viral load (VL) under triple therapy with either PI, NNRTI, or InSTI based regimen at week 48 (W48). The aims of these virological sub-studies were to assess HIV cellular reservoir size, HIV residual viremia and HIV RNA quantification in semen until W48.

Methods: HIV total DNA was measured using the real-time PCR kit GENERIC HIVDNA Cell® (Biocentric®, Bandol, France) with a limit of quantification [LOQ] of 10 copies/PCR. Ultra-sensitive plasma VL (USpVL) and semen HIV VL (1/5 dilution) were determined using COBAS® HIV-1, v2.0 (Roche Molecular Systems, Branchburg, NJ, USA). For USpVL, the limit of detection (LOD) was defined as an undetected PCR signal. Generalized estimating equation was used to compare the changes from baseline of total HIV DNA, plasma seminal VL and plasma blood residual viremia within and between the 2 groups over time.

Results: Characteristics of sub-study population were similar to those of global trial population. Paired D0 and W48 HIV total DNA were obtained in 119 patients. 45% and 44% of patients showed a HIV DNA below the LOQ at D0 and W48 respectively. Median (IQR) HIV DNA was 1.7 log_{10} c/10^6 PBMC (<1.3-2.3) at D0 and 1.6 (<1.3-2.4) at W48 in the 4D arm versus 1.9 (<1.3-2.3) and 1.7 (<1.3-2.3) in the 7D arm. Plasma residual viremia was measured in 116 patients at D0 and W48 with a proportion of patients with USpVL detectable of 17.3 % and 26.9% respectively in the 4D arm and 21.9% and 29.7 % in the 7D arm. Semen HIV RNA was measured in 78 patients with a proportion of semen VL detectable in 2.3% at D0 and 6.7% at W48 in the 4D arm versus 6.1% and 9.1 % in the 7D arm. There is no significant evolution in HIV DNA, residual viremia and semen VL between D0 and W48 and no significant difference between arms.

Conclusion: No change was observed during the first year of 4/7 days maintenance therapy in plasma residual viremia level or in HIV cellular reservoir size, as in the 7/7 days. These findings are reassuring the potency of a 4D/7 maintenance strategy on virological suppression at the level of residual viremia.

503 CLINICAL SIGNIFICANCE OF gp120 POLYMORPHISMS, TMR IC_{50}FC AND HIV-1 SUBTYPE IN BRIGHTE

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Background: The ongoing Ph3 BRIGHTE study is evaluating Fostemsavir (FTR), an investigational prodrug of the first-in-class attachment inhibitor temsavir (TMR), in heavily treatment-experienced (HTE) participants with multi-drug resistant HIV-1 infection who are unable to form a viable regimen from fully active ARV agents. We present the impact of key baseline (BL) factors on short-term virologic outcome and durability of response to FTR in the Randomized Cohort (RC).

Methods: RC participants, with 1-2 fully active ARVs were randomized (3:1) to blinded FTR 600 mg (n=203) or placebo (n=69) BID plus failing regimen for 8 days of functional monotherapy, followed by open-label FTR 600mg BID plus optimized background therapy (OBT; n=272). The impact of BL factors: gp120 polymorphisms, TMR IC_{50} fold-change (FC), and HIV-1 subtype, on change in HIV-1 RNA from Day 1 to 8, proportion of participants with a clinically relevant (>0.5log_{10}) decrease in HIV-1 RNA at Day 8, and HIV-1 RNA <40 c/mL at W96, was evaluated.

Results: Overall, 46% (122/263) of evaluable RC participants had a relevant gp120 polymorphism present at BL. Median change in HIV-1 RNA at Day 8 was lower among monotherapy participants with vs without BL gp120 polymorphisms of interest (-0.65 log_{10} vs -1.03 log_{10}). However, 55% (48/88) of participants with BL gp120 polymorphisms achieved a viral load reduction >0.5 log_{10} at Day 8. BL TMR IC_{50}FC from reference was observed over a broad range (0.05 to >5,000-fold; median 0.99-fold) with 74% (195/263) and 87% (229/263) of evaluable participants with TMR IC_{50}FC <10- and <100-fold, respectively. While monotherapy participants with TMR IC_{50}FC >100-fold at BL had a median change in HIV-1 RNA of <0.5 log_{10} at Day 8, this did not prevent a decline >0.5 log_{10}. In fact, 38% (8/21) of participants with BL TMR IC_{50}FC >100-fold achieved >0.5 log_{10} decline over this time. The majority of participants in the RC (79%, 216/272) had HIV-1 subtype B virus. Similar proportions of monotherapy participants with subtype B (66%, 108/163) vs non-B (65%, 26/40) virus achieved >0.5 log_{10} decline in HIV-1 RNA at Day 8; although the number of participants with non-B subtype, including AE, was small (n= 40 and 1, respectively).

Conclusion: In BRIGHTE, BL gp120 polymorphisms of interest, TMR IC_{50}FC, and HIV-1 subtype did not reliably predict virologic outcome at Day 8 of FTR functional monotherapy and did not impact durability of response (HIV-1 RNA <40 c/mL) to FTR + OBT through 96 weeks of therapy, among HTE participants in the RC.

Table. Virologic Response to FTR at Day 8 of Functional Monotherapy and Week 96 by Baseline Factors in the Randomized Cohort

	Randomized Cohort Monotherapy[a] FTR 600 mg BID (N=203)			Randomized Cohort Total FTR 600 mg BID + OBT (N=272)	
	Median Change in HIV-1 RNA from Day 1 to Day 8 log_{10} c/mL (min, max)[b]	n	Virologic Response >0.5 log_{10} c/ml from Day 1 to Day 8 n (%)	n	HIV-1 RNA <40 c/mL at Week 96 n (%)
Baseline gp120 Polymorphisms Sequenced	-0.92 (-2.70, 1.25)	194	127 (65)	263	160 (61)
No pre-defined polymorphisms of interest in gp120	-1.03 (-2.70, 1.25)	106	79 (75)	141	87 (62)
With pre-defined polymorphisms of interest in gp120[c]	-0.65 (-2.17, 1.16)	88	48 (55)	122	73 (60)
S375H/I/M/N/T	-0.82 (-2.17, 1.16)	64	38 (59)	86	52 (60)
M426L	-0.36 (-1.92, 0.35)	22	10 (45)	32	18 (56)
M434I	-1.04 (-2.03, 1.16)	9	5 (56)	17	9 (53)
M475I	0.47 (0.47, 0.47)	1	0	3	3 (100)
Multiple pre-defined polymorphisms of interest in gp120	- 1.18 (-1.92, 1.16)	8	5 (63)	16	9 (64)
Baseline TMR IC50 FC Category Phenotyped	-0.88 (-2.70, 1.25)	194	126 (65)	263	160 (61)
≤0.5	-1.02 (-2.11, 1.25)	71	50 (70)	93	50 (54)
>0.5 - 1	-1.08 (-2.70. 0.24)	27	21 (78)	39	23 (59)
>1 - 10	-0.89 (-2.46, 0.80)	53	36 (68)	63	44 (70)
>10 - 50	-0.69 (-2.11, 1.16)	19	9 (47)	26	19 (73)
>50 - 100	-0.61 (-1.14, -0.07)	3	2 (67)	8	5 (63)
>100 - 1,000	-0.18 (-2.17, 0.35)	10	4 (40)	16	7 (44)
>1,000 - 5,000	-0.32 (-1.29, 0.47)	7	3 (43)	11	8 (73)
>5,000	-0.24 (-1.92, -0.01)	4	1 (25)	7	4 (57)
HIV-1 Subtype at Baseline All subtypes	-0.88 (-2.70, 1.25)	203	134 (66)	272	163 (60)
B	-0.92 (-2.70, 1.25)	163	108 (66)	216	125 (58)
F1	-0.76 (-1.61, 0.28)	14	9 (64)	20	14 (70)
BF1	-0.87 (-1.75, -0.01)	10	7 (70)	14	10 (71)
C	-0.82 (-2.02, 0.05)	6	5 (83)	9	4 (44)
A1	-0.10 (-0.32, 0.13)	2	0	2	1 (50)
AE	0.47 (0.47, 0.47)	1	0	2	1 (50)
Other[d]	-1.08 (-2.11, 1.16)	7	5 (71)	9	8 (89)

a. FTR Monotherapy refers to functional monotherapy where FTR is given on a background of failing ARV therapy.
b. Does not include participants with missing Day 1 or Day 8 HIV-1 RNA values.
c. Pre-defined polymorphisms of interest in gp120 domain are S375H/I/M/N/T, M426L/P, M434I/K, M475I. No participants had M426P or M434K present at Baseline
d. Other includes: Non-analyzable/Not reported, G; AG; D; A; BF; Recombinant virus/Mixtures.

504 A HIGHLY POTENT AND SAFE ALLOSTERIC HIV-1 INTEGRASE INHIBITOR, STP0404

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Background: Allosteric HIV-1 integrase inhibitors (ALLINIs) are a new class of HIV-1 inhibitors, targeting HIV-1 maturation process. While great efforts have been made for the discovery of ALLINIs, clinical development of ALLINIs

has not been successful mainly due to their preclinical limitations. We recently discovered a highly potent and safe IN inhibitor STP0404 with outstanding antiviral efficacy and preclinical properties, which will be pursued for its clinical evaluations in early 2020.
Methods: Anti-HIV activity of STP0404 was determined by tissue cultures. Electron microscopy and X-ray crystallographic methods were employed for understanding the action mechanism and binding site of STP0404. STP0404 resistance mutations were selected in tissue cultures, and their locations were confirmed by X-ray crystallography. The physicochemical properties and ADMET-related experiments were carried out by standard methods. The preclinical animal toxicity studies have been completed in rats and dogs: rats at 100, 300, and 600 mg/kg for 28 days and beagle dogs at 30, 60, and 90 mg/kg for 28 days. A nano-formulation study was conducted to confirm the possibility of long acting. Finally, testing the effect of STP0404 on HIV-1 rebound from latency infected reservoir T cells also has been completed.
Results: We confirmed excellent tissue culture antiviral activities of STP0404 against both wild-type and Raltegravir-resistant HIV-1 strains with sub-nanomolar EC_{50} values. The co-crystal structure confirmed its binding site to the cleft formed between two IN monomers and known to be the host LEDGF/p75 binding site, and EM study validated its activity to block HIV-1 maturation by mislocalizing HIV-1 RNA genomes outside of viral capsid. Two STP0404 resistant mutations (Y99H and A128T) were selected and co-crystal structure confirmed their locations near the STP0404 binding site. STP0404 also showed outstanding in vivo PK profiles and ADMET properties. There was no significant GLP toxicity issues observed in rodent and non-rodent species. We check the therapeutic potential of long-acting ARV due to the pmol-range potency. Finally, STP0404 displayed effective suppression of the HIV-1 rebound in lately infected T cells.
Conclusion: STP0404 is a highly potent and safe ALLINI with picomolar EC_{50} values in tissue culture as well as outstanding preclinical properties in animals, which will be soon pursued for its clinical evaluations for oral application as well as long-acting formulations.

Summary of GLP toxicology study

	Study*	Results	Comments
Genetic Toxicity	Ames	Negative	STP0404 had no gene mutation-inducing potential in any of the 5 bacterial strains
	Chromosome aberration	No effects	STP0404 had no chromosomal aberrations-inducing potential in the CHL/IU cells
	Micronucleus test in Rats	No effects	STP0404 had no micronucleus-inducing and bone marrow cell proliferation inhibitory potentials
Safety Pharmacology	FOB in Rat	No effects	There was no effect on CNS
	Respiratory in Rat	No effects	There was no effect on the respiratory system
	CV in Dog	No effects	There was no effect on CV system
4-wk GLP repeated toxicity study	Rat 4w+R2w Tox study	No issues	There were no test article-related clinical signs and toxic changes at doses until 600 mpk
	Dog 4w+2w Tox study	No issues	There were no test article-related clinical signs and toxic changes at doses until 90 mpk

*All GLP toxicology studies were carried out by INA Research in Japan, and the histopathology studies were evaluated by Anapath in Switzerland

505 PRECLINICAL DEVELOPMENT OF SECOND GENERATION HIV-1 MATURATION INHIBITORS

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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 bind inside a six-helix bundle that assembles at the junction of CA and SP1 in the immature Gag lattice. Proof-of-concept for MIs was established with bevirimat (BVM), which was found safe and effective in reducing viral load in infected individuals. However, a single amino acid polymorphism in the SP1 region of Gag (V7A) reduced susceptibility to BVM.
Methods: We identified three C-28 alkyl amine BVM derivatives (compounds A-C) that exhibited potent activity against BVM-resistant polymorphs. These compounds were characterized for in vitro activity against i) a panel of primary HIV-1 clinical isolates representing subtypes A-G and ii) a set of viruses resistant to the approved classes of HIV-1 drugs. In vitro metabolic stability was characterized in human, rat, mouse, dog and monkey liver S9 fractions. Binding to human plasma proteins was determined using i) equilibrium dialysis and ii) in vitro activity assays employing human serum concentrations of 0-40%. In vivo pharmacokinetic studies were carried out in mice. Resistance selection experiments were carried out using both subtype B and C isolates.
Results: All compounds exhibit potent antiviral activity. Compound A exhibited an average IC_{50} value of 7.3nM against a panel of 12 primary isolates including those with the BVM-resistant SP1 V7A genotype (n=5). Compounds B and C inhibit HIV-1 with average IC_{50} values against V7 virus of 7.9 and 14.9nM and against A7 isolates of 48.2 and 138.7nM, respectively. A, B and C inhibit drug resistant virus with average IC_{50} values of 3.1, 1.0 and 1.2nM, respectively (n=6). All compounds were metabolically stable in liver S9 fractions across species, demonstrated plasma protein binding of >99% and were orally bioavailable in the mouse. By using low concentrations of inhibitor, resistance-conferring mutations were identified.
Conclusion: As resistance to approved HIV therapies develops new drugs will be needed. MIs employ a novel mechanism to block HIV replication and could replace drugs that are no longer effective due to resistance. Compounds A-C exhibit pre-clinical development profiles similar or superior to MI drug candidates that have advanced to the clinic. Based on these results, we plan to continue development activities for each compound.

506 PHASE II TRIAL OF VPU INHIBITOR BIT225 IN COMBINATION WITH ANTIRETROVIRAL THERAPY

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Background: Vpu is a HIV-1 encoded membrane protein with multiple regulatory functions that enhance HIV-1 replication fitness and promote innate immune evasion in multiple cell types including monocytes. BIT225 inhibits HIV-1 replication in myeloid cells in vitro. BIT225 has been studied in patients with chronic HIV-1 infection receiving antiretroviral therapy (ART).
Methods: A randomized, placebo controlled, double-blind, Phase 2 study of BIT225 in individuals with HIV-1 commencing ART (males and females, aged 18 to 65 years, viral load >5,000 copies/mL; CD4+count >100 cells/mm_3, ART naïve). HIV-1 infected individuals recruited from two sites in Thailand were treated with either BIT225 or placebo in addition to ART (Atripla) for 12 weeks. Individuals were randomized 2:1 (BIT225: placebo). Markers of viral replication and immune functions were investigated.
Results: Thirty-six patients were enrolled. Plasma HIV-1 RNA levels declined with similar viral decay kinetics in both cohorts over the 12 week study period. In contrast, significant changes were observed for multiple immune markers between the 2 cohorts. Levels of the monocyte activation marker sCD163 showed significantly greater reduction from baseline ($P<0.05$, general linear model, two-way ANOVA) in the BIT225 treated cohort compared to ART alone over the 12 week treatment period. There was a statistically significant increase in activated CD8+, CD4+ cells, and NK cells in the BIT225 cohort. There was a transient statistically significant increase in plasma IL-21 production in the first 3 weeks of BIT225 therapy. There were no significant changes to plasma IL-6, TNF-alfa, and interferon-gamma in either cohort over the treatment period.
Conclusion: The addition of BIT225 to ART resulted in unique stimulation of multiple arms of the innate immune system. The increased numbers of CD8+, CD4+ and NK cells are consistent with enhanced recognition of HIV-1 infected cells. Vpu has been associated with reducing cell surface expression/function of numerous cellular proteins/receptors involved in viral antigen presentation to CD4+, CD8+ T cells and NK cells. The production of IL-21 by Tfh, Th17, and/or NK cells is a unique immunological consequence of addition of BIT225 to ART and offers the potential for treatment targeting different HIV-1 compartments during standard therapy.

507 COMPARABLE EFFICACY OF IBALIZUMAB IN COMBINATION WITH 1 OR 2 FULLY ACTIVE AGENTS

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Background: Current guidelines recommend a regimen containing at least two, preferably three, fully active agents to suppress viremia in HIV treatment-

experienced patients. However, identifying three fully active agents presents a challenge for some multidrug resistant (MDR) HIV patients. Ibalizumab (IBA), a CD4-directed post-attachment HIV-1 inhibitor, is approved for MDR patients failing their ART regimen. We sought to determine if IBA had comparable and durable virologic efficacy in patients with one versus two other fully active agents.

Methods: Patients received IBA 2000mg loading dose followed by 800mg doses every 2 weeks up to Week 25 in TMB-301. An optimized background regimen (OBR) with ≥1 additional fully active agent was added 7 days after starting IBA. Following completion of TMB-301, eligible patients continued to receive IBA every 2 weeks under study TMB-311.

Results: In TMB-301, 12 of the 40 patients had one fully active agent paired with IBA (OSS1) and 18 patients had two fully active agents with IBA (OSS2). Baseline median viral load (VL) and CD4 counts were 65,000 and 20,000 copies/mL and 57 and 89 cells/mm_3 for the OSS1 and OSS2 patients, respectively. In OSS1 patients, fully active agents in addition to IBA were fostemsavir (n=6), DTG (n=4), TDF (n=1), and RPV (n=1). Of these, 11 (92%) had >0.5log_{10} VL decrease on IBA functional monotherapy after 7 days. At Week 25, 5 of the 7 OSS1 completers (71%) achieved <50 copies/mL, of which three were on fully active DTG. At Week 96, 5 of 7 OSS1 patients (71%) maintained viral suppression, which continued until they transitioned to commercial supply (some up to Week 124). In OSS2 patients, 13 of 18 (72%) reached a >0.5log_{10} VL decrease after IBA functional monotherapy. At Week 25, 9 patients (50%) with OSS2 achieved <50 copies/mL, 7 of which were on a fully active DTG regimen, demonstrating similar virologic efficacy when IBA is paired with one or two fully active agents. At Week 96, viral suppression was maintained in 9 patients and they continued on IBA until commercial was available (some up to Week 140).

Conclusion: Subgroup analyses of TMB-301/311 data show significant efficacy of IBA among patients with one or two other fully active agents, with durable responses regardless of the number of active agents. Patients who combined IBA with DTG showed impressive rates of suppression. Data support the long-term efficacy of IBA-based regimens that include two or three fully active agents.

508 A PHASE I DOSE-ESCALATION TRIAL OF HUMAN MONOCLONAL ANTIBODY N6LS IN HEALTHY ADULTS

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Background: Developing monoclonal antibodies that broadly neutralize HIV-1 (bnMAbs) through passive transfer is a key goal in the prevention and treatment of HIV-1 infection. N6LS is a bnMAb isolated from a patient who was HIV infected for 21 years and was not on antiretroviral treatment. It was produced as an IgG1 with an LS mutation to the Fc region to increase half-life through increased binding affinity to the neonatal Fc receptor. N6LS targets the CD4-binding site (CD4bs) of the HIV-1 envelope glycoprotein and is a member of the VRC01 class of CD4bs antibodies. It is broader and more potent than VRC01, neutralizing up to 98% of viral strains. N6LS achieves this via two recognition characteristics. First, it is minimally insensitive to mutations in the variable gp120 V5 loop that typically diminish contacts and interrupt binding in other CD4bs antibodies. Second, it binds at a unique angle that avoids steric clashes with the highly glycosylated V5 region, which is a major mechanism of resistance for other bnMAbs in this class.

Methods: We conducted a first-in-human dose-escalation open-label phase 1 clinical trial of N6LS in healthy HIV-1 negative adults aged 18-50 to determine its safety, tolerability, and pharmacokinetic (PK) profile. Three groups received a single IV dose of 5, 20, or 40 mg/kg, and one group received a single SC dose of 5 mg/kg. Two groups received three doses of either 5 mg/kg SC or 20 mg/kg IV at 12-week intervals.

Results: We enrolled 23 volunteers between June 18, 2018 and February 12, 2019, including 9 (39%) males and 14 (61%) females. 22 participants received all N6LS administrations for a total of 42 product administrations. N6LS was safe and well tolerated with no SAEs or dose-limiting toxicities. No infusion reactions occurred. All reported reactogenicity was mild to moderate in severity. Initial PK up to 4 weeks following initial N6LS administration from 21 subjects showed that maximum (C_{max}) and 4 week post-infusion serum concentrations increased proportionally with antibody dose (Table 1). Estimated half-life exceeded 30 days in all 15 subjects with at least 12 weeks of PK results. This preliminary analysis has shown that N6LS demonstrates linear PK with a promising half-life for infrequent administration.

Conclusion: N6LS was safe and well tolerated by IV and SC administration and displayed encouraging PK parameters. Given its high neutralization breadth and potency, N6LS is a promising candidate for inclusion in HIV-1 prevention and therapeutic strategies.

Table 1. N6LS mean pharmacokinetic parameters by group

Group and dose	C_{MAX}	AUC	4 weeks post-infusion conc.
		Mean (SD)	
Intravenous Dosing			
5 mg/kg (n=3)	101 (23)	746 (72)	32 (2.3)
20 mg/kg (n=7)*	589 (236)	4363 (1751)	96 (25)
40 mg/kg (n=3)	1717 (50)	11814 (1321)	254 (38)
Subcutaneous Dosing			
5 mg/kg (n=8)*	27 (10)	541 (219)	15 (6.1)

Pharmacokinetic 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
*combined values from single dose arm and first dose of multiple dose arms

509 PREEXISTING RESISTANCE AND B/F/TAF SWITCH EFFICACY IN AFRICAN AMERICANS

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Background: The BRAAVE 2020 study is evaluating the safety and efficacy of switching to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) among virologically suppressed adults with HIV in the US who identify as Black or African American. Here, we present resistance analyses and impact on virologic outcomes at Week 24.

Methods: Participants with prior treatment failure and documented resistance to NNRTIs, PIs and/or NRTIs were eligible for enrollment with the exception of tenofovir resistance (K65R/E/N, 3 or more thymidine analogue mutations [TAMs], or T69-insertions); primary INSTI resistance (-R) was exclusionary. Pre-existing drug resistance was assessed with historical genotypes and retrospectively with baseline proviral DNA genotyping (GenoSure Archive, Monogram Biosciences). Participants with exclusionary resistance detected post-randomization were allowed to remain on study. Outcomes were determined by last on-treatment HIV-1 RNA through Week 24.

Results: Of the 493 participants analyzed for efficacy, 328 switched to B/F/TAF and 165 stayed on their 3-drug baseline regimen (SBR). Cumulative baseline protease and reverse transcriptase data from historical and/or proviral genotypes were available for 96% (471/493). Pre-existing primary NRTI-R, NNRTI-R, and PI-R substitutions were observed in 15% (70/471), 21% (101/471), and 13% (60/471), respectively. The most commonly detected NRTI-R substitutions were M184V/I in 11% (51/471) and TAMs in 7.2% (34/471). Baseline integrase data were available for 91% (450/493). Primary INSTI-R was detected post-randomization in 4.2% (19/450) by proviral genotype. Resistance substitutions were similar across treatment groups (Table 1). Among B/F/TAF-treated participants, >99% (326/328) were suppressed at their last visit through Week 24 including 100% (44/44) with NRTI-R (31 of whom had archived M184V/I), 99% (68/69) with NNRTI-R, 100% (34/34) with PI-R, and 100% (15/15) with INSTI-R. Four participants were analyzed for resistance development on study (3 B/F/TAF, 1 SBR); none had treatment emergent resistance to study drugs.

Conclusion: Pre-existing resistance was common among suppressed Black Americans switching to B/F/TAF, notably M184V/I, TAMs, and NNRTI-R. High rates of virologic suppression were maintained through 24 weeks of B/F/TAF treatment and there were no failures with resistance, indicating that B/F/TAF is an effective treatment option for patients with or without pre-existing resistance to NNRTIs, PIs, or non-tenofovir NRTIs.

Table 1. BRAAVE 2020 Pre-existing Resistance and Virologic Suppression at Week 24 (Last On-treatment Observation Carried Forward)

Resistance Category	Proportion of Participants (n/N)			
	B/F/TAF		SBR	
	Total	HIV-1 RNA <50 copies/mL	Total	HIV-1 RNA <50 copies/mL
All participants	328	99.4% (326/328)	165	98.2% (162/165)
Baseline PR/RT data	95.4% (313/328)	99.4% (311/313)	95.8% (158/165)	98.1% (155/158)
NRTI-R	14.1% (44/313)	100% (44/44)	16.5% (26/158)	100% (26/26)
M184V/I	9.9% (31/313)	100% (31/31)	12.7% (20/158)	100% (20/20)
TAMs	6.4% (20/313)	100% (20/20)	8.9% (14/158)	100% (14/14)
NNRTI-R	22.0% (69/313)	98.6% (68/69)	20.3% (32/158)	93.8% (30/32)
RPV-R[1]	8.9% (28/313)	100% (28/28)	7.6% (12/158)	91.7% (11/12)
PI-R	10.9% (34/313)	100% (34/34)	16.5% (26/158)	96.2% (25/26)
Baseline IN data	91.8% (301/328)	99.3% (299/301)	90.3% (149/165)	98.7% (147/149)
INSTI-R	5.0% (15/301)	100% (15/15)	2.7% (4/149)	100% (4/4)

1. Rilpivirine (RPV) associated resistance defined as having ≥1 of the following substitutions in RT: L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, or M320I/L.

510 TRANSMITTED DRUG RESISTANCE IN PEOPLE LIVING WITH DIAGNOSED HIV IN CALIFORNIA

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Background: Increased antiretroviral use for treatment and prevention raises concern that rates of transmitted drug resistance may increase. We analyzed a population-based dataset of HIV-1 pol sequences to estimate the prevalence of transmitted drug resistance-associated mutations (DRAMs) in people living with HIV in California from 2008-2018 and evaluated the transmission potential of identified mutations.

Methods: HIV-1 pol sequences reported to the California HIV surveillance system were analyzed via the SIERRA HIV Drug Resistance Database to determine resistance mutations and COMET to determine subtype. This analysis was limited to sequences that were obtained within 3 months of an HIV diagnosis with documentation of no previous exposure to antiretrovirals. DRAMs were defined based on the CDC surveillance resistance mutation list. We used HIV-TRACE to construct genetic transmission networks. Clustering was defined as two or more linked sequences with a pairwise genetic distance of ≤ 1.5%. Among ART-naïve persons, we compared the frequency of clustering of sequences with at least one DRAM compared with sequences without any DRAMs.

Results: Of 17,103 sequences (93.9% subtype B) obtained within 3 months of an HIV diagnosis, antiretroviral history was available for 5,740 sequences and 3,616 sequences had documentation of no prior antiretroviral exposure. Of the 3,616 sequences from antiretroviral-naïve persons, 1,480 (40.9%) clustered with at least one other sequence in 212 dyads and 194 larger clusters ranging from 3 to 28 sequences (median=4). In most clusters (83.3%), male-to-male sexual contact was the most common reported risk behavior. The prevalence of any DRAM in a sequence from an antiretroviral-naïve person was 20.0%; NNRTI, NRTI, and PI mutations were detected in 11.7%, 7.5%, and 4.3% of sequences, respectively. The integrase region was sequenced in a subset of 473 persons and the prevalence of an integrase DRAM was 1.5%. Compared to sequences without a mutation, a higher proportion of sequences with an NNRTI mutation clustered (rate ratio [RR] 1.20) whereas a lower proportion of NRTI mutations clustered (RR=0.70) [Table].

Conclusion: This population-based drug-resistance analysis demonstrated sustained DRAM transmission, particularly NNRTI mutations, among antiretroviral-naïve people. Although reassuring that NRTI mutations were associated with less clustering, a proxy for reduced further transmission, this finding should continue to be monitored as exposure to NRTIs increases with the expansion of pre-exposure prophylaxis.

Table. DRAM prevalence by ART class and by select mutations[1] and frequency of clustering with ART-naive HIV-infected people living with HIV

DRAM class and selected mutations	Total N	Prevalence	Clustering N	Clustering %	Rate ratios of clustering (95% confidence intervals)
Any DRAM	723	20.0%	305	42.2%	1.04 (0.94-1.14)
NNRTI mutation	423	11.7%	206	48.7%	1.20 (1.08-1.33)
NRTI mutation	273	7.5%	78	28.6%	0.70 (0.58-0.85)
PI mutation	156	4.3%	61	39.1%	0.96 (0.79-1.18)
K103N (NNRTI)	288	8.0%	142	49.3%	1.24 (1.09-1.40)
K103S (NNRTI)	50	1.4%	38	76.0%	1.90 (1.62-2.24)
M41L (NRTI)	65	1.8%	14	21.5%	0.51 (0.32-0.82)
T69N (NRTI)	52	1.4%	5	9.6%	0.23 (0.10-0.53)
T215S (NRTI)	43	1.2%	16	37.2%	0.89 (0.60-1.31)
T215D (NRTI)	39	1.1%	11	28.2%	0.67 (0.41-1.11)
M184V (NRTI)	35	1.0%	8	22.9%	0.55 (0.30-1.00)
L90M (PI)	57	1.6%	35	61.4%	1.50 (1.21-1.85)

[1]A prevalence cutoff of 1% was used for select mutations included in the table.
Abbreviations: DRAM, drug resistance-associated mutations; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

511 TRENDS IN TRANSMITTED DRUG RESISTANCE IN SPAIN THROUGH THE PERIOD 2007-2018

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Background: Initial regimens currently recommended by treatment guidelines include high genetic barrier antiretrovirals (ARVs), thus it may be of interest to evaluate drug resistance mutations (DRM) and, specially, clinically relevant resistance. Here, we present data on trends in DRM and clinically relevant transmitted drug resistance to ARVs recommended for first-line treatment in Spain.

Methods: We analysed 6090 RT & Pro Fasta sequences from CoRIS (2007-2018). As Integrase resistance is not part of routine testing in naïve patients in Spain, we run a surveillance programme (2012-2018) and tested 1404 patients. We evaluated the prevalence of Transmitted DRM using the WHO 2009 list, and clinically relevant resistance with Stanford v8.8 Algorithm. First line regimens for each study period were those recommended by the Spanish treatment guidelines (GESIDA).

Results: Our results indicated a similar trend in NNRTIs and NRTIs TDR prevalence with values ranging from 2.4-5%. In regard to INsTIs TDR, we also described similar values with no significant changes over years. However, we observed a decrease in PIs TDR from 2016 (≤1% of prevalence). Clinically Relevant resistance to recommended first 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 2007-2018 are shown in the enclosed table.

Conclusion: While NNRTIs and NRTIs DRM prevalence remained stable in Spain through 2007-2018, we observed a slightly decrease in PIs and INsTIs DRM prevalence. Clinically relevant TDR to approved first line regimens showed a slow decline from 2007 to 2018. Resistance to INsTIs remains at very low levels. These findings, together with the very low prevalence of resistance to recommended first line NRTIs in 2015-2018 reinforce GESIDA recommendations on baseline resistance testing and test and treat strategies when starting PIs or INsTIs based regimens.

Period	NRTIs (%)	NNRTIs (%)	PIs (%)	INsTIs (%)
2007 (n=482)	3.3	5.6	1.4	*
2008-2009 (n= 1169)	3.5	4.3	0.6	*
2010-2011 (n=1298)	1.6	4.5	0.6	*
2012 (n=555)	2.5	4.7	1.1	
2013 (n=577)	1.2	8.1	0.9	0.2 (n=194)
2014 (n=582)	1.7	10.1	1.4	0 (n=98)
2015-2017 (n=821)	2.1	*	*	0.2 (n=817)
2018 (n=606)	0.8	*	*	1.0 (n=295)

*ARVs not recommended for 1st line

512 US HIV DRUG RESISTANCE: IMPLICATIONS FOR CURRENT AND FUTURE PrEP REGIMENS

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Background: HIV pre-exposure prophylaxis (PrEP) is a critical HIV prevention tool and a key component of plans to end the HIV epidemic, but its effectiveness might be diminished by drug resistant virus; M184V and K65R mutations have both been associated with PrEP failure. The U.S. National HIV Surveillance System (NHSS) collects HIV sequence data from clinical drug resistance testing. We used NHSS data to describe the prevalence of drug resistance mutations (DRMs) to approved (TDF/FTC) and investigational (cabotegravir, CAB) PrEP drugs among people with diagnosed HIV infection without evidence of recent viral suppression.

Methods: We analyzed all reverse transcriptase (RT) and integrase (IN) sequences in NHSS for people with HIV infection (PWH) diagnosed through December 2018 without evidence of viral suppression in 2018. DRMs were detected via the SIERRA web service and defined by the CDC HIV-1 surveillance mutation list. We reported DRM prevalence for nucleoside reverse transcriptase inhibitors (nRTIs), including TDF and FTC, and for integrase strand transfer inhibitors (INSTIs), including CAB. For people with >1 sequence, we reported combined DRMs from all sequences.

Results: In all, 268,065 people had ≥1 sequence and no evidence of viral suppression in 2018. Of the 232,429 people with ≥1 RT sequence, TDF/FTC DRMs were identified for 40,809 (17.6%) people (Table), including M184V (16.0%) and K65R (2.1%). Of the 80,669 people with ≥1 IN sequence, DRMs reported to affect CAB were identified for 3,308 (4.1%) people, including N155H (1.8%) and R263K (0.3%). Mutations affecting TDF/FTC and CAB were more common among females, blacks/African Americans, and for people with a transmission risk factor of injection drug use (IDU) or men who have sex with men who also reported IDU.

Conclusion: We report DRM prevalence among all PWH with RT or IN sequences in NHSS and without evidence of recent viral suppression to describe possible sources of HIV exposure for people on PrEP. We document an established reservoir of M184V and low prevalence of K65R and DRMs predicted to affect CAB. While M184V reduces susceptibility to FTC, its impact on PrEP efficacy remains unclear as it also reduces viral fitness and increases susceptibility to TDF. Differences in DRM prevalence by sex, race/ethnicity, and transmission risk suggest differential risk for exposure to HIV strains that might impact PrEP. Continued DRM monitoring is essential for identifying potential threats to PrEP effectiveness in an era of expanding use.

Table: Prevalence of selected drug resistance mutations among people with diagnosed HIV infection with ≥1 sequence reported to NHSS and without evidence of viral suppression in 2018, United States (N=268,065)

Sequence type (total people)	Mutation type	Total people with mutation (%)
Reverse transcriptase (N=232,429)	≥1 nRTI mutation	60,339 (26.0)
	≥1 TDF/FTC mutation	40,809 (17.6)
	≥1 FTC mutation	40,476 (17.4)
	M184V	37,074 (16.0)
	K70E	1,838 (0.8)
	≥1 TDF mutation	6,876 (3.0)
	K65R	4,838 (2.1)
Integrase (N=80,669)	≥1 INSTI mutation	5,085 (6.3)
	≥1 CAB mutation	3,308 (4.1)
	N155H	1,463 (1.8)
	R263K	263 (0.3)

513 COUNTRY-LEVEL DRIVERS OF NNRTI RESISTANCE IN SOUTHERN AFRICA

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Background: The rise in the prevalence of drug resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) in HIV-infected individuals initiating antiretroviral therapy (ART) is a major problem in countries of southern Africa. Understanding the dynamics and drivers of NNRTI resistance at the country level is of critical importance for planning future ART programs.
Methods: We first collected survey data on pretreatment drug resistance (PDR) to NNRTIs in nine countries of southern Africa from 2000 to 2018, including 66 studies and 14,639 individuals. We then fitted a mechanistic transmission model to key indicators of the local HIV epidemics (HIV prevalence, ART coverage and AIDS mortality) and the levels of PDR using a hierarchical Bayesian framework. For each country, we estimated the rate at which treatment failure with NNRTI resistance (TFNR) occurs during ART. We further explored the association between TFNR and socio-economic covariates.
Results: The model reliably described the local dynamics of HIV and the rise of NNRTI PDR, with the exception of Malawi and Zambia where data quality was insufficient. Predicted levels of NNRTI PDR in 2018 ranged between 4.7% (95% credible interval: 2.2, 9.8) in Mozambique and 32.8% (26.4, 38.7) in Namibia. The main driver of NNRTI resistance was the conjunction of ART coverage and the rate of TFNR. Estimates of the rate of TFNR were lowest in Botswana (0.002 per year; 0, 0.006) and highest in the Republic of South Africa (0.14 per year; 0.11, 0.17). The regional average of this rate was 0.07 per year (0.04, 0.25) corresponding to a probability of 8% (4, 22) that patients initiating ART show treatment failure due to the acquisition of NNRTI resistance after one year. TFNR was associated with external health expenditure (Pearson correlation: -0.43; -0.59, -0.19) and out-of-pocket health expenditure (0.39; 0.01, 0.75).
Conclusion: Even with the introduction of dolutegravir, NNRTIs will remain a central component of first-line regimen in southern Africa. Between-country comparison shows that NNRTI PDR can be controlled despite high levels of ART coverage, as in Botswana, likely because of better patient management and lower exposure to ART before treatment initiation. Our results suggest that the ability to control PDR is associated with features of the healthcare financing system at the national level. Additional data on NNRT PDR and ART management is urgently needed in some countries of southern Africa.

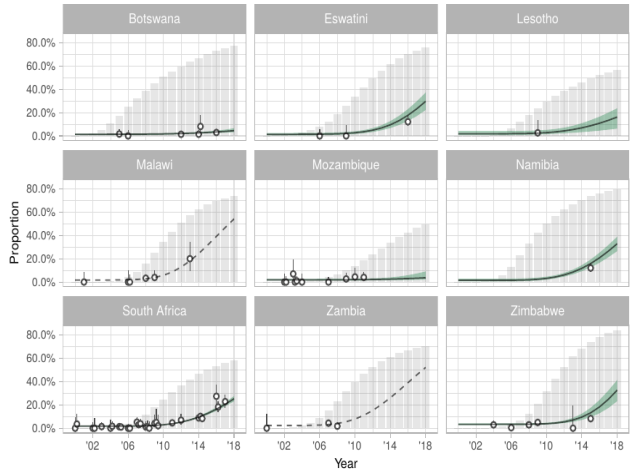


Figure 1: Evolution of pretreatment drug resistance (PDR) to NNRTI in nine countries of southern Africa from 2000 to 2018 following the roll-out of antiretroviral therapy (black lines and green areas show model-predicted PDR [median and 95% credible intervals], with the dashed lines highlighting countries excluded for low data quality; black circles show survey data [proportion and 95% credible intervals]; and gray bars show model-predicted coverage of antiretroviral therapy in each country).

514 ADVANCE TRIAL: HIGHER RISK OF TREATMENT-EMERGENT RESISTANCE ON FIRST-LINE TDF/FTC/EFV

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Background: In low- and middle-income countries, most treatment-naïve people living with HIV (PLWH) take first-line treatment with no baseline resistance testing. In the SINGLE trial, there was a significantly higher risk of treatment-emergent drug resistance in the TDF/FTC/EFV arm (1.7%) compared with the ABC/3TC/DTG arm (0.0%). In South Africa, over 10% of treatment-naïve patients have transmitted NNRTI drug resistance.
Methods: We conducted a 96-week, open-label randomised trial in South Africa, comparing TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV. Inclusion criteria included age ≥12 years, no prior ART >30 days, and HIV-1 RNA >500 copies/mL. There was no screening for baseline drug resistance, consistent with South African treatment guidelines. Patients with at least one HIV RNA result above 1000 copies/mL after 24 weeks of randomised treatment were genotyped prospectively, together with a test of their stored baseline sample. For this analysis, virological failure was classified as HIV RNA >1000 copies/mL at Week 12 or 24, >200 copies/mL at Week 24 or >50 copies/mL at Week 48 or later, while taking randomised treatment. The number of genotyped patients with treatment-emergent WHO major NRTI or NNRTI mutations was compared between the arms (Fishers exact test).
Results: We randomised 1053 PLWH between February 2017 and May 2018: 99% black, 59% female, mean age 32 years, with mean CD4 336 cells/uL. At week 48, the percentage of participants with HIV RNA <50 copies/mL was 83.8% for TAF/FTC/DTG, 84.9% for TDF/FTC/DTG and 78.6% for TDF/FTC/EFV. As shown in Table 1, NRTI or NNRTI emergent resistance at virological failure was more common for first-line treatment with TDF/FTC/EFV (10/14; 71%) compared with the combined TAF/FTC/DTG and TDF/FTC/DTG arms (2/23; 9%), p<0.01. The most common treatment-emergent NRTI mutations were M184V (n=5), K65R (n=2); most common NNRTI mutations were K103N (n=3), and P225H (n=2). Of the 10 patients developing NRTI or NNRTI RAMS at VF in the TDF/FTC/EFV arm, 8 (80%) already had at least one NRTI or NNRTI RAM at baseline. No treatment-emergent integrase mutations were observed.
Conclusion: In the ADVANCE study, there were similar rates of virological failure between the arms. However the patients in the TDF/FTC/EFV arm were significantly more likely to develop NRTI or NNRTI mutations at VF (71%) compared to the DTG arms (9%). Most patients with treatment-emergent resistance already had NRTI or NNRTI mutations at baseline.

Treatment arm	TAF/FTC/DTG	TDF/FTC/DTG	TDF/FTC/EFV
N	n=351	n=351	n=351
Virological failure (VF)	59 (17%)	68 (19%)	48 (14%)
VF with resistance test results	9	14	14
Treatment-emergent NRTI mutations	0 (0%)	2 (14%)	8 (57%)
Treatment-emergent NNRTI mutations	0 (0%)	0 (0%)	7 (50%)
Treatment-emergent NRTI or NNRTI mutations	0 (0%)	2 (14%)	10 (71%)
Any baseline NRTI or NNRTI mutations in patients with treatment-emergent NRTI or NNRTI mutations	-	2 (100%)	8 (80%)

515 PRETREATMENT AND ACQUIRED ANTIRETROVIRAL DRUG RESISTANCE IN 4 AFRICAN COUNTRIES

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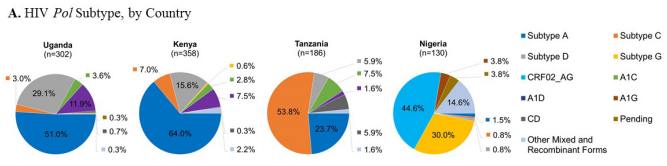
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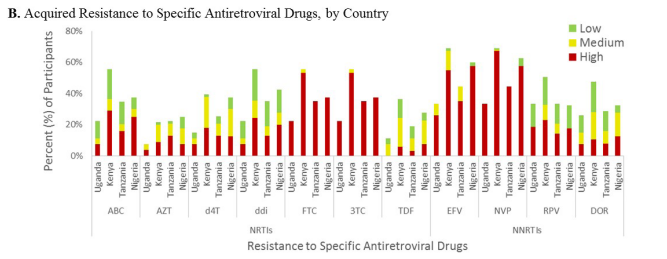
Background: Standardized HIV management protocols that emphasize adherence counseling and forego genotypic testing for HIV drug resistance (HIVDR) have facilitated expanded access to antiretroviral therapy (ART) in resource-limited settings. However, emerging HIVDR could jeopardize the success of such approaches. We characterized HIVDR among ART-naïve and experienced participants in the ongoing African Cohort Study (AFRICOS).

Methods: From January 2013 to July 2019, adults with HIV RNA ≥1000 copies/mL underwent HIVDR testing upon enrollment at 12 clinics in Uganda, Kenya, Tanzania, and Nigeria. ART history was obtained by medical record review. HIV pol subtype was assigned using five tools to achieve a consensus assignment. We calculated resistance scores for specific drugs and tallied major mutations to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) using Stanford HIVDB 8.8 and SmartGene IDNS software. For ART-naïve participants, World Health Organization surveillance drug resistance mutations (SDRMs) were noted.

Results: Of 1024 eligible participants, 976 (95.3%) underwent HIVDR testing with median age 36 (interquartile range [IQR] 30-43) years and median CD4 295 (IQR 142-478) cells/mm$_3$. Among 710 ART-naïve participants, SDRMs were seen in 75 (10.6%), with highest prevalence in Nigeria (15/90, 16.7%) and Uganda (38/275, 13.8%). Pre-treatment major NNRTI mutations were seen in 57 (8.0%) and NRTI mutations in 29 (4.1%), including 37 (5.2%) with K103N 10 (1.4%) M184V/I, respectively. Among 266 ART-experienced participants, 153 (57.5%) had major NNRTI and 124 (46.6%) major NRTI resistance mutations, again led by K103N (86/266, 32.3%) and M184V/I (116, 43.6%). Variations by country were seen in Pol subtypes (Figure Panel A) and acquired resistance to specific drugs (Figure Panel B), with 51 (19.2%) participants showing medium or high-level resistance to both tenofovir and lamivudine.

Conclusion: There was a moderate prevalence of pre-treatment HIVDR. Participants on failing ART regimens had a high burden of HIVDR that potentially limits the efficacy of standard regimens containing tenofovir and lamivudine. Programmatic gaps need to be addressed to prevent HIVDR propagation, particularly with rollout of new first-line ART in Africa. Management strategies that emphasize adherence counseling while delaying ART switch may promote accumulation of drug resistance mutations and should be reconsidered.





516 HIV VIROLOGIC FAILURE AND DRUG RESISTANCE AMONG HOSPITAL INPATIENTS IN MALAWI

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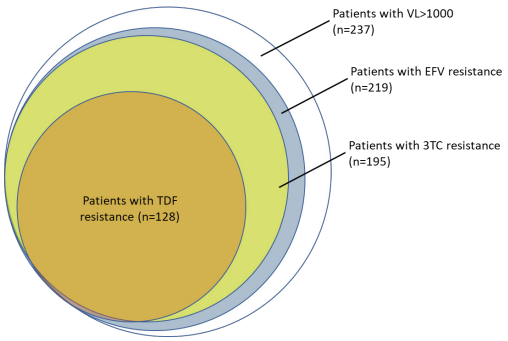
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Background: Since antiretroviral therapy (ART) scale-up in high prevalence settings, most HIV+ hospital inpatients are taking ART at admission. However, few data exist on the prevalence of ART failure or HIV drug resistance (DR) in this population. We conducted a large cohort study, nested in a TB screening trial, to describe the proportion of adult inpatients established on ART with virological failure (viral load [VL] >1000 copies/ml), and HIVDR.

Methods: Patients were eligible if taking ART for ≥6 months at admission. Stored plasma samples from admission were tested for HIV-1 RNA by real time qPCR. HIVDR mutations were detected by ultra deep sequencing on Illumina MiSeq platform for patients with VL >1000 copies/ml. Interpretation of HIVDR mutations used the Stanford HIVDR Algorithm. Drug resistance was defined as having intermediate or high-level resistance to specific drugs.

Results: Overall, 814/1316 (61.9%) patients recruited between Oct 2015 and Sept 2017 were on ART for ≥6 months. 28/814 patients had missing VL. 252/786 (32.1%) of patients had VL >1000 copies/ml. Of these, mean age was 38 years, 62% were female and median CD4 was 60 cells/μL, and 97.6% patients reported being treated with first-line ART (lamivudine[3TC], tenofovir[TDF] and efavirenz[EFV]). Successful sequencing and HIVDR results were available for 237/252 (94.0%). 195/237 (82.3%) of samples were resistant to 3TC, 128/237 (54.0%) to TDF and 219/237 (92.4%) to EFV. Protease and integrase inhibitor resistance was rare (1/233 and 2/225 had major mutations respectively). 84/237 (35.4%) patients had thymidine analog-associated mutations (TAMs). 127/237 (53.6%) of patients were resistant to all 3 drugs in their ART regimen, and 196/237 (82.7%) to at least 2. Assuming patients with VL<1000 copies/ml had no HIVDR, the prevalence of HIVDR to at least 2 drugs was 25.4% in all inpatients on ART ≥6 months. 2-month mortality was higher in patients with HIVDR to ≥2 or more drugs (28.1%) compared to ≤1 drugs (9.8%, p=0.014).

Conclusion: These data demonstrate high prevalence of virological failure and HIVDR in hospitalised patients in Malawi. Critically, HIVDR was associated with increased mortality and therefore targeted interventions for virological failure are warranted. The high prevalence of resistance to first-line nucleotide-reverse transcriptase inhibitors is concerning, and has public health implications.



Venn diagram showing the number of patients with intermediate or high level HIV drug resistance among inpatients established on ART for ≥6 months and with HIV viral load >1000 copies/ml at hospital admission.
ART antiretroviral therapy; VL viral load; EFV efavirenz; 3TC lamivudine; TDF tenofovir

517 HIGH LEVELS OF DRUG RESISTANCE IN ART-NAIVE AND PLWH FAILING FIRST-LINE ART IN HAITI

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Background: We assessed drug resistance in a sample of patients at GHESKIO in Port-au-Prince, Haiti (largest provider of HIV care in the Caribbean), to inform treatment guidelines.
Methods: From September 2018 to July 2019, we conducted HIV genotypes for patients who were ART-naïve or with virologic failure on first-line ART; tenofovir (TDF)/lamivudine (3TC)/dolutegravir (DTG) (TLD) replaced efavirenz (EFV)/ TDF/3TC as first-line ART in November 2018. Resistance was defined by the Stanford HIV Drug Resistance Database score: ^{3}15 at least low-level resistance; ^{3}30 at least intermediate resistance.
Results: HIV genotypes were conducted for 266 patients who were ART-naïve and 91 on NNRTI-based first-line ART. Of those, 56.7% were female and median age was 35 (IQR: 26, 44). Among ART-naïve patients, 24.8% had intermediate or higher resistance to EFV, with score >30 (27.5% among females). NRTI resistance (score >30) was detected in 8.6%, including 3.4% for both TDF and 3TC; M184V/I was detected in 7.5%, K65R/N in 2.3%, and both mutations in 1.9%. Among patients failing a first-line NNRTI-based regimen, 91.2% had EFV resistance score >30. NRTI resistance (score >30) was detected in 63.7%, including 35.2% for both TDF and 3TC. M184V/I was detected in 46.2%, K65R/N in 28.6%, and both mutations in 15.4%. Rates of PI resistance were low. Less than 1% of patients had intermediate or high-level resistance to any PI.
Conclusion: There are high levels of NNRTI and NRTI resistance among ART-naïve and ART-experienced adults and children in Haiti. The use of EFV-based ART regimens for pregnant women as an alternative first line is of concern, as ART resistance testing is not conducted. DTG and PI based regimens should be prioritized. The high rate of abacavir resistance in children, and TDF cross-resistance, limits future treatment options in that age group. High levels of TDF and 3TC resistance in adults warrant caution in the implementation of new guidelines and roll out of TLD in patients failing NNRTI-based therapy

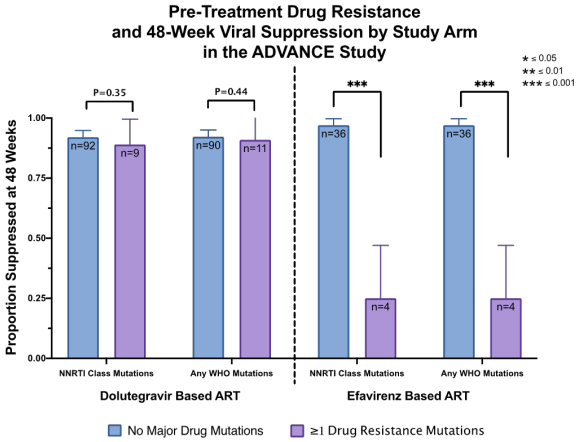
Table 1: Proportion of Patients with Genotypic Resistance, by Treatment Regimen, and Drug

At Least Low-Level Resistance (Score of ≥15 by Stanford HIV Drug Resistance Database)								
Treatment Group	EFV	Any NRTI	TDF	AZT	ABC	3TC/FTC	TDF and 3TC	Any PI
ART-Naive	25.6%	9.4%	4.5%	2.3%	8.6%	8.6%	4.5%	3.0%
Failing First-Line NNRTI	92.3%	64.8%	47.3%	6.6%	65.6%	64.8%	46.2%	3.3%
At Least Intermediate-Level Resistance (Score of ≥30 by Stanford HIV Drug Resistance Database)								
Treatment Group	EFV	Any NRTI	TDF	AZT	ABC	3TC/FTC	TDF and 3TC	Any PI
ART-Naive	24.8%	8.6%	3.4%	1.5%	4.6%	8.3%	3.4%	0.8%
Failing First-Line NNRTI	91.2%	63.7%	35.2%	6.6%	57.8%	63.7%	35.2%	0.0%
Specific Mutations in the Reverse Transcriptase or Integrase Gene Associated with Resistance								
Treatment Group	M184V/I	K65R/N	K103N	L100I		K101P	M41L or L210W	
ART-Naive	7.5%	2.3%	20.7%	1.5%		0.4%	0.4%	
Failing First-Line NNRTI	46.2%	28.6%	62.6%	11.0%		5.5%	1.1%	

518 PRETREATMENT HIV DRUG RESISTANCE AND 48-WEEK VIROLOGIC OUTCOMES IN THE ADVANCE TRIAL

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Background: Increasing prevalence of pretreatment HIV drug resistance (PDR) has motivated guideline changes to avoid non-nucleoside reverse transcriptase (NNRTI)-based first-line antiretroviral therapy (ART) regimens. Empiric data on the performance of ART regimens in the face of PDR are lacking in sub-Saharan Africa.
Methods: The ADVANCE study is a randomized controlled trial in South Africa that compares efavirenz (EFV) with dolutegravir (DTG), both with two NNRTIs, as first-line ART. We performed pre-treatment genotypic drug resistance testing in 197 randomly selected participants with next generation sequencing using the Illumina platform at KRISP and set detection thresholds for resistant variants at >20%, 5-20%, 2-5%. For our primary outcome, we compared the proportion of individuals who achieved virologic suppression (<40 copies/mL) at 48-weeks with EFV versus DTG-based ART, by presence or absence of PDR at 20% threshold, defined with the WHO drug resistance mutation (DRM) list. In secondary analyses, we assessed the effect of resistance at 2 and 5% thresholds on outcomes and the effect of PDR on treatment failure, redefined as virologic failure, death or loss from observation.
Results: We successfully sequenced pre-treatment HIV RNA from 165 individuals, of whom 48 (29%) received EFV and 117 (71%) received DTG. Twenty of 165 (12%) had ≥1 DRMs, with no difference in PDR by study arm, sex (56% female), age (median 32 years) or pre-treatment CD4 count (median 284). The most common mutation was K103N (9%); K65R and M184V were both found in only 2 (1%) of individuals. The proportion achieving our primary outcome was similar in the EFV (36/40, 90%) and DTG groups (93/101, 91%), P=0.69. However, rates of confirmed virologic suppression among those with and without PDR was 25% (1/4) and 97% (35/36) in the EFV-arm, and 89% (8/9) and 92% (85/93) in the DTG arms, respectively (P<0.001 for interaction between PDR and treatment arm). These trends were similar when redefining PDR thresholds at 2-5% and 5-20%, and when redefining failure to include death and loss from observation.
Conclusion: PDR, primarily to NNRTIs, was associated with significantly diminished efficacy of EFV-based, but not DTG-based three drug ART in South Africa. These data support the use of integrase inhibitors as initial therapy in individuals with known drug resistance or in populations with a very high prevalence of circulating NNRTI PDR.



519 IMPACT OF PREEXISTING DRUG RESISTANCE ON RISK OF VIROLOGIC FAILURE IN SOUTH AFRICA

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Background: There is conflicting evidence on the impact of pre-existing HIV drug resistance mutations (DRM) in patients infected with non-B subtype virus initiating first-line antiretroviral therapy (ART). Using next-generation sequencing, we assessed the impact of HIV DRMs on the risk of virologic failure (VF) in South African patients initiating an NNRTI-based ART regimen.
Methods: We performed a case-cohort substudy of the HIV Drug Resistance Surveillance Study (DRSS), which enrolled 1,000 peri-urban and rural patients initiating first-line efavirenz/tenofovir/emtricitabine in KwaZulu-Natal. Pre-ART DRMs were detected by multiplexed Illumina sequencing of HIV pol and sequence analysis performed using PASeq software. Individual genotypic susceptibility scores at varying minority variant (MV) thresholds (0.5-20%) were calculated using the Stanford HIV database. DRMs present at ≥20% of the viral population were labeled as "majority" variants likely detectable by Sanger sequencing. Weighted Cox proportional hazards models estimated the association between pre-ART DRMs and risk of VF, defined as confirmed HIV-1 RNA ≥1,000 copies/mL after ≥5 months of ART.
Results: The evaluable case-cohort sample included 178 participants from the randomly selected subcohort (16 with VF, 162 without VF) and 83 additional participants with VF. In the random subcohort, 16% of participants harbored at least one majority DRM that conferred intermediate or greater ART resistance (Stanford score ≥30). The presence of any significant majority DRM was associated with a 3-fold risk of VF (p=0.002). In those with <2 active drugs due to majority DRMs, the risk of VF increased to 9.2-fold (p<0.001) compared to those with 3 active drugs. Thirteen percent of participants in the random subcohort harbored any MV DRMs in the absence of majority DRMs. The most commonly detected high-level majority DRMs (K103N, V106M, M184V) were rarely detected as MVs. Presence of MVs alone had no significant impact on the risk of VF. Inclusion of pre-ART MVs with majority DRMs improved the sensitivity, but reduced the specificity of predicting VF of first-line ART.

Conclusion: In a cohort of participants from KwaZulu-Natal, the presence of majority DRMs increased the risk of VF, an effect largely driven by the presence of dual-class resistance. The detection of drug-resistant minority variants alone did not significantly increase the risk of VF, but their inclusion with majority DRMs affected the sensitivity/specificity of predicting VF.

520 TENOFOVIR DIPHOSPHATE IN DRIED BLOOD SPOTS PREDICTS VIROLOGIC FAILURE AND RESISTANCE

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Background: Tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) is a measure of cumulative adherence and exposure to TFV-based antiretroviral therapy (ART). This adherence biomarker has been associated with viral suppression and found to predict future viremia in persons living with HIV (PLWH) receiving tenofovir disoproxil-fumarate (TDF)-based ART. However, little is known about its utility in the context of virologic failure (VF) and drug resistance in resource-limited settings.

Methods: Participants within a prospective clinical cohort of PLWH who initiated TDF-based ART in 2 clinical sites in KwaZulu-Natal, South Africa, were evaluated. DBS samples were collected from participants who received at least 6 months of ART and developed VF, defined as an HIV VL >1000 copies/mL (cases), and in a selected group of participants who had an HIV VL <1000 copies/mL (controls, matched by site, age, gender, race and duration of ART). Cases were categorized as having VF without resistance or having VF with resistance using genotypic resistance testing. Concentrations of TFV-DP in DBS were quantified using a validated LC-MS/MS method. One-way ANOVA was used to compare the concentrations of TFV-DP in DBS at the time of the last study visit between controls, participants with VF without resistance and participants with VF with resistance. Data are presented as mean [SD] or median (IQR).

Results: A total of 1000 participants (500 at each site) were enrolled in the cohort. Of these, 288 (45 cases) had available DBS samples, which were included in the analysis. Median age was 31 (26, 38) years and 170 (59%) were women. TFV-DP concentrations in DBS in controls were higher than in participants with VF with resistance and VF without resistance (808 [503] vs. 589 [495] vs. 527 [555] fmol/punch; P<0.01; Table), respectively.

Conclusion: TFV-DP in DBS was associated with VF and drug resistance in South African PLWH on TDF-based ART. Participants with VF who developed drug resistance had TFV-DP concentrations in the mid-range of cumulative exposure, but higher than those who did not develop resistance. These results suggest that moderate cumulative drug exposure is required to develop ART resistance. Future research on the clinical utility of TFV-DP in DBS to prevent the development of VF and drug resistance is needed.

Table. Concentrations of TFV-DP in DBS in controls vs. cases among PLWH on TDF-based ART in South Africa.

Category (n)	TFV-DP [fmol/punch] Mean (SD)	P value
Controls vs Cases with Virologic Failure (n=288)		
Control (243)	808 (503)	<0.01
VF with resistance (31)	589 (495)	
VF without resistance (14)	527 (555)	

521 TRENDS AND CHARACTERISTICS OF HIV-1 DRUG RESISTANCE IN THE UNITED STATES (2012-2018)

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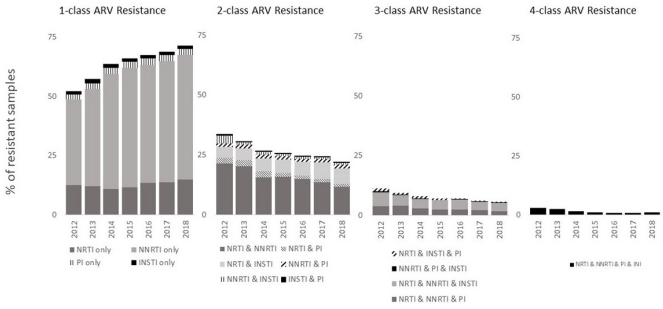
Background: The prevalence of transmitted and acquired HIV-1 drug resistance impacts effectiveness of antiretroviral therapy in both treatment-naïve and treatment-experienced people living with HIV. This analysis utilized data from a large, representative commercial patient testing database to assess trends in HIV-1 resistance prevalence in the modern treatment era.

Methods: Samples from HIV-1-infected individuals in the United States submitted for genotypic resistance testing to 4 antiretroviral (ARV) classes [protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and integrase strand transfer inhibitors (INSTIs)] between July 1, 2012 and June 30, 2018 were analyzed. All samples were collected as part of routine clinical care and evaluated using Monogram Biosciences GenoSure PRIme assay.

Results: Of 84,611 samples evaluated, 27,911 (33.0%) demonstrated reduced susceptibility to at least one ARV. Between 2012 and 2018, resistance to NRTIs (54.8% to 40.8%) and PIs (14.7% to 8.3%) steadily declined. The proportion of samples with reduced susceptibility to at least one INSTI decreased between 2012 and 2015 (20.3% to 14.0%), stabilizing from 2015 to 2018. Multiclass (≥2 ARV classes) resistance declined between 2012 and 2018. The proportion of resistant samples with 2-, 3-, and 4-class resistance, respectively, decreased from 33.5% to 21.9%, 11.3% to 5.5%, and 3.1% to 1.1%. (Figure) This trend corresponds to increasing proportions of samples with resistance to NNRTIs in the absence of NRTI, PI, and INSTI resistance (2012-2018: 36.2% to 52.6%). Among samples with multiclass resistance, 78.7% were still susceptible to at least 1 ARV in the NNRTI class, 93.4% to ≥1 NRTI, 97.9% to ≥1 PI, and 93.7% to ≥1 INSTI; of these, 29.1% were susceptible to a single INSTI. The proportion of resistant samples with reduced susceptibility to multiple ARV classes increased with older age (21-30 yrs: 21.5%; 31-40: 30.4%; 41-50: 38.1%; 51-60: 41.4%; >60: 42.4%). No associations between degree of resistance and gender or geographic region were observed.

Conclusion: Decreasing prevalence of multiclass ARV resistance was observed in testing data, in addition to declines in NRTI, PI, and INSTI resistance. These trends correspond with the availability of newer treatment options with favorable cross-resistance profiles, improved efficacy, and more convenient formulations leading to better adherence.

Figure. Class-specific resistance among samples with 1-, 2-, 3-, and 4-class resistance.



522 PREVALENCE OF RESISTANCE AND LIMITED THERAPEUTIC OPTIONS IN PATIENTS VIREMIC ON ART

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Background: Although current ART has led to improved rates of prolonged virologic suppression, some patients remain viremic under ART. We evaluated the prevalence of resistance and therapeutic options among viremic subjects on ART in a large multicentric study.

Methods: All HIV infected adults on ART for ≥6 months on Oct 1, 2018 at 3 French sites from the Dat'AIDS cohort (NCT02898987) were included. We compared individuals with last confirmed HIV RNA >50 c/mL vs ≤50c/mL. For each viremic subject, mutations were analyzed to assess cumulative ARV resistance genotype [ANRS algorithm (version 29; 2018)], genotype sensitivity score (GSS) and the number of active drugs (AD). Limited therapeutic options (TO) was defined as resistance to 3 of 4 ARV classes (maraviroc and enfuvirtide were not considered) and ≤2 AD among 5 specified drug groups (3TC or FTC, ABC or TDF, ≥1 NNRTI, ≥1 PI/r, ≥1 INSTI), based on cumulative genotype. $\chi 2$ and Mann-Whitney tests were used for comparisons.

Results: Of 5,429 individuals under follow-up, 215 (3.97%) had HIV RNA >50 c/mL. Excluding 7 subjects with no available genotype, characteristics of the 208 viremic vs virologically suppressed subjects are shown in Table. Adherence issues and social problems were found in 64.9% and 49.5% of viremic individuals, respectively. On cumulative genotype, 8.2% of viremic subjects had resistance to 3 or 4 ARV classes and 50.4 % to none; susceptibility to TDF,

ETR, DRV/r and DTG was 92.1%, 82%, 98.6% and 95.7%, respectively. Number of AD was ≥3 in 85.6% of viremic subjects, while last ART regimen had a GSS ≥3 in 68.2% and a GSS=2 in 24%. The proportion of subjects with limited TO was 4.33% (n=9) of viremic subjects and 0.17% of the total study population. Among these 9 subjects, all had an AIDS history, with mean nadir CD4 of 53/mm$_3$, and 5/9 zenith HIV RNA >6 log$_{10}$ c/mL. If we extrapolate our results to all patients under care in France (2016 estimation: 112,877; 95% CI: 111,635-114,053), we would obtain an estimate of 192 (95% CI: 190-194) HIV infected adults with limited TO.

Conclusion: Few individuals on ART ≥6 months had persistent viremia; they very rarely harbored multi-resistant viruses for which it is not possible to construct a suppressive ARV regimen. In this context of poor adherence-related viremia without great loss of TO, interventions to improve compliance, rather than new ARV classes, are needed.

Table: Characteristics of patients with and without HIV RNA <50c/mL

	HIV RNA >50 c/mL "Viremic" group N = 208	HIV RNA <50 c/mL "Controlled" group N = 5,214	p
Gender: female	38.0%	32.1%	0.07
Mean age, years	47.2	48.9	0.06
MSM	25%	43.5%	< 0.0001
Non-French native	41.4%	29.8%	0.0004
CDC Stage C	41.4%	20.2%	< 0.0001
Zenith HIV RNA >5 log$_{10}$ c/mL	73.1%	18.7%	< 0.0001
Nadir CD4 <200/mm^3	63.9%	43.4%	< 0.0001
Last CD4 <200/mm^3	22.1%	3.4%	< 0.0001

523 FOUR-CLASS RESISTANCE IS RARE IN TREATMENT-EXPERIENCED PATIENTS ACROSS EUROPE

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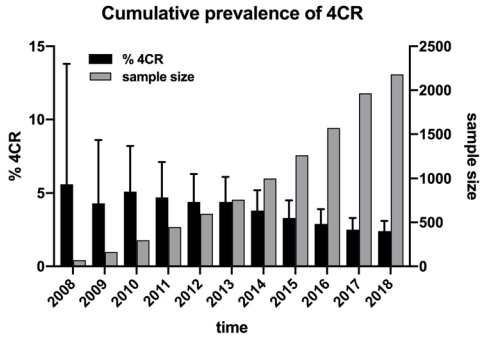
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Background: While most HIV-1 patients starting antiretroviral therapy (ART) in recent years achieve and maintain undetectable viral load, patients with a long ART history and failure of multiple therapy lines may have accumulated substantial drug resistance, challenging the possibility for virus control both at individual and population level. However, the prevalence of patients harboring virus with resistance to the four main drug classes (4CR) is largely unknown.

Methods: From the EuResist database, we selected treated patients with protease, reverse transcriptase and integrase genotype information available at one or more time points. HIV-1 sequences were interpreted by the Stanford HIVdb 8.8 algorithm and cumulative scores were generated at each sequencing time point. 4CR was defined as high-level resistance to at least one drug in each of the four classes. The frequency of 4CR at each calendar year was estimated as the number of unique patients with 4CR divided by the number of unique patients with at least one sample, up to that year.

Results: Complete four classes HIV-1 genotype information was available from 2643 distinct patients on ART contributing 3544 genotype data from Italy (49.9%), Germany (24.7%), Portugal (8.1%), Luxembourg (7.5%), Sweden (7.0%) and Belgium (2.7%). 66% were male and risk groups included 45.3% MSM, 18.6% drug users and 18.3% heterosexuals. Subtype B virus was harbored by 70.1% of patients and the most prevalent non-B subtypes were G (14.0%) and A1 (7.5%). Overall, 65 patients (2.5%) had 4CR. The prevalence of 4CR declined from 5.6% [95%CI: 1.6-13.8] in 2008 to 2.4% [95%CI: 1.8-3.1] in 2018 (P <0.001, chi-square test for trend; see figure). Patients with 4CR were older (49+/-12 vs. 46+/-11, P = 0.001) and harbored more often subtype B virus (85.3% vs. 69.7%, P = 0.013) with respect to patients without 4CR. No association was demonstrated between 4CR and gender or risk groups.

Conclusion: In a large population of patients across Europe with complete HIV-1 genotype information, the prevalence of 4CR appears to be relatively low and possibly declining over recent years. Continuous surveillance of this challenging population is warranted to provide effective treatment at the individual level and define factors predicting accumulation of resistance over time.



524 PRO 140 IN VITRO ACTIVITY IN HTE SUBJECTS WITH A 4-CLASS DRUG-RESISTANT HIV-1 VIRUS

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Background: PRO 140 is a novel humanized form of a mouse immunoglobulin G4 CCR5-directed monoclonal antibody with nanomolar potency in inhibiting HIV-1 cell entry through the CCR5 coreceptor. The aim of this study was to analyze HIV-1 tropism and in vitro susceptibility to PRO 140 according to MVC exposure in a cohort of heavily treatment-experienced (HTE) HIV-1-infected patients (pts) harboring a documented 4-class drug-resistance to NRTIs, NNRTIs, PIs, InSTIs, enrolled in the Italian PRESTIGIO Registry.

Methods: Plasma RNA (viremic pts) or PBMC DNA (non-viremic pts) was used for Sanger sequencing and Next Generation Sequencing (NGS, Illumina platform) of the gp120-V3 region followed by geno2pheno [coreceptor] interpretation. Viral tropism and susceptibility to PRO 140 were assessed through a home-made phenotypic assay based on pseudotyped viruses expressing patient derived Env protein and luciferase as reporter gene. Pts demographics and laboratory data are described as median (Q1-Q3), mean (±SD) or frequency (%).

Results: Among 25 pts, 20 (80%) were male, median age 50 years (44-53), time since HIV-1 diagnosis 23 years (19-26), time on ART 20 years (16-23), 14 (56%) with a previous AIDS diagnosis, 17 (68%) with maraviroc (MVC) exposure, a median CD4+ count 207 cells/µl (73-326) and a median viral load 4.58 log$_{10}$ copies/mL (4.02-5.11), with 2 pts with HIV-RNA<40 copies/mL. CCR5-tropic virus was observed in 36%, 43%, 36% accordingly to Sanger, NGS and the phenotypic assay; the overall concordance among the three methods was 65% while pairwise agreement ranged from 76% (NGS vs phenotypic assay) to 86% (Sanger vs phenotypic assay). All 9 viruses with CCR5-tropic phenotype were susceptible in vitro to PRO 140, with median IC$_{50}$ 0.4 (0.3-0.7) nM, comparable to the IC$_{50}$ of the reference wild-type CCR5-tropic AD8 virus (mean IC$_{50}$ 0.7±0.4 nM). There was a variation between MVC-naïve (n=3; median IC$_{50}$=0.70, IQR=0.50-1.2 nM) and MVC-exposed (n=6; median IC$_{50}$=0.35, IQR=0.30-0.40 nM) pts (p=0.087 [Wilcoxon rank-sum test]) (Table 1). Current exposure to MVC was not associated with different PRO 140 activity (p=0.376).

Conclusion: In this group of HTE pts with MDR virus, all CCR5-tropic strains were fully susceptible to PRO 140 and they were not significantly impacted by MVC exposure. PRO 140 can thus play a key role in subjects with very limited therapeutic options and CCR5-tropic virus.

Table 1. Tropism results according to different virological methods and IC_{50} PRO 140 in the 9 patients from the PRESTIGIO Registry who were tested for PRO 140 susceptibility

Patient ID	HIV-1 RNA (copies/mL)	CD4+T-cells/µL	Percent of X4 variants by deep sequencing setting FPR at 3.5%[a]	FPR by Sanger (%)[b]	Phenotypic tropism	IC_{50} (mean±SD) PRO 140
25	1,104	240	32.7	4.4	R5	0.3±0.2
27	13,835	168	0.1	not done	R5	1.2±0.3
37	12,580	207	0.1	69.8	R5	0.4±0.3
55	17,888	326	0.0	54.7	R5	0.7±0.2
58	2,986	518	0.0	51.3	R5	0.5±0.3
90	84,534	201	0.6	16.4	R5	0.8±0.6
117	6,718,473	34	0.1	51.2	R5	0.3±0.1
32	<40	550	16.6	0.6[c]	R5	0.3±0.2
82	<40	942	83.8	54.7	R5	0.4±0.3

[a]Viruses were considered non-R5-tropic by NGS when >2% viral species had a false-positive rate (FPR) <=3.5% (*Swenson LC et al., J Infect Dis 2011*). [b]Viruses were considered non-R5-tropic by Sanger when FPR was <=10% (*European guidelines on the clinical management of HIV-1 tropism testing. Lancet Infect Dis. 2011*). [c]FPR was determined on plasma RNA.
NGS: Next Generation Sequencing by Illumina platform. FPR: False Positive Rate. SD: standard deviation.

525 SUSCEPTIBILITY TO bNAbs OF TRANSMITTED HIV VARIANTS AMONG RECENT INFECTIONS IN FRANCE

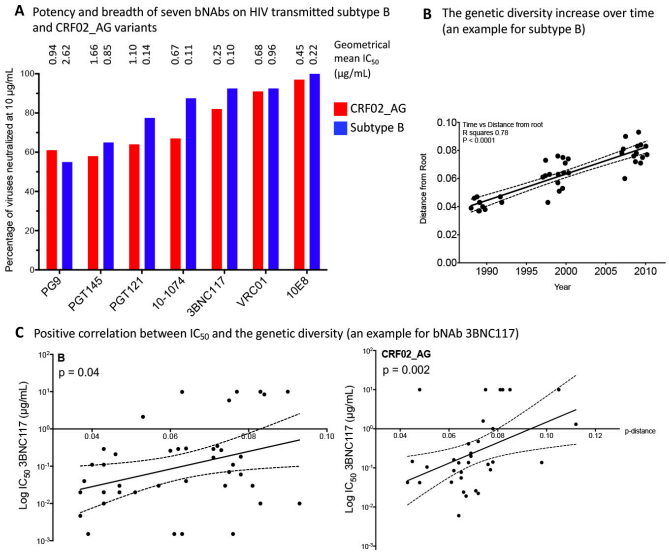
Karl Stefic[1], Mélanie Bouvin-Pley[1], Asma Essat[2], Clara Visdeloup[1], Alain Moreau[1], Cécile Goujard[2], Marie-Laure Chaix Baudier[3], Martine Braibant[1], Laurence Meyer[2], Francis Barin[1], for the ANRS PRIMO Cohort Study Group
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Background: Pre-existing resistance to broadly neutralizing antibodies (bNAbs) restrains their use for prevention and treatment of HIV infection. In addition, an increasing resistance of HIV to neutralization over time has been observed arguing for a prospective monitoring of the sensitivity to bnAbs of all prevalent HIV subtypes. Here, we analyzed the susceptibility to bNAbs of HIV transmitted variants among recently infected individuals in France with a focus on evolution over time.

Methods: We assessed the sensitivity to seven bnAbs against a panel of 73 early-transmitted subtype B and CRF02_AG viruses (the most prevalent subtypes in Europe) over a 25-year period of the French epidemic (1987-2012). Samples were obtained during acute/recent infection from individuals included in the ANRS PRIMO cohort. Env pseudoviruses were constructed and neutralization assays on TZM-bl cells were performed using bnAbs targeting the CD4-binding site (CD4bs; VRC01, 3BNC117), the V1/V2-glycan region (PG9, PGT145), the V3-glycan region (PGT121, 10-1074), and the gp41 membrane proximal external region (MPER; 10E8).

Results: Participants' median CD4 count was 506 cells/mm_3, median viral load was 5.1 log_{10} copies/mL and the estimated time from infection was 41 days. bNAbs targeting the CD4bs and 108E were the most potent and broadly neutralizing. VRC01 neutralized 92.5% of all variants at the target concentration of 10 µg/mL. 3BNC117 IC_{50}s were the lowest of all bNAbs (respectively 0.01 et 0.25 µg/mL for B and CRF02_AG variants; Mann-Whitney P<0.05). CRF02_AG were more resistant than B viruses regarding bNAbs targeting V3 (64-67% of the strains neutralized at 10 µg/mL vs 78-88%, respectively). This resistance was associated with the absence of the glycosylation site N332 (p<0.01). Both subtypes were more resistant to bNAbs targeting V2 (55-65% of the strains neutralized at 10 µg/mL). Finally, we observed an increased resistance to several bNAbs over the course of the epidemic - especially those targeting the CD4bs – which correlated with the continuous diversification of Env sequences over time (Spearman P<0.05).

Conclusion: Of the bNAbs in clinical development tested here, none neutralized 100% of T/F variants, indicating that combinations will be required to achieve a full coverage for prevention and treatment. As in other countries, we confirmed the natural drift of HIV towards higher resistance to bNAbs for the most prevalent subtypes spreading in France, arguing for a continuous surveillance of HIV transmitted variants around the globe.



526 INVESTIGATION OF INTEGRASE-INHIBITOR RESISTANCE MUTATIONS IN gp41 IN CLINICAL SAMPLES

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Background: In vitro studies have suggested that resistance to HIV Integrase strand transfer inhibitors (INSTI) can occur outside the integrase gene, including in env, but it remains unclear whether such mutations arise in vivo. Using a large database of clinically-derived HIV-1 sequences, we sought to identify mutations in gp41 that were associated with exposure to INSTI in vivo.

Methods: We identified 146 consenting participants of the BC-CfE Drug Treatment Program (DTP), infected with HIV-1 subtype B, whose physicians had ordered a genotypic INSTI resistance test following ≥3 months of INSTI exposure and whose genotype was susceptible to all INSTI (HIVdb v8.8 score <15). We then performed gp41 genotyping on these same samples. For comparison, we assembled reference datasets of subtype B Integrase (INT) and gp41 sequences from INSTI-naïve DTP participants collected during routine clinical drug resistance testing. Amino acids (AA) significantly over- or under-represented among INSTI-treated and -naïve participants at all INT and gp41 codons were identified by Fisher's exact test. Analyses were restricted to AA observed ≥5 times and multiple comparisons were addressed using the Benjamini-Hochberg method (q-values).

Results: INT and gp41 sequences from participants treated with raltegravir (79; 54%), elvitegravir (27; 18%) or dolutegravir (40; 27%) were collected after a median of 32 (Q1-Q3: 13-56) months of INSTI exposure. Overall, 16% of INSTI-experienced participants were antiretroviral-naïve at the time of their first INSTI prescription, while 84% had prior NNRTI- and/or PI-based cART. INT sequences from 146 INSTI-treated and 2472 INSTI-naïve individuals were compared. Gp41 genotyping was successful for 115 (79%) INSTI-treated individuals; these were compared to sequences from 1222 INSTI-naïve individuals. Lower frequencies of the gp41 polymorphisms I182V (OR=0.40, p=9.1x10-6, q=0.0085) and H209R (OR=0.47, p=1.9x10-4, q=0.086) were observed in INSTI-experienced individuals at these positions. No significant differences in AA frequencies were observed in INT sequences (all q>0.2).

Conclusion: Differences in gp41 amino acid frequencies in INSTI-experienced vs. -naïve individuals were observed only at highly polymorphic positions. No substitutions in gp41 previously associated with INSTI resistance in vitro were identified, suggesting that these may arise rarely in vivo.

527 MAPPING RESISTANCE OF POTENT HIV-1 ENTRY INHIBITORS TARGETING PREFUSION CONFORMATION

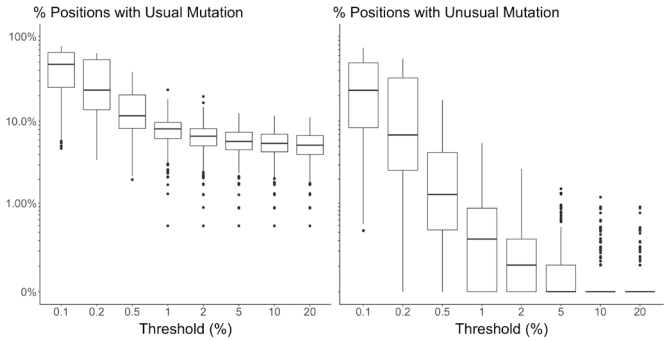
Yen-Ting Lai[1], Megan Demouth[1], Adam Dingens[2], Amarendra Pegu[1], Jesse Bloom[2], John R. Mascola[1], Peter D. Kwong[1]
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Background: The entry of HIV-1 into target cells is a critical event in the viral life cycle and an attractive target for drug development. The HIV-1 envelope protein (Env), comprised of three gp120 subunits and three gp41 subunits, binds to cell-surface receptors before triggering the fusion of viral and host cell membranes. Entry inhibitors targeting the gp41 (Enfuvirtide) or co-receptor CCR5 (Maraviroc) have been approved by FDA for HIV-1 treatment. To date, no entry inhibitors targeting the gp120 have been FDA-approved although a promising small-molecule lead, fostemsavir (the prodrug of active compound BMS-626529), is currently in phase III clinical trials. We previously reported the crystal structure of BMS-626529 in complex with HIV-1 Env trimer, revealing its molecular basis of entry inhibition. This drug binds to a conserved pocket beneath the ß20-ß21 hairpin between the inner and outer domains of gp120, suggesting that drug binding blocks the conformational changes required for viral fusion to occur. We also identified BMS-818251, a derivative of BMS-626529, which is >10-fold more potent in pseudovirus neutralization assays. Crystal structure of BMS-818251 revealed interactions between a tail functional group and the Env that likely contributed to the higher neutralization potency.
Methods: We characterized the viral suppression efficacy of BMS-818251 in ex vivo cell cultures that were derived from HIV-1 patients. In addition, we used a site-saturated mutational library of BG505 Env to map the potential resistance mutations of BMS-818251 and BMS-626529.
Results: BMS-818251 exhibited superior viral suppression than BMS-616259 in HIV-1+ CD4 T-cell culture from two patients. The minimal inhibition concentration of BMS-818251 was >10-fold lower than BMS-626529, consistent with our previous observation in pseudovirus neutralization assays. In addition, we observed viral rebound in the cell culture of one patient treated with the highest concentration of BMS-626529 tested, suggesting selection of pre-existing resistance mutations. Viral rebound was not observed for BMS-818251 in the two samples tested. Mapping of resistance mutations by the BG505 mutation library revealed distinct resistance profiles by BMS-818251 and BMS-626529, suggesting different level of selection pressure between these two compounds.
Conclusion: Our data support further development of BMS-818251, which represents a novel class of HIV-1 drugs targeting gp120, as a next-generation entry inhibitor.

528 META-ANALYSIS OF UNUSUAL AND APOBEC MUTATIONS IN HIV-1 POL NEXT-GENERATION SEQUENCES

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Background: Next generation sequencing (NGS) for HIV-1 genotypic resistance testing is subject to detection of artifactual mutations resulting from PCR error and APOBEC-mediated G-to-A hypermutation. We hypothesize that the presence of large numbers of unusual mutations at a mutation call frequency NGS threshold suggests the threshold is too low and that many of the detected mutations may be caused by PCR error or G-to-A hypermutation rather than HIV-1 replication.
Methods: We systematically analyzed HIV-1 pol Illumina NGS data from published studies to characterize the distribution of usual and unusual amino acid mutations at 8 NGS thresholds: 20%, 10%, 5%, 2%, 1%, 0.5%, 0.2% and 0.1%. At each threshold we quantified the number of unusual mutations (defined as having prevalence of <0.01% in HIV-1 group M population Sanger sequences) or signature APOBEC mutations.
Results: Eight studies containing 855 samples from 821 persons in the NCBI sequence read archive were analyzed. As the NGS threshold was lowered, there was a progressive increase in the proportion of positions with both usual and unusual mutations and a progressive increase in the proportion of mutations that were unusual (Figure). The median proportion of positions with an unusual mutation increased from 0% to 0.3% between the 20% and 1% thresholds and then increased to 1.3% at the 0.5% threshold, 6.9% at the 0.2% threshold, and 23.2% at the 0.1% threshold. In 2 of 3 studies reporting plasma HIV-1 RNA levels, the proportion of positions with unusual mutations was inversely associated with virus levels. Although the complete set of signature APOBEC mutations (n=296) was much smaller than the complete set of other unusual mutations (n=14,940), signature APOBEC mutations outnumbered non-APOBEC unusual mutations in one-sixth of samples at the 0.5%, 1% and 2% thresholds.
Conclusion: The marked increase in the proportion of unusual mutations at thresholds below 1% and in samples with lower virus loads suggest that many detected unusual mutations may derive from PCR error. However, in some samples, APOBEC-mediated G-to-A hypermutation may be a greater contributor to sequence artifacts than PCR error. Post hoc analyses of NGS data that quantify the numbers of unusual and signature APOBEC mutations at different NGS thresholds may be useful to avoid selecting a threshold that is too low and that poses an unacceptable risk of identifying artifactual mutations.



529 ABSENCE OF GS-6207 PHENOTYPIC RESISTANCE IN HIV Gag CLEAVAGE SITE AND OTHER MUTANTS

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Background: GS-6207 is a potent, first in class, multistage inhibitor of HIV-1 capsid function with the potential to be used as a subcutaneous (SC) long-acting agent with dosing every 3 months or longer. In the clinic, a single SC injection of GS-6207 (50 mg to 450 mg) in people living with HIV (PLWH) showed a rapid and strong antiviral effect, with a >1.8 mean $\log_{10}$ decrease in HIV-1 RNA at day 10. Mutations in HIV-1 gag near protease (PR) cleavage sites have emerged with the use of protease inhibitors (PIs), resulting in increased fitness and/or PI-resistance. Here we have characterized the activity of GS-6207 in mutants with HIV-1 gag cleavage site mutations, as well as mutants with resistance to other drug classes.
Methods: HIV mutations were inserted into the pXXLAI infectious clone either by site-directed mutagenesis or by cloning of plasma samples. Infectious clones with HIV gag cleavage site mutations, or HIV gag-PR fragments from treatment-naïve or experienced PLWH were evaluated using a standard 5-day antiviral assay (MT-2-cells). Isolates with resistance mutations against the 4 major drug classes (NRTI, NNRTI, PI, INSTI) were tested phenotypically using a single-cycle assay (Monogram Biosciences).
Results: In all, 19 HIV gag cleavage site mutants (single and double mutants with L363F/M, A364V, Q430R, A431V, K436E, I437T/V, L449H/V/F, P453L, and/or PR mutations V82A and I84V) as well as 55 patient derived clones were analyzed phenotypically. GS-6207 EC_{50} fold-change compared to wild-type (WT) ranged from 0.3 to 2.1 in these mutants, similar to the control drug. In contrast, high levels of reduced susceptibility to PIs (>500 fold) and maturation inhibitors (MIs) (>70 fold) were noted in some mutants. Testing of isolates with resistance mutations against the 4 main classes of drugs (n=40) indicated WT susceptibility to GS-6207 (fold-change ranging from 0.3 to 1.1), while highly reduced susceptibility was observed for control drugs of each class.
Conclusion: HIV gag cleavage site mutations did not impact the activity of GS-6207, while some conferred resistance to MIs and PIs. Similarly, GS-6207 activity was not affected by naturally occurring variations in HIV gag, in contrast to the loss of activity observed for MIs in nearly half of the mutants. Finally, the activity of GS-6207 was not affected by the presence of resistance mutations to the 4 main ARV classes. These data support the evaluation of GS-6207 in PLWH with multi-class resistance.

530 SUSCEPTIBILITY OF NRTI-RESISTANT HIV-2 ISOLATES TO A NEW NRTI, GS-9131

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Background: Management of HIV-2 infection is hampered by the limited number of active ARV drugs and the rapid acquisition of drug resistance-associated mutations (DRAMs). There is still a strong need for new ARV effective on HIV-2, especially for patients infected by multi-drug resistant viruses. GS-9131 is the prodrug of GS-9148, a new NRTI with low potential for mitochondrial toxicity and renal accumulation that previously demonstrated its in vitro efficacy against wild-type (WT) and NRTI-mutant HIV-1 isolates, except those harbouring the Q151M complex. Here, we report GS-9131 antiviral activity on HIV-2 clinical isolates.

Methods: Phenotypic susceptibility to GS-9131 was assessed for 13 HIV-2 isolates, and references strains of HIV-1 (BRU) and HIV-2 (ROD), using the ANRS assay. Briefly, viruses were cultured without GS-9131 and with 6 dilutions of the drug, ranging from 6250 to 0.002 nM. At days 3 or 4, viral replication was assessed by RT-PCR on the supernatant. All but one of the 13 HIV-2 isolates exhibited major DRAMs in the reverse transcriptase gene (K65R, Q151M, M184V and/or S215Y/F), according to the ANRS list (Table).

Results: GS-9131 exhibited a potent activity against WT HIV-2 isolates (IC_{50}= 3.4 and 4.4 nM). The sole presence of K65R mutation or M184V mutation increased the IC_{50} for GS-9131 (12.0 and 27.0 nM for K65R, and 16.6 nM for M184V). GS-9131 had a lower activity on 2 isolates displaying a combination of 2 DRAMs (K65R+M184V and M184V+S215Y, IC_{50} = 108 and 134 nM, respectively). All isolates harbouring a Q151M mutation were highly resistant to GS-9131 (with IC_{50} ranging from 178 to >6250 nM), regardless of associated-NRTI mutations.

Conclusion: GS-9131 exhibits potent in vitro activity against WT HIV-2 isolates. Regarding the 3 main resistance genotypic profiles described in HIV-2-infected patients failing NRTI-based regimens (K65R, Q151M and M184V), our data showed that isolates harbouring only K65R or M184V mutations presented moderate increases in IC_{50} for GS-9131, while the presence of a Q151M mutation rendered HIV-2 isolates highly resistant to GS-9131. These in vitro data suggest that GS-9131 might offer an attractive, new therapeutic opportunity for persons living with HIV-2, either at initiation of antiretroviral therapy or for second-line regimens, as it retained potential for some activity against K65R and M184V mutants.

			IC_{50} (nM) [fold-change]
Isolate number	HIV group	NRTI-associated mutations	GS-9131
BRU	HIV-1 M	Wild-type	6.4
ROD	HIV-2 A	Wild-type	4,4
#01	HIV-2 B	Wild-type	3.4 [0.8]
#02	HIV-2 B	K65R	12 [2.7]
#03	HIV-2 B	K65R	27 [6.1]
#04	HIV-2 A	M184V	16.6 [3.8]
#05	HIV-2 B	M184V+S215Y	134 [30.5]
#06	HIV-2 A	K65R+M184V	108 [24.5]
#07	HIV-2 A	Q151M	178 [40.5]
#08	HIV-2 A	Q151M	777 [177]
#09	HIV-2 A	Q151M+184V	243 [55]
#10	HIV-2 A	K65R+Q151M+M184V	3500 [795]
#11	HIV-2 A	Q151M+M184V+S215F	>6250
#12	HIV-2 B	Q151M	>6250
#13	HIV-2 A	Q151M	>6250

531 PHENOTYPIC DORAVIRINE SUSCEPTIBILITY AFTER NNRTI EXPOSURE IN THE PRESTIGIO REGISTRY

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Background: Doravirine (DOR) is an NNRTI recently licensed for first-line ART showing superior genetic barrier to resistance and partial cross-resistance with older NNRTI. We investigated susceptibility to DOR in patients with documented 4-class drug-resistance to NRTI, NNRTI, PI, INSTI (4CR), enrolled in the Italian PRESTIGIO Registry.

Methods: Recombinant HIV-1 expressing patient derived PR-RT were generated from plasma samples from 20 4CR patients failing ART. In vitro susceptibility to DOR was assessed through a TZM-bl cell based phenotypic assay measuring fold-change (FC) values with respect to the NL4-3 virus. Patient demographics and laboratory data were described by median (Q1-Q3) or frequency (%). Statistical analysis included Mann-Whitney and Spearman correlation tests.

Results: Overall, 18 (90%) patients were male, median age 51 years (43-53), time since HIV-1 diagnosis 22 years (18-26), time on ART 19 years (16-22), 11 (55%) with a previous AIDS diagnosis, median viral load (VL) 4.42 log_{10} copies/mL (3.36-5.15) and median CD4+ cell count 195 cells/µL (75-278); 11 patients (55%) were receiving NNRTI (ETR=10, RPV=1), while 7 (35%), 5 (25%), 8 (40%) patients had been exposed to 1, 2 and 3 NNRTI, respectively, with a median time of exposure to NNRTI of 1529 days (353-2169). Globally, median DOR FC was 9.8 (1.8-65.7), while FC were 17.9 (7.4-80.1) and 3.7 (0.7-53.5)(p=0.105) in patients with and without current NNRTI pressure, respectively. According to Stanford HIVdb algorithm, intermediate to high-level resistance to DOR was predicted in 13/20 (65%) cases. DOR FC values correlated with the number of NNRTI mutations (r = 0.548; p=0.010) and with the DOR resistance level by HIVdb algorithm (r = 0.754; p=0.0001) but not with the number of previously experienced NNRTI (r = -0.167; p=0.483), VL (r = -0.121; p=0.612), time of exposure to NNRTI (r = 0.044; p=0.855) or time elapsed since last exposure to NNRTI (r = -0.330; p=0.155). Median DOR FC values were significantly higher in viruses harbouring major DOR RAMs according to both HIVdb (FC 100 [41.9-100] vs. 6.2 [1.2-17.2], p=0.003) and IAS-USA lists (FC 100 [38.4-100] vs. 6.2 [1.2-20.2], p=0.007). However, both Stanford low-level and intermediate resistance groups included FC values spanning >1 log.

Conclusion: DOR activity decreases with increasing number of NNRTI mutations and is inferred with fair accuracy by HIVdb and the IAS list, independently from the extent and time of NNRTI exposure.

532 HIV A1 OR B DO NOT DIFFERENTIALLY IMPACT CABOTEGRAVIR IN VITRO POTENCY OR DURABILITY

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Background: The Phase 3 FLAIR study evaluates monthly i.m. Long Acting (LA) cabotegravir (CAB) and rilpivirine (RPV) as maintenance therapy in suppressed HIV infected adults over 48 weeks and demonstrated non-inferiority to 3 drug daily oral ART. A total of 3/283 (1%) participants (PTS) who received CAB+RPV LA had confirmed virologic failure (CVF). All 3 CVFs occurred among 8 PTS in that study arm with subtype A1 virus and all 3 had baseline integrase (IN) substitution L74I, as did 2/5 PTS who maintained viral suppression. All 8 PTS with subtype A1 virus were sensitive to CAB at baseline. 174/283 (61%) PTS in the LA arm had subtype B, 7% with L74I without CVF. Given the apparent clustering of CVF among A1 and presence of L74I, we sought to determine the impact of L74I and subtype A1 compared to subtype B IN on CAB sensitivity.

Methods: IN genotypes and phenotypic sensitivity to CAB were generated at Monogram Biosciences. Site directed mutants were generated in subtype B NL4-3 and a consensus A1 IN sequence derived from the 3 CVF baseline IN sequences. In vitro susceptibility to CAB was assayed and compared across virus subtypes. The in vitro durability of CAB was tested against bulk infected cultures at various CAB concentrations for 3 weeks.

Results: All baseline, A1 IN sequences (8/283 subjects) were sensitive to CAB with IC_{50} fold-change (FC) ranging from 0.7-1. The 3 CVF sequences at the failure timepoint had CAB FC IC_{50} values of 5.22 – 9.36 and substitutions at L74I and G140R or Q148R. The site-directed mutants L74I/G140R (FC 0.87 A1 vs 0.58 B) or L74I/Q148R (FC 4.1 A1 vs 4.4 B) in the A1 background resulted in similar IC_{50} FC compared to subtype B background. Across both subtypes, time to viral breakthrough was similar at the lowest CAB concentration (1nM) and no viral breakthrough was detected at 3 weeks for CAB concentrations of 5nM or 410nM ($1xPAEC_{90}$). The genotypes of the breakthrough viruses will be presented.

Conclusion: The FLAIR study demonstrated CAB+RPV LA was noninferior to oral ART at Week 48 with 3 CVFs harboring HIV subtype A1 with baseline L74I. In vitro virologic assessments do not indicate a differential sensitivity to CAB between subtypes A1 or B in viruses containing IN mutations observed in the CVFs. However, our evaluations cannot determine if HIV subtype A1 with L74I has greater likelihood of selection of additional INSTI mutations under selection pressure. Other factors may contribute to the risk of CVF and require further investigation.

533 HLA GENOTYPE IS ASSOCIATED WITH PRETHERAPY ACCESSORY InSTI RESISTANCE MUTATION L74I

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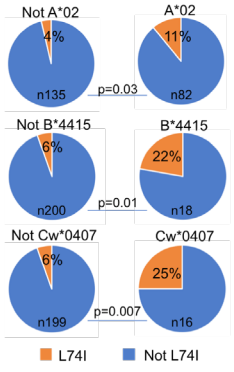
Background: Naturally-occurring HLA-driven polymorphisms in HIV-1 may confer decreased susceptibility to antiretroviral therapies, but our knowledge of such polymorphisms in non-B subtypes remains incomplete. Here, we examine whether HLA-genotype is associated with pre-therapy integrase strand transfer inhibitors (INSTI) resistance mutations in a treatment-naïve Ugandan cohort.

Methods: HIV-1 integrase bulk sequencing and HLA-genotyping were performed on pre-therapy-initiation plasma and PBMC collected between 2005-2010 from n=511 INSTI-naïve participants in the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort. RIP 3.0 was used for HIV-1 subtyping. Major INSTI-associated resistance mutations were defined by the Stanford HIV database version 8.8 as T66AIK, E92Q, G118R, E138KAT, G140SAC, Y143RCH, S147G, Q148HRK, N155H, R263K. Only one minor mutation, L74I, was included due to recent reports linking it to cases of INSTI-treatment failures in subtype A1. R was used for all statistical and phylogenetic analyses. Multivariable logistic regression models were described for six resistance-mutation-HLA-genotype pairs that had n=8 or more individuals from which resistance mutations were observed.

Results: We identified major INSTI mutations in 1.2% (6/511) of participants: T66I (n=1; subtype D), E138K (n=3; all subtype D), and E138T (n=2; all subtype A1). L74I was found in 6% (n=16/247 subtype A1) and 4% (n=8/200 subtype D) of individuals. None of these polymorphisms, when occur alone, were associated with reduced INSTI susceptibility according to Stanford HIVdb. Multivariate logistic regression analyses revealed associations between A*02, B*4415 and Cw*0407 with L74I (p=0.03, 0.01, 0.007, Fig 1) after adjusting for gender, age, subtype, and interactions between subtype and HLA-genotypes. Cohort prevalence of A*02, B*4415 and Cw*0407 were 37%, 10% and 9%, respectively. Sequences containing L74I did not cluster into a monophyletic group in phylogenetic analyses.

Conclusion: Our data suggest that certain polymorphisms associated with INSTI resistance in specific viral subtypes may be HLA-driven. L74I have not been previously associated with HLA-escape in any viral subtype, suggesting the epitope responsible is not immuno-dominant. Lack of phylogenetic clustering suggests results are not attributable to viral founder effects. Effects of L74I on INSTI-based therapy, its link to HLA-genotypes, and whether it lowers genetic barrier to INSTI require additional large-scale population-level validation.

Figure 1. HIV-1 integrase mutation L74I is associated with specific HLA-genotypes (subtype A1).



534 HIV-1 VIRAL REBOUND AFTER BICTEGRAVIR, DOLUTEGRAVIR, AND CABOTEGRAVIR WASHOUT

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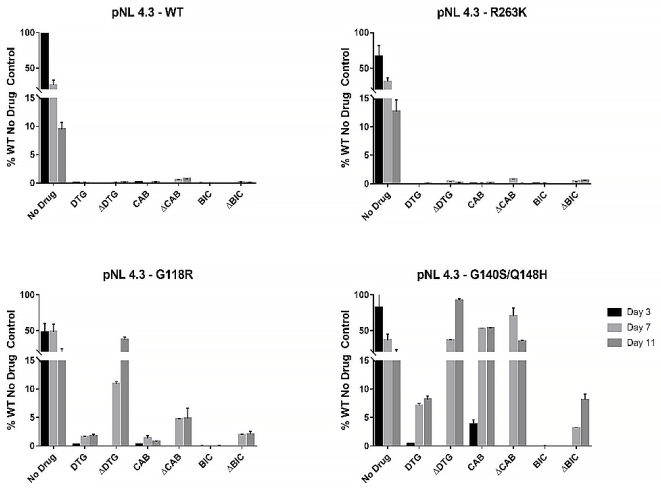
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Background: In past studies, we performed in vitro washout experiments to show a more durable suppression of wild-type (WT) and integrase-resistant HIV-1 by dolutegravir (DTG) as compared to Raltegravir (RAL) or Elvitegravir (EVG) following release of drug pressure. In this study, we were interested in reproducing these observations on two newly developed integrase strand transfer inhibitors (INSTIs), Bictegravir (BIC) and Cabotegravir (CAB).

Methods: Site directed mutagenesis generated pNL4-3 plasmid constructs harbouring Wild Type (WT), R263K, G118R, and G140S/Q148H integrase. MT-2 cells were infected with WT or resistant clones to establish IC_{50} and IC_{90} concentrations. MT-2 cells were then subjected to maximal drug pressure, using 20 times the IC_{90} for each drug. Three days post-exposure, drugs were washed out from the cells. Viral rebound was assessed at days 3, 7 and 11 post-infection.

Results: BIC showed a higher genetic barrier to resistance than DTG and CAB, based on IC_{50} values. The R263K G118R, G140S/Q148H clones showed 1-, 1.4-, and 3.5-fold resistance to BIC relative to WT, respectively. This compares to 3.5-, 1.7- and 6.6-fold resistance to DTG and 0.8-, 6.4-, and 6.8-fold resistance to CAB against R263K, G118R, and Q140S/Q148H clones, respectively. In our washout experiments, WT and R263K were viral suppressed by all three drugs during selective pressure (20 x IC_{90}) and following drug washout (day 11). With G118R infected cells, viral rebound occurred following DTG washout with minimal increase in replication following CAB washout and no rebound following BIC washout. The G140S/Q148H clones were not susceptible to CAB prior to and following drug washout. While DTG could suppress replication t of G140S/Q148H infected cells, viral rebound occurred following washout (day 7). In contrast, BIC successfully suppressed replication through the 11 days of infection, showing minimal rebound after drug removal.

Conclusion: Overall, we observed an extended duration of viral suppression of HIV-1 replication following release of drug pressure with BIC than either DTG or CAB. This included WT virus and viruses harboring mutations conferring low-level, moderate and high-fold drug resistance. These findings show that BIC may be pharmacologically more forgiving than DTG and CAB.



535LB MUTATIONS IN THE HIV-1 ENVELOPE GLYCOPROTEIN CONFER BROAD DRUG RESISTANCE

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Background: We recently reported that, in vitro, HIV-1 can acquire resistance to the potent IN inhibitor, dolutegravir (DTG), by acquiring mutations in the envelope (Env) glycoprotein that enhance viral spread via cell-to-cell transmission. The aim of this study is to clarify the mechanism of Env-mediated HIV-1 drug resistance.

Methods: Virus replication in the presence of ARVs was measured by propagating viruses in a spreading infection in SupT1 cells. Sensitivity to neutralizing antibodies (NAbs) was measured using TZM-bl indicator cells. gp120 shedding from virus particles was measured by western blotting. To examine possible in vivo relevance of Env-mediated drug resistance, we performed single-genome sequencing using plasma from 5 patients failing a raltegravir (RTG)-containing regimen (La Rosa et al., 2016).

Results: We demonstrated that the gp41 mutations Env-A539V and A556T, which enhance viral cell-to-cell transmission, provide a replication advantage over WT in the presence of not only DTG but also other classes of ARVs targeting RT and PR. Moreover, Env-A539V compensated for viral fitness defects induced by drug resistance mutations in the viral enzymes and increased resistance to ARVs when coupled with these mutations, suggesting that the Env mutations may be a "stepping-stone" on the path to high-level drug resistance. Interestingly, Env mutations that show enhanced cell-to-cell transmission cluster in the gp120 C1 domain and gp41 heptad repeat 1, which are located at the gp120/gp41 interface and are crucial for stabilizing the gp120-gp41 interaction. Indeed, we observed that the Env mutations reduced gp120 shedding from virus particles. In addition, Env-A539V decreased the sensitivity of HIV-1 to NAbs that recognize the CD4-induced Env conformation, suggesting that this mutation decreases the efficiency with which Env transitions from the unliganded state. Sequencing of viruses from RTG-failure patients revealed the presence of several mutations in the highly conserved gp120/gp41 interface in the absence of resistance mutations in IN.
Conclusion: These results demonstrate that mutations in Env can contribute to broad HIV drug resistance in vitro. Moreover, we established a relationship between Env stability, drug resistance, and the efficiency of viral cell-to-cell transmission. These findings offer mechanistic insights into Env-mediated drug resistance in culture, and suggest, preliminarily, that Env-mediated drug resistance may also occur in vivo.

536 HIV DRUG RESISTANCE ACROSS ANATOMICAL TISSUES

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Background: HIV drug resistance can be an obstacle to successful antiretroviral therapy (ART), but the vast majority of studies on drug resistance have focused on studying blood. Here, we present evidence of drug resistance across multiple tissues in two persons with HIV.
Methods: Last Gift study participant 3 (LG03) was a 72-year-old man with HIV and metastatic pancreatic cancer with no previous history of drug resistance. LG05 was a 57-year old man with HIV and amyotrophic lateral sclerosis with pre-existing resistance to nucleoside reverse transcriptase inhibitors (NRTI) and protease inhibitors (PI) identified by the GenoSure Archive NGS-based assay. Both had suppressed HIV RNA in blood plasma collected within 7 hours from death. Tissues were isolated via a rapid autopsy and HIV DNA was extracted from gut (ileum and duodenum), lymph nodes (axillary and aortic), kidney and spleen. 72 3.5-kb pol single genome amplicons were prepared in a single library and sequenced (Illumina MiSeq). Reads were mapped to HIV HXB2, and consensus sequences generated. Mutations at sites of drug resistance were determined (Stanford HIV Drug Resistance Database) and analyzed for each variant.
Results: Despite no previous diagnosis of ART failure with drug resistance, in tissues LG03 had mutations associated to (NRTI) including D67N, K70R, T215F, and K219Q/E in 9 kidney, 3 aortic lymph node, and 3 axillary lymph nodes SGA variants, but not in his duodenum or ileum (Table 1). In tissues, LG05 had NRTI resistance associated mutations (D67N, K70R, T215F, and K219Q/E) in 1 duodenum, 1 ileum, and 3 spleen SGA variants. Nonpolymorphic mutations associated with PI included M46I, I54V, V82T, I84V, and L90M. These mutations matched those identified in the GenoSure Archive assay.
Conclusion: This study found high rates of resistance associated mutations in proviruses across tissues in persons with HIV who were fully suppressed on ART. The pattern of HIV drug resistance associated mutations across PBMC and tissues was not consistent for either LG03 or LG05 (table 1). These discrepancies were pronounced between PBMC DNA (based on the GenoSure Archive assay) and non-circulating tissues. These findings highlight that HIV drug resistance might be present in various tissue reservoirs without prior diagnosis, and that just sampling in one compartment, like PBMC, is likely to miss the full repertoire of HIV drug resistance that is present.

Table 1. Summary of resistance mutations in tissues in virally suppressed participants of the Last Gift Study

	Location	Total Clones	Any Major PR	Any NRTI	Any NNRTI
LG03	Duodenum	6	0.0%	0.0%	0.0%
	Ileum	10	0.0%	0.0%	0.0%
	Kidney	10	0.0%	90.0%	60.0%
	Lymph Nodes Aortic	6	0.0%	50.0%	16.7%
	Lymph Nodes Axillary	6	0.0%	50.0%	16.7%
LG05	Duodenum	5	20.0%	20.0%	0.0%
	Ileum	6	16.7%	16.7%	0.0%
	Spleen	5	60.0%	60.0%	20.0%

Note: Frequencies are based on the number of SGA variants that contained one or more drug resistance mutations out of the total number of SGA variants.

537 HIV DRUG RESISTANCE IN FEMALE SEX WORKERS FROM THE DOMINICAN REPUBLIC AND TANZANIA

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Background: Female sex workers (FSW) are at high risk of HIV infection and sex work is known to play an important role in HIV transmission dynamics across settings. Low socioeconomic status, gender discrimination, and stigma associated with HIV and sex work may limit access to HIV care for FSW. We analyzed HIV drug resistance among HIV-infected FSW in the Dominican Republic (DR) and Tanzania who are enrolled in a longitudinal study of the social determinants of HIV outcomes.
Methods: Plasma samples were collected at study entry. Samples with viral loads >1,000 c/mL were retrospectively tested for HIV drug resistance and antiretroviral (ARV) drugs. HIV genotyping was performed using the ViroSeq HIV-1 Genotyping System. ARV drug testing was performed using a qualitative assay that detects 22 ARV drugs in five drug classes. Chi-square tests were used to evaluate factors associated with drug resistance.
Results: Among 410 enrolled FSW, 144 (35.1%) had a viral load >1,000 c/mL (50 from the DR, 94 from Tanzania). Genotyping results were obtained for 138 (95.8%) of 144 participants. Major drug resistance mutations were detected in 54 (39.1%) of the 138 samples (22 [15.9%] had non-nucleoside reverse transcriptase inhibitor resistance, 3 [2.2%] had nucleoside/nucleotide reverse transcriptase inhibitor resistance, 29 [21.0%] had multi-class resistance). ARV drugs were detected in 36 (25.0%) of the 144 cases; 19 (52.8%) of the 36 samples had only one or two drugs detected. The frequency of resistance was higher in the DR than Tanzania (27/50 [54.0%] vs. 27/88 [30.7%], p=0.011) and was higher among those with ≥1 ARV drug detected (31/35 [88.6%] vs. 23/103 [22.3%] with no drugs detected, p<0.0001). Seven participants with ≥1 ARV drug detected lacked corresponding resistance mutations; those individuals were at risk of acquiring additional drug resistance. K103N was the most common mutation detected among all 138 cases; M184V was the most common mutation detected among the 35 cases with ≥1 ARV drug detected.
Conclusion: In this cohort of FSW, nearly 40% of participants with viral loads >1,000 c/mL had HIV drug resistance and >20% had multi-class resistance. Drug resistance was associated with study site and ARV drug use. ARV drugs were detected in 25% of the participants who had a viral load >1,000 c/mL; in more than half of those cases, only one or two drugs were detected. These findings highlight the need for improved HIV care and treatment among FSW.

538 RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS AMONG MSM IN THE US: HPTN 078

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Background: Increasing viral suppression with antiretroviral therapy (ART) is a critical step in curbing the HIV epidemic. Integrase strand transfer inhibitor (INSTI)-based ART regimens are now recommended for first-line ART in the United States (US), but pre-treatment resistance testing does not routinely include testing for INSTI resistance. The HIV Prevention Trials Network (HPTN) 078 study evaluated an HIV prevention strategy in men who have sex with men (MSM) in four US cities. We analyzed INSTI resistance in MSM recruited for participation in HPTN 078.

Methods: HIV-infected MSM were recruited in Atlanta, GA; Baltimore, MD; Birmingham, AL; and Boston, MA (N=155 with a viral load >1,000 c/mL; screening/enrollment 2016-2017); 85% were Black, 76% reported a prior positive HIV test, and 65% reported prior or current ART. Population sequencing and next-generation sequencing (NGS) methods were performed using samples collected at study entry. HIV drug resistance was evaluated using the Stanford v8.7 algorithm.HIV-infected MSM were recruited in Atlanta, Georgia; Baltimore, Maryland; Birmingham, Alabama; and Boston, Massachusetts (N=155; screening/enrollment 2016-2017). Population sequencing and next-generation sequencing (NGS) methods were performed using samples collected at study entry (all available samples with a viral load >1,000 copies/mL). HIV drug resistance was evaluated using the Stanford v8.7 algorithm.
Results: High-level INSTI resistance was detected in 11 (8.0%) of 138 cases with integrase test results. All 11 cases had high-level resistance to elvitegravir; four also had high-level resistance to raltegravir and intermediate-level resistance to the second-generation INSTIs, bictegravir and dolutegravir. All cases with INSTI resistance also had resistance to additional drug classes (multi-class resistance); 11 had NRTI resistance, including five who also had NNRTI resistance, and one who also had PI resistance. NGS data for the integrase region was available for 114 (82.6%) of the 138 samples. NGS identified 10 additional cases with lower-level INSTI resistance (5%-45%); five of those 10 cases also had resistance to drugs in other drug classes. Potential transmitted resistance mutations were detected in three (37.5%) of eight MSM who reported no prior HIV diagnosis; two cases had INSTI resistance mutations (one had E92Q+M184V, one had T97A).
Conclusion: High prevalence of INSTI resistance and intermediate-level resistance to second generation INSTIs was observed among viremic MSM recruited for the HPTN 078 study. Many of those with INSTI resistance had multi-class resistance, further limiting their ART options. Two cases of potential transmitted INSTI resistance mutations were identified. These findings highlight the need for improved HIV care in this high-risk population, and the importance of including baseline integrase resistance testing when selecting ART regimens for MSM in the US.

539 EXPANDED SPECTRUM OF ANTIRETROVIRAL-SELECTED HIV-2 MUTATIONS

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Background: There has been no systematic review of treatment-selected HIV-2 mutations.
Methods: We reviewed published HIV-2 sequences to identify previously unreported ARV-selected HIV-2 mutations. Prevalence of each PR, RT, and IN mutation was determined by ARV status. Nonpolymorphic mutations (NPMs) were defined as occurring in <1% of ARV-naïve persons. Nonpolymorphic treatment selected mutations (NP-TSMs) were defined as NPMs significantly associated with ARV therapy (Fishers Exact Test; p<0.05 after adjusting for multiple comparisons [Holm's test]). Established drug-resistance mutations (DRMs) were determined by literature review. Correlated NP-TSMs were defined as mutation pairs with a Spearman coefficient >=0.2 and p<0.05.
Results: We analyzed PR sequences from 481 PI-naïve and 232 PI-treated persons; RT sequences from 332 NRTI-naïve and 252 NRTI-treated persons; and IN sequences from 236 INSTI-naïve and 60 INSTI-treated persons. In PR, 12 NP-TSMs occurred in >=11 persons: V33I, K45R, V47A, I50V, I54M, T56V, V62A, A73G, I82F, I84V, F85L, and L90M. Additional PR NPMs at HIV-1 DRM positions G48V, I54L, I82L, and I84L occurred in 2-3 persons. Among novel PR-TSMs, V33I correlated with V47A and I50V; K45R with I47A; T56V with I54M; and F85L with A73G. In RT, 9 NP-TSMs occurred in >=10 persons: K40R, A62V, K70R, Y115F, Q151M, M184VI, and S215Y. Additional RT NPMs at HIV-1 DRM positions M41I, D67N, N69T, K70N, I75V, and S215F occurred in 6-9 persons. The novel RT-TSM K40R correlated with S215Y. In IN, 11 NP-TSMs occurred in >=4 persons: Q91R, E92AQ, T97A, G140S, Y143G, Q148R, A153G, N155H, H156R, and R231 5-amino acid insertions. Additional IN NPMs at HIV-1 DRM positions H51Y, E92G, G118R, G140A, Y143CHR, Q148HK, and R263K occurred in 1-3 persons. Among novel IN-TSMs, A153G correlated with E92A and N155H; H156R with E92Q and T97A.
Conclusion: This systematic review of HIV-2 PR, RT, and IN sequences confirmed an ARV association of established HIV-2 DRMs and identified novel NP-TSMs. 32 NP-TSMs were significantly selected by ARVs in PR, RT, and IN. 20 additional NPMs at HIV-1 DRM positions were not statistically significant after multiple comparison adjustment. Most of the 9 novel NP-TSMs co-occurred with an established HIV-2 DRM. These results will improve approaches to predicting HIV-2 ARV susceptibility. Further clinical and phenotypic studies of HIV-2 drug resistance will be helpful in delineating it's nuances and unique features.

540 HIV VIRAL BLIPS IN ADULTS TREATED WITH InSTI-BASED REGIMENS THROUGH 144 WEEKS

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Background: The clinical impact of viral blips on virologic failure and resistance development depends on the resistance barrier and forgiveness of the regimen. Here, we investigated the blip frequency and virologic outcomes of those experiencing blips among treatment-naïve people with HIV (PWH) initiating therapy on bictegravir (B)/emtricitabine (F)/tenofovir alafenamide (TAF), dolutegravir (DTG)/abacavir (ABC)/lamivudine (3TC), or DTG + F/TAF through 144 weeks of treatment in Studies 1489 and 1490.
Methods: PWH with at least one on-treatment post-baseline HIV RNA value were included in this analysis. HIV RNA and last observation carried forward (LOCF) outcome data through week 144 were used. A blip was an HIV RNA value ≥50 c/mL preceded and followed by HIV RNA <50 c/mL, after achieving confirmed suppression (two consecutive HIV RNA values <50 c/mL).
Results: Of the 1240 participants with confirmed suppression, 143 (11.5%) had ≥1 blip through week 144 with similar blip frequencies between treatment arms (Table 1). An average of 1.3% of participants experienced blips per study visit, which was similar between treatment arms (Table 1). A total of 186 blip events occurred in the 143 individuals; 110 experienced a single blip and 33 experienced multiple blips. Of the 186 blips, 87 (46.8%) were low-level (50-199 c/mL) and 99 (53.2%) were ≥200 c/mL. The proportions of participants with blips <200 c/mL or ≥200 c/mL were similar between treatment arms (Table 1). Most with blips ≥200 c/mL had adherence ≤95% by pill count (69.2%), while those with blips <200 c/mL mostly had adherence >95% (63.1%) (Table 1). Of participants without blips, 98.7% (1083/1097) had HIV RNA <50 c/mL at week 144 or last visit vs. 91.0% (71/78) with blips ≥200 c/mL (p<0.01), or vs. 96.9% (63/65) with blips <200 c/mL (p=0.2). The 7 with blips ≥200 c/mL and HIV RNA ≥50 c/mL at week 144 were all on DTG-based regimens, and 6/7 had evidence of continued low adherence. Of the 21 individuals included in the overall resistance analysis population, 5 experienced blips and none had emergent resistance to study drugs (Table 1).
Conclusion: Viral blips were infrequent and similar among PWH treated with B/F/TAF, DTG/ABC/3TC, or DTG + F/TAF. Blips ≥200 c/mL but not <200 c/mL were associated with adherence ≤95%. High level blips of ≥200 c/mL were associated with lower suppression at week 144 due to poor adherence; however, none developed resistance on these 3-drug regimens with high barriers to resistance.

Table 1. HIV Viral Blips Through Week 144

PWH	Study 1489		Study 1490		All n=1240
	B/F/TAF n=308	DTG/ABC/3TC n=309	B/F/TAF n=306	DTG + F/TAF n=317	
Any blip; n (%)	39 (12.7%)	49 (15.9%)	32 (10.5%)	23 (7.3%)	143 (11.5%)
p-value[a]	0.3		0.2		
Blips per visit; %	1.4%	1.8%	1.1%	0.8%	1.3%
p-value[b]	0.1		0.3		
Blips <200 c/mL; n (%)	18 (5.8%)	17 (5.5%)	19 (6.2%)	11 (3.5%)	65 (5.2%)
p-value[a]	0.9		0.1		
Adherence >95%	10/18 (55.6%)	12/17 (70.6%)	13/19 (68.4%)	6/11 (54.5%)	41/65 (63.1%)
Adherence ≤95%	8/18 (44.4%)	5/17 (29.4%)	6/19 (31.6%)	5/11 (45.5%)	24/65 (36.9%)
Blips ≥200 c/mL; n (%)	21 (6.8%)	32 (10.4%)	13 (4.2%)	12 (3.8%)	78 (6.3%)
p-value[a]	0.2		0.8		
Adherence >95%	4/21 (19.0%)	9/32 (28.1%)	6/13 (46.2%)	5/12 (41.7%)	24/78 (30.8%)
Adherence ≤95%	17/21 (81.0%)	23/32 (71.9%)	7/13 (53.8%)	7/12 (58.3%)	54/78 (69.2%)
Resistance Analysis Population; n	0	7	8	6	21
With blips	0	3	0	2	5
Emergent Resistance to Study Drugs; n	0	0	0	0	0

a. p-value was from 2-sided Fisher's exact test.
b. p-value was from 2-sided Student's t-test.

541 INVESTIGATION OF CLASSIC AND HIV-RELATED FACTORS FOR HEPATIC STEATOSIS AMONG PWID

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Background: Numerous studies show a link between visceral adiposity and metabolic disorders. Fatty liver is an established risk factor for cirrhosis and liver cancer and is increasing among aging persons living with HIV (PWH). We investigated the prevalence and correlates of hepatic steatosis, assessed non-invasively by elastography with controlled attenuation parameter (CAP), in a community cohort of HIV+ and HIV- people who inject drugs (PWID) and to determine if these associations varied by HIV infection or antiretroviral therapy (ART) regimen.
Methods: Adults from the AIDS Linked to the Intravenous Experience (ALIVE) study with validated liver elastography and CAP measurement from January 2017 to December 2018 were included. CAP >= 270 dB/m was considered significant steatosis. Multivariable logistic regression estimated odds ratios (OR) for association of steatosis with demographic (age, gender, race), behavioral (at-risk alcohol use, current injection drug use), clinical (liver stiffness, HCV exposure, BMI, waist circumference, blood pressure, blood glucose, serum cholesterol), and HIV related factors (HIV RNA, CD4, ART regimen).
Results: Of 1109 participants, 68% were male, 79% were black 40% reported recent drug use, 78% were anti-HCV+ and 35% were HIV infected (75% on ART; 65% had detectable HIV RNA). Median CAP score was 218 dB/m (IQR, 190 – 258) and prevalence of hepatic steatosis was 25%. In multivariable analysis, steatosis was significantly associated with obesity/overweight, [OR= 8.2 (5.1 – 13)] increased waist girth [OR=4.2 (2.8 – 6.2)] and liver fibrosis[OR=1.3 (1.1 – 1.6)]. Among HIV+'s , steatosis was strongly associated with undetectable HIV RNA [OR=1.6 (1.0 – 2.4)] and INSTI based ART [OR=1.8 (1.1 – 2.9)]. In sensitivity analyses, each measure of adiposity (hepatic steatosis, elevated BMI, elevated waist circumference) was individually associated with INSTI use.
Conclusion: Classic metabolic risk factors were strongly associated with hepatic steatosis in this community based PWID. While HIV did not independently increase risk, HIV-related factors of viral suppression and INSTI use were associated, contributing partly although not exclusively via adiposity. As HIV-infected PWID age on effective therapy, and with curative treatment for HCV, prevalence and morbidity of hepatic steatosis will likely increase.

Table 1. HIV Viral Blips Through Week 144

PWH	Study 1489		Study 1490		All n=1240
	B/F/TAF n=308	DTG/ABC/ 3TC n=309	B/F/TAF n=306	DTG + F/TAF n=317	
Any blip; n (%)	39 (12.7%)	49 (15.9%)	32 (10.5%)	23 (7.3%)	143 (11.5%)
p-value[a]	0.3		0.2		
Blips per visit; %	1.4%	1.8%	1.1%	0.8%	1.3%
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Blips <200 c/mL; n (%)	18 (5.8%)	17 (5.5%)	19 (6.2%)	11 (3.5%)	65 (5.2%)
p-value[a]	0.9		0.1		
Adherence >95%	10/18 (55.6%)	12/17 (70.6%)	13/19 (68.4%)	6/11 (54.5%)	41/65 (63.1%)
Adherence ≤95%	8/18 (44.4%)	5/17 (29.4%)	6/19 (31.6%)	5/11 (45.5%)	24/65 (36.9%)
Blips ≥200 c/mL; n (%)	21 (6.8%)	32 (10.4%)	13 (4.2%)	12 (3.8%)	78 (6.3%)
p-value[a]	0.2		0.8		
Adherence >95%	4/21 (19.0%)	9/32 (28.1%)	6/13 (46.2%)	5/12 (41.7%)	24/78 (30.8%)
Adherence ≤95%	17/21 (81.0%)	23/32 (71.9%)	7/13 (53.8%)	7/12 (58.3%)	54/78 (69.2%)
Resistance Analysis Population; n	0	7	8	6	21
With blips	0	3	0	2	5
Emergent Resistance to Study Drugs; n	0	0	0	0	0

a. p-value was from 2-sided Fisher's exact test.
b. p-value was from 2-sided Student's t-test.

542 RELATIONSHIPS BETWEEN HEPATIC STEATOSIS AND FRAILTY DIFFER BY HIV SEROSTATUS

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Background: Frailty and sarcopenia are associated with abdominal obesity and obesity-related comorbidities but their relationship with non-alcoholic fatty liver disease (NAFLD) in people living with HIV (PLWH) has not been described. We assessed the associations between NAFLD, sarcopenia, and components of a frailty-related phenotype (FRP) in Multicenter AIDS Cohort Study (MACS) participants.
Methods: MACS cardiovascular disease sub-study participants (40-70 years old) were included. NAFLD was defined as the ratio of liver/spleen in Hounsfield units (HU) < 1.0 on abdominal CT scans in men without chronic viral hepatitis or heavy alcohol use; FRP as having 3 of the following: weakness, slowness, weight loss, exhaustion, and low physical activity; sarcopenia as an appendicular skeletal muscle index [ASMI (kg)/height (m)^2] ≤7.26 kg/m$_2$. Wilcoxon rank sum and Fisher's exact tests compared between-group parameters. Multivariate regression assessed the relationship between NAFLD and a FRP controlling for HIV serostatus, study site, age, race, subcutaneous adipose tissue (SAT) density (HU), smoking status, alcohol use, liver fibrosis (FIB-4 >3.25), depression, and physical activity level (by international physical activity questionnaire). The final model included a NAFLD*HIV interaction.
Results: HIV- (n=200) and HIV+ (n=292) men had a median age of 55 and 52 years, BMI of 27 and 25 kg/m$_2$, and were 32% and 41% non-white, respectively. HIV+ men had a median CD4+ T lymphocyte count of 609 cells/mL, and 9.3 years on antiretroviral therapy. NAFLD prevalence was 21% in HIV- men vs 16% in HIV+ men; FRP 12% in HIV- vs 17% in HIV+. Among men with NAFLD, FRP was more prevalent in HIV- (21% vs 11% HIV+). In multivariate analysis, NAFLD, smoking, depression, and low physical activity were associated ($p<0.05$) with a FRP. In stratified adjusted models, HIV- men with NAFLD had 2.6 times higher probability [95% CI: 1.2-5.7] of FRP. This association was not seen in HIV+ men. The probability of a FRP was higher among HIV-men with NAFLD (10% vs 27% in men with NAFLD) but lower among HIV+ men (18% vs 13% in men with NAFLD). Sarcopenia was not associated with increased risk of NAFLD.
Conclusion: NAFLD was more prevalent in HIV- men, and independently associated with a FRP among HIV- men but not men living with HIV despite the latter's increased prevalence of frailty. The mechanisms of the muscle-liver-adipose tissue axis underlying NAFLD might differ by HIV serostatus.

543 NAFLD AND LIVER FIBROSIS PREDICT HIGH CARDIOVASCULAR RISK IN HIV-MONOINFECTED PATIENT

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Background: Non-alcoholic fatty liver disease (NAFLD) is strongly associated to cardiovascular disease (CVD) in the general population. In people living with HIV (PLWH), this association has not been investigated yet. The aim of this study is to assess the impact of NAFLD and liver fibrosis on cardiovascular risk in PLWH.
Methods: 1410 HIV infected patients from three prospective cohorts (LHIVPA in Palermo, LIVEHIV in Montreal, MHMC in Modena) were evaluated with Transient Elastography (TE). Exclusion criteria were: significant alcohol intake, coinfection with hepatitis B or C virus and failure of TE examinations defined as IQR value > 30%. NAFLD and significant liver fibrosis were defined as controlled attenuation parameter (CAP) ≥ 288 dB/m and as liver stiffness measurement (LSM) > 7 kPa, respectively. Cardiovascular risk was assessed with Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator, according to American College of Cardiology, in patients aged 40 – 75 years, and categorized as: low if < 5%, borderline if 5 – 7.4%, intermediate if 7.5 – 19.9% and high if ≥ 20%. Patients with previous cardiovascular events were considered as high risk, regardless of age.
Results: 941 HIV mono-infected patients (mean age 53 years, 74% males, 98% on ART) were included. 423 (45%), 128 (13.6%), 260 (27.6%) and 130 (13.8%) patients were categorized as low, borderline, intermediate and high ASCVD risk, respectively. Previous cardiovascular events were found in 8.5%. Prevalence of NAFLD and significant liver fibrosis was 20% and 17%, respectively. The distribution of ASCVD risk classes by NAFLD and fibrosis categories is shown in the Table. Overall, intermediate and high ASCVD risk were more frequent in patients with NAFLD ($p < 0.001$) and liver fibrosis ($p < 0.05$). In multivariate logistic regression, NAFLD (OR 2.16, 95% CI 1.44 – 3.26), liver fibrosis (OR 1.75 , 95% CI 1.11 – 2.75) and time to HIV diagnosis (OR 1.04, 95% CI 1.02 – 1.06, $p < 0.001$) were independently associated with higher ASCVD risk.
Conclusion: Both NAFLD and liver fibrosis are predictors of cardiovascular disease in PLHIV. Prevention of CVD, possibly with lifestyle modifications, should be strengthen in PLHIV with NAFLD, in particular in those with longer HIV duration.

Table. Distribution of Atherosclerotic Cardiovascular Disease Risk Classes by NAFLD and significant liver fibrosis categories

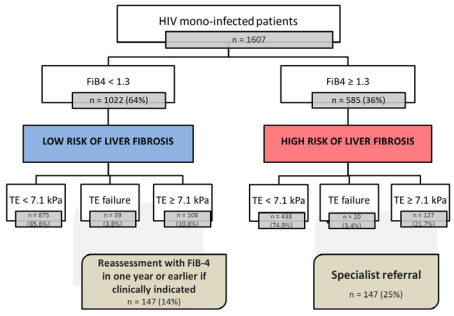
		ASCVD Risk Classes				
	n=941	Low	Borderline	Intermediate	High	p value
NAFLD (CAP ≥ 288 dB/m)	n=192	75 (39%)	14 (7%)	69 (36%)	34 (18%)	0.0005
Absence of NAFLD (CAP < 288 dB/m)	n=749	348 (46%)	114 (15%)	191(26%)	96 (13%)	
Significant Liver Fibrosis (TE > 7kPa)	n=164	57 (35%)	22 (13%)	59 (36%)	26 (16%)	0.016
Absence of liver fibrosis (TE ≤ 7 kPa)	n=777	366 (47%)	107 (14%)	201 (26%)	103 (13%)	

544 "FIB-4 FIRST" STRATEGY IN A NAFLD PATHWAY ASSESSMENT FOR HIV MONOINFECTED PATIENTS

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Background: Non-alcoholic fatty liver disease (NAFLD) is the main cause of liver disease in people living with HIV (PLWH). Even if transient elastography (TE) is a feasible and effective option to assess both NAFLD and fibrosis, it is not largely accessible. Fibrosis-4 (FIB-4) index at the threshold of 1.3 is used to exclude fibrosis in patients at risk for NAFLD from the general population. FIB-4 could be used to triage PLWH in need for further evaluation for NAFLD and associated liver fibrosis. The aims of this study were: i) to estimate the proportion of TE examinations which would be spared using a FIB-4 first strategy in PLWH; ii) to determine prevalence and associated cofactors of discordance (false negativity) between TE and FIB-4 in patients classified as low-risk fibrosis category by FIB-4.
Methods: 1607 HIV mono-infected patients from three cohorts (LIVEHIV in Montreal, LHIVPA in Palermo, MHMC in Modena) were included if they fulfilled the following criteria: available TE and FIB-4 within 3 months; absence of significant alcohol intake and of coinfection with hepatitis B or C. NAFLD was defined as a controlled attenuation parameter (CAP) ≥ 248 dB/m. Significant fibrosis and cirrhosis were defined as liver stiffness measurement ≥ 7.1 and ≥ 13 kPa, respectively. Failure of TE examination was defined as IQR value >30%. A FIB-4 threshold of 1.3 was used to categorize patients as low or high-risk for fibrosis. Multivariable logistic regression analysis was used to identify cofactors associated with discordance between TE and FIB-4 in low-risk category.
Results: Prevalence of NAFLD and liver fibrosis was 37% and 15%, respectively. 1022 patients (64%) were stratified as low risk: 108 (11%) had significant liver fibrosis by TE (of whom 78 patients had NAFLD and 13 patients had cirrhosis) (see Figure). After adjusting for sex, CD4 nadir, viral load, time to HIV diagnosis and diabetes, BMI ≥ 25kg/cm$_2$ (Odds Ratio [OR] 3.66, 95% CI: 2.29-5.84) and low HDL cholesterol (OR 1.72, 95% CI: 1.06-2.78) were independently associated with discordance between TE and FIB-4 in patients with FIB-4 <1.3.
Conclusion: A FIB-4 first risk-stratification model could save more than 50% of TE examinations, helping resource optimization in HIV clinics. Patients stratified as low risk by FIB-4 should be considered for referral for TE examination in case of multiple risk factors for NAFLD, in particular overweight and low HDL cholesterol.

Figure: Impact of implementation a FiB-4 First Strategy to triage PLWHIV patients entering a NAFLD assessment pathway.



545 TRYPTOPHAN CATABOLISM IS ALTERED AMONG PERSONS WITH HIV WHO HAVE STEATOSIS

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Background: Tryptophan catabolism as measured by the kynurenine-to-tryptophan ratio and concentrations of tryptophan metabolites are altered in persons with HIV (PWH). We aimed to explore if steatosis was associated with kynurenine-to-tryptophan ratio and quinolinic acid in PWH.
Methods: PWH were recruited from the Copenhagen comorbidity in HIV infection (COCOMO) study. We used an unenhanced CT liver scan to measure liver attenuation and defined steatosis as a liver attenuation ≤ 48 Hounsfield Units corresponding to moderate to severe steatosis. Concentrations of tryptophan metabolites in serum were measured using liquid chromatography-tandem mass spectrometry. Information on smoking and physical activity was collected through questionnaires, and anthropometry was performed by trained medical professionals. We performed multiple linear regression modelling of log-transformed biomarker levels adjusted for age, sex, smoking status, waist-to-hip ratio and physical activity. Furthermore, we explored if IFN-γ mediated the effects of steatosis on tryptophan catabolism.
Results: Among 799 PWH with both CT liver scan and measured kynurenines, steatosis was present in 61 (7.6%) (Table). KTR was 27.2 [95% Confidence Interval (CI): 25.1; 29.4] (nmol/µmol) among those with steatosis and 25.3 [95%CI: 24.8; 25.8] in those without steatosis, p=.046. Quinolinic acid concentrations were higher among those with steatosis compared to those without (466nM [95%CI: 425; 512] vs. 384nM [95%CI: 375; 394], p<.001). In adjusted analyses, steatosis was independently associated with 14% [95%CI: 4; 25] higher concentration of quinolinic acid, p=.005. After additional adjustment for IFN-γ, steatosis remained associated with 12% [95%CI: 3; 21] higher concentration of quinolinic acid. Kynurenine-to-tryptophan ratio was not associated with steatosis in adjusted analyses, p=.82
Conclusion:
Serum levels of quinolinic acid were significantly higher among PWH with steatosis as defined by CT compared to PWH without steatosis, and this was not mediated by IFN-γ. There was no difference in kynurenine-to-tryptophan ratio. As quinolinic acid may impose oxidative stress, our findings suggest pro-inflammatory changes in the kynurenine pathway of tryptophan metabolism accompany steatosis in the context of HIV infection. However, the specific pathoaetiologic mechanisms underlying these changes should be explored in translational studies.

	Steatosis	
	+ N=61	- N=738
Age years (SD)	54 (10)	51 (11)
Male sex, n (%)	55 (90)	632 (49)
Smoking status, n (%)		
• Current	11 (18)	217 (29)
• Former	28 (46)	259 (35)
• Never	21 (34)	248 (34)
Physical activity, n (%)		
• Sedentary	14 (23)	55 (7.5)
• Moderately Active	39 (64)	544 (74)
• Very Active	4 (7)	103 (14)
Waist-hip-ratio (SD)	1.0 (0.1)	0.9 (0.1)
CD4⁺ count, cells/nL		
• <200	1 (1.6)	12 (1.6)
• 200-349	7 (11)	35 (4.7)
• 350-500	8 (13)	104 (14)
• >500	45 (74)	580 (79)
CD4⁺ nadir <200 cells/nL, n (%)	31 (61)	278 (38)

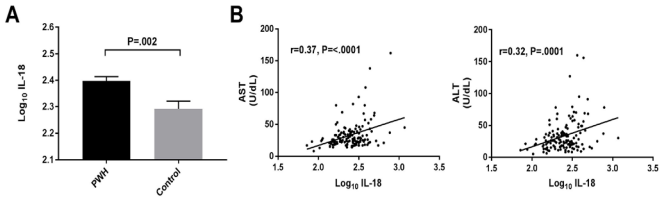
546 IL-18 IS ASSOCIATED WITH HEPATOSTEATOSIS AND HIGHER LIVER ENZYMES IN PEOPLE WITH HIV

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Background: People with HIV (PWH) are at increased risk of development of nonalcoholic fatty liver disease (NAFLD). In addition to insulin resistance and obesity, chronic inflammation is important in the pathogenesis of NAFLD. IL-18, a member of the pro-inflammatory IL-1 family, is regulated by inflammasomes in response to pathogens and danger signals. IL-18 is elevated in PWH and has been implicated in inflammation associated with obesity and NAFLD in people without HIV. We hypothesized that IL-18 may play a role in NAFLD progression in PWH.
Methods: IL-18 was measured by ELISA (R&D) in an observational cohort of PWH and matched uninfected controls in the Boston area. Participants with known hepatitis C and excessive alcohol use were excluded. Liver lipid content was assessed by liver/spleen CT attenuation ratio (an estimate of hepatosteatosis in which a lower ratio indicates higher lipid content). IL-18 was log transformed to approximate a normal distribution.
Results: A total of 134 PWH and 59 HIV-uninfected controls were included in the current analysis. PWH had higher log$_{10}$ IL-18 (2.40 ±0.19 [mean ±SD] vs 2.29 ±0.22, p=0.002), AST (33.3 ±12.9 vs 26.6 ±14.0 U/dL, p=0.01), and ALT (33.4

±25.8 vs 23.8 ±16.6 U/dL, p=0.002) compared to control group. In PWH, log_{10} IL-18 was associated with ALT (r=0.32, p=0.0001), AST (r=0.37, p=<0.0001), triglycerides (r=0.26, p=0.003), FIB-4 score (r=0.25, p=0.003), HIV plasma viral load (r=0.21, p=0.02), caspase-1 (r=0.31, p=0.0003), MCP-1 (r=0.32, p=0.0003), IL-6 (r=0.19, p=0.047), and LPS (r=0.22, p=0.03), and inversely associated with liver/spleen ratio (r=-0.23, p=0.02), HDL (r=-0.31, p=0.0003) and CD4+/CD8+ ratio (r=-0.2, p=0.02). The relationship between log_{10} IL-18 with AST (β=33.5, p=0.0006) and ALT (β=37.9, p=0.001) remained significant after adjusting for age, gender, BMI, HIV RNA, and CD4+ count. In controls, log_{10} IL-18 was also associated with ALT (r=0.37, p=0.004) and inversely associated with HDL (r=-0.27, p=0.04).

Conclusion: We demonstrated significant relationships of IL-18 with liver transaminases and hepatosteatosis, suggesting the potential role of the inflammasome and IL-18 pathway in NAFLD progression in PWH. The relationship of IL-18 with LPS and MCP-1 may indicate IL-18's actions via known causes of NAFLD including intestinal microbial translocation and MCP-1/CCR2 signaling. Further studies are necessary to elucidate precise mechanisms involving IL-18 and inflammatory pathways in NAFLD development in PWH.



Panel A: Log_{10} IL-18 is higher in PWH compared to people without HIV. Height of the bar represents the mean and error bar represents the standard error of the mean
Panel B: Log_{10} IL-18 levels are associated with AST and ALT

547 EASL BIOMARKERS DIFFER IN PREDICTING NAFLD, NASH, AND FIBROSIS IN HIV +/– INDIVIDUALS

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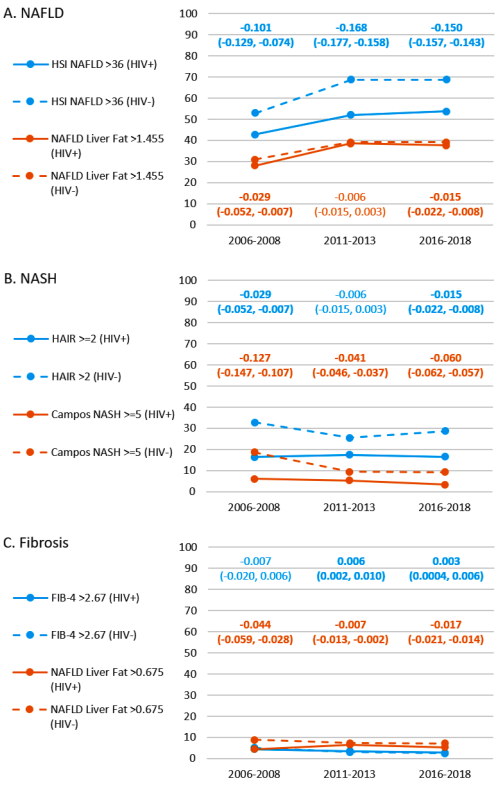
Background: Fatty liver is a major health concern for people living with HIV as well as for the general US population. This study sought to compare 2 EASL-recommended biomarker-based risk scores with high sensitivity and specificity for diagnosing each of the 3 stages of fatty liver disease; NAFLD, NASH, and fat-induced fibrosis over 3 calendar periods.

Methods: All HIV(+) and HIV(-) individuals in OPERA were included if all 6 scores could be calculated during one of the calendar periods of interest (2006-2008, 2011-2013, 2016-2018) and they had no diagnoses of viral hepatitis, celiac, sclerosing cholangitis, or alcohol abuse. To mitigate outliers, average scores were obtained over each period to identify NAFLD (HSI NAFLD score > 36 or NAFLD Liver Fat score > -1.455), NASH (HAIR score >= 2 or Campos NASH score >= 5) and fibrosis (Fib-4 index > 2.67 or NAFLD Liver Fat score > 0.675). Results were age and sex standardized using the HIV(-) population as the standard and risk differences were estimated.

Results: This study included 7,583 HIV(+) and 1,645 HIV(-) in 2006-2008; 25,347 HIV(+) and 65,903 HIV(-) in 2011-2013; and 46,229 HIV(+) and 100,699 HIV(-) persons in 2016-2018. Prevalence estimates varied substantially depending on the score used. HIV(+) persons were much more likely to have all biomarkers required for the 6 tests (>80%) than the HIV(-) persons (<25%). Among HIV(+) persons, after age/sex standardization, NAFLD prevalence increased over the years, ranging from 43-54% with HSI NAFLD score and 28-39% with NAFLD Liver Fat score; NASH prevalence remained stable, ranging from 16-17% with HAIR score and 3-6% with Campos NASH score; fibrosis prevalence remained stable, ranging from 3-4% with FIB-4 and 4-7% with NAFLD Liver Fat score (Fig). HIV(+) persons had a lower standardized prevalence of NAFLD and NASH than HIV(-) persons at most time points with either score (Fig).

Conclusion: Despite similar published predictive values among EASL-recommended biomarker risk scores, calculated prevalence of NAFLD, NASH and liver fibrosis based on these scores differed significantly in the OPERA cohort. The selection of a study population among whom all scores could be calculated likely disproportionally included individuals at higher risk of fatty liver disease, thus overestimating the true prevalence especially among those without HIV. Further clinical validation of these scores is required before broad utilization in the staging of fatty liver disease.

Figure. Prevalence and risk difference of NAFLD, NASH and liver fibrosis, age and sex standardized to the OPERA HIV- population



548 AN RCT OF RALTEGRAVIR- VERSUS EFAVIRENZ-BASED ART IN HIV-HCV COINFECTION

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Background: Drug induced liver injury following initiation of ART is more common in HIV/HCV coinfected patients; however comparative data on hepatotoxicity of ARVs used in this population are lacking as HIV/HCV coinfected patients are largely excluded from clinical trials. We compared hepatotoxicity, virological, and clinical outcomes between raltegravir (RAL)- and efavirenz (EFV)-based ART in HIV/HCV coinfected patients starting 1st-line ART in Vietnam.

Methods: This RCT allocated patients 1:1 to RAL/TDF/FTC or EFV/TDF/FTC between June 2014 and February 2017. Eligibility: HIV infection, ART-naïve, age ≥18, met Vietnam guidelines for ART (CD4 <500 cells/µl or WHO stage 3 or 4 disease), HCV infection (positive HCV antibody and HCV RNA), AST and ALT ≤80 U/L, creatinine clearance ≥60 ml/min, negative HBSAg, no evidence of decompensated cirrhosis, and not on rifampicin. We tested AST, ALT, bilirubin every month and CD4, HIV RNA, HCV RNA, fibroscan, and lipids at w0, 24, 48, and 72. We compared the rates of ALT and AST toxicity > grade 2 (primary outcome) and time to AIDS or death by arm using Kaplan Meier curves and log rank test. We compared the proportions of HIV RNA suppression at w72 by Chi-Square test.

Results: We screened 207 and enrolled 80 participants (39 on RAL, 41 on EFV; median age 32; 88% male, 75% with history of IDU). EFV was associated with higher incidence of ALT and AST elevation (73.0% vs. 62.2%, P=0.14 and 61.8% vs. 42.5%, P=0.10, respectively). The majority of liver events occurred during the first 12 weeks. 5 patients (6%) died (2 in RAL arm died of TB; 3 in EFV arm died of TB, CNS infection, and suicide). 18 developed AIDS events (9 each arm). There were no significant differences in time to AIDS or death (P=0.94) or proportions of HIV RNA <150 copies/mL at w72 (87.9% in RAL, 85.7% in EFV, P=1.00). EFV was associated with a lower CD4 cell gain (170 vs. 224 cells/µL, P=0.52), higher HDL gain (0.37 vs. 0.17 mmol/L, P=0.11), lower reduction

in fibroscan reading (-0.40 vs. -0.70 kPa, P=0.83), and significantly higher incidence of CNS AEs (41.5% vs. 5.3%, P<0.001).
Conclusion: This first pilot RCT showed that EFV was associated with higher risk of hepatotoxicity, lower reduction of fibroscan score, and significantly higher risk of CNS toxicity in HIV/HCV coinfected participants. Our study provides further support to 2019 WHO guidelines which recommends moving away from EFV-based as a preferred 1st-line ART.

Figure A. Hepatotoxicity between raltegravir and efavirenz-based 1st-line therapy over 72 weeks

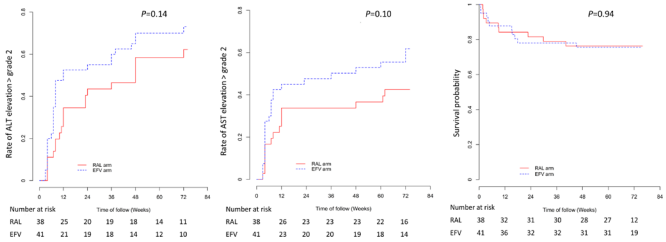


Figure B. Survival between raltegravir and efavirenz over 72 weeks

549 HEPATIC STEATOSIS ASSOCIATED WITH EXPOSURE TO ELVITEGRAVIR AND RALTEGRAVIR

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Background: Treatment with integrase strand transfer inhibitors and nucleotide analogues may be associated with weight gain in people living with HIV (PLWH). Overweight is associated with fatty liver. Here we studied the association of antiretrovirals and moderate-severe hepatic steatosis.
Methods: PLWH without prior or current viral hepatitis or alcohol intake above recommendations were included in 2015-16. Liver steatosis was assessed by unenhanced CT liver scan. Moderate-severe hepatic steatosis was defined by liver attenuation ≤ 48 Hounsfield units. Association with antiretroviral exposure was presented as odds ratio with 95% CI after adjustment for age, sex, body mass index and duration of HIV infection.
Results: PLWH included in the study were predominantly male (86%), European (87%), MSM (73%) and with undetectable HIV RNA (97%). Of 516 PLWH, 37 (7.2%) had moderate-severe hepatic steatosis. The mean treatment duration was 11 years. Moderate-severe hepatic steatosis was associated with any (OR 3.67 (1.29;10.46)) and cumulative (OR 1.19 (1.01;1.41) per year) exposure to raltegravir (number exposed (Nexp) = 59) and with cumulative exposure to elvitegravir (OR 2.84 (1.58;5.10) per year) (Nexp = 63)). The association with cumulative exposure to elvitegravir with emtricitabine/tenofovir disoproxil fumarate (OR 3.06 (1.63;5.75)) or with emtricitabine/tenofovir alafenamide ((OR 3.62 (0.73;17.81)) were comparable. Further, moderate-severe hepatic steatosis was associated with cumulative exposure (OR 1.22 (1.02;1.47) per year) to stavudine (Nexp = 86). Test for interaction with stavudine and raltegravir or elvitegravir were statistically non-significant (P=0.79 and P=0.45). Any exposure (Nexp) to abacavir (268), didanosine (78), emtricitabine (263), lamivudine (424), tenofovir disoproxil fumarate (416), tenofovir alafenamide (33), zidovudine (262), efavirenz (338), etravirine (14), nevirapine (113), rilpivirine (25), atazanavir (137), darunavir (135), lopinavir (61) or dolutegravir (67) was not associated with moderate-severe steatosis.
Conclusion: Moderate-severe hepatic steatosis in PLWH without viral hepatitis or excessive alcohol intake was associated with cumulative exposure to stavudine, elvitegravir and raltegravir. Prospective trials are required to establish a causal association.

550 BENEFITS OF RILPIVIRINE FOR LIVER FIBROSIS IN HIV/HCV COINFECTED SUBJECTS

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Background: Recent studies have described that treatment with rilpivirine (RPV) induces antifibrotic effects in various models of chronic liver disease[1]. Our objective was to analyse whether HIV-infected patients with some degree of liver stiffness measured by transition elastography (TE) and treated with RPV-based regimens showed any improvement. [1]Martí-Rodrigo A, Alegre F, Moragrega ÁB, et al. Gut epub ahead of print doi:10.1136/ gutjnl-2019-31837
Methods: From a 4009 HIV-infected patients cohort in stable follow-up, patients who had some degree of liver-stiffness measured by TE (> 5.2Kpa) and at least 2 TE measurements were selected. A case-control study of exposed and non-exposed subjects to RPV was designed. In cases the exposure to RPV should have started in the period between the two TE measures (baseline and final). Case and control groups were matched for chronic hepatitis C (CHC), sustained virological response (SVR), years of HIV diagnosis (+3 years) and time elapsed between TE measures (+6 months).
A linear model of repeated measures (GLM-RM) of the TE was carried out, controlling for HCV coinfection, time of SVR, time of HIV-infection, time elapsed between TE and BMI measures.
Results: 120 case and 120 control subjects were selected without significant differences in gender (84% male), UDVP transmission (43%), CDC C stage (28%), and undetectable HIV viral load (85%). The median time between TE measurements was 51 (29-68) months. Main variables related to liver stiffness at baseline and final moments are shown in table. In the GLM-RM analysis a significant decrease was found in the measure of TE in case group, (mean difference of -1.9Kpa [CI95% -3.0 - -0.8]; p <0.01) and not in control (mean difference of -0.5Kpa [CI95% -1.6 - 0.6]; p = 0.4). This difference in the case group was found only in subjects who had CHC, mean difference of -2.9Kpa ([CI95% -4.6 - -1.3]; p <0.01).
Conclusion: In patients co-infected with HIV / HCV receiving an ART based on RPV, a significant reduction in liver stiffness measured by TE was observed.

	Control(Baseline)		Case(Baseline)	p	Control(Final)		Case(Final)	p
ET (kPa) §	7(6-9)		7(6-9)	ns	6(5-8)		7(5-8)	ns
BMI §	25(22-28)		25(22-28)	ns	25(23-28)		26(23-29)	ns
HIV-infection §	17(5-21)		16(5-21)	ns				
CHC treated ¥	43(73)		50(85)	ns				
SVR ¥	40(93)		46(92)	ns				
Time after SVR§	20(7-50)		24(9-38)	ns				
GLM-MR	**Control(VHC+)**	**p**	**Case(VHC+)**	**p**	**Control(VHC-)**	**p**	**Case(VHC-)**	**p**
ET baseline*	8.7(7.0-10.4)		10.8(9.1-12.5)		8.2(6.5-9.8)		8.6(6.9-10.3)	
ET final*	8.9(7.4-10.4)		7.9(6.4-9.4)		6.9(5.4-8.3)		7.6(6.1-9.2)	
Diference*	0.2(-1.4 - 1.9)	ns	-2.9(-4.6 - -1.3)	**<0.01**	-1.3(-2.9 - 0.3)	ns	-0.9(-2.6 - 0.7)	ns

§Median (p25th-p75th), ¥N (%) * Marginal Mean (CI95%) adjusted by time of HIV-infection, time between TE, BMI at time of TE measurement

551 ACCURACY OF FIBROSIS-4 FOR CIRRHOSIS IN HIV+ PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC) may develop in the absence of cirrhosis in HIV, and determining how often this occurs can provide insights into mechanisms of carcinogenesis. Studies evaluating the prevalence of cirrhosis in the setting of HCC among HIV+ patients often rely on non-invasive markers, such as the Fibrosis-4 Index for Hepatic Fibrosis (FIB-4). However, the accuracy of FIB-4 for cirrhosis in the setting of HCC has not been determined among HIV+ patients.
Methods: We conducted a cross-sectional study among HIV+ patients in the Veterans Aging Cohort Study with a HCC diagnosis from 1999-2015 and evaluated the accuracy of FIB-4 for medical record-confirmed cirrhosis. HCC diagnoses were identified in the VA cancer registry. FIB-4 was calculated using the age, alanine aminotransferase, aspartate aminotransferase, and platelet count obtained closest, but within one year prior, to the date of HCC diagnosis. Medical records were reviewed to abstract evidence of cirrhosis within one year prior to the date of HCC diagnosis. Cirrhosis was confirmed if: 1) liver histopathology report indicated cirrhosis (METAVIR stage F4 or Ishak fibrosis score ≥5); 2) abdominal imaging indicated cirrhosis (nodular contour of liver, splenomegaly with ascites, or esophageal varices); 3) endoscopy identified esophageal varices or portal gastropathy; 4) paracentesis was performed; or 5) clinician note reported ascites, spontaneous bacterial peritonitis, variceal hemorrhage, or hepatic encephalopathy. The diagnostic accuracy of FIB-4 was

determined by calculation of the positive predictive value (PPV), sensitivity, specificity and area under the receiving operator curve (AUROC).
Results: Incident HCC was diagnosed in 302 HIV+ patients (median age, 56 [IQR, 51-61] years; 299 [99%] male). After chart review, 203 (67.2%, [95% CI, 61.6-72.5%]) had evidence of cirrhosis. Cirrhosis was most commonly identified by radiology (63%) and pathology (32%). Median FIB-4 was 4.37 (IQR, 2.42-7.71) for those with cirrhosis and 2.87 (IQR, 1.66-4.83) for those without cirrhosis ($p<0.001$). FIB-4 identified patients with cirrhosis with an AUROC of 0.67 (95% CI, 0.60-0.73). FIB-4 >4.0 had a PPV of 78.9% to confirm the presence of cirrhosis with a sensitivity of 55.2% and specificity of 69.7% (Table 1).
Conclusion: The diagnostic accuracy of FIB-4 for cirrhosis in the setting of HIV and HCC is modest and may result in misclassification of cirrhosis in this population.

Table 1. Positive predictive value, sensitivity, and specificity of FIB-4 values for cirrhosis at the time of hepatocellular carcinoma diagnosis among HIV+ patients.

FIB-4 value	No cirrhosis by chart review (n=99)	Cirrhosis by chart review (n=203)	PPV	Sensitivity	Specificity
≥1.45	81	194	70.5%	95.6%	18.2%
>3.25	42	131	75.7%	64.5%	57.6%
>3.50[a]	36	121	77.1%	59.6%	63.6%
>4.00	30	112	78.9%	55.2%	69.7%
>4.50	26	96	78.7%	47.3%	73.7%
>5.00	22	91	80.5%	44.8%	77.8%
>5.50	18	84	82.4%	41.4%	81.8%
>5.88[a]	15	76	83.5%	37.4%	84.8%
>6.00	14	75	84.3%	36.9%	85.8%
>7.00	8	58	87.9%	28.6%	91.9%

[a]Previously established FIB-4 thresholds for detection of cirrhosis in Butt AA, et al. JAMA Intern Med. 2015;175:178-85 and Li J, et al. J Viral Hepat 2014; 21:930-7

552 PLASMA MIR-99A AND MIR-100 PREDICT LIVER FIBROSIS PROGRESSION IN HIV/HCV SUBJECTS

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Background: The lack of available biomarkers to diagnose and predict different stages of liver disease, such as NAFLD and NASH, with a non-invasive strategy is currently one of the main challenges that clinicians are facing. Recent evidence indicates that the plasma levels of specific microRNAs (miRs) may be significantly altered in subjects with liver injury, including HIV infected individuals.
Methods: Large-scale deep sequencing analysis of small RNA expression was performed on plasma samples from 46 HIV-1/HCV co-infected subjects that did not exhibit liver fibrosis at the time of sampling. After a mean of 10.3 years, 26 of the former subjects developed liver fibrosis (F2-4) and 20 remained without signs of liver fibrosis (F0-1). Twenty one healthy uninfected donors were also analyzed.
Results: At the time of sampling, there were not significant clinical differences between liver fibrosis progressing and non-progressing subjects (i.e. sex, age, AST, ALT, GGT, platelets, FIB-4, liver fibrosis). A total of 1355 different miRs were identified. When compared with healthy donors, HIV-1/HCV subjects showed significant (fold change> 2 and adjusted $p< 0.05$) dysregulated expression of 44 miRs, 38 of them upregulated (ranging from 13.8 to 2.0 fold increase). Previously described circulating miRs associated with NAFLD in the general population, miR-122, miR-34a and miR-192, were also found here within the 38 upregulated miRs. Of the 38 upregulated miRs, 7 (miR-885-5p, miR-100-5p, miR-193-5p, miR-99a-5p, miR-203a-3p, miR-5588-5p and miR-99a-3p) were significantly upregulated in the 26 subjects that progressed to liver fibrosis when compared to the 20 subjects that did not progressed ($p< 0.005$). Two of these miRs, miR-99a-5p and miR-100-5p, were highly associated with liver fibrosis progression ($p< 0.0001$) and displayed a significant linear correlation with liver fibrosis values of the entire study cohort ($r= 0.51$, $p= 0.0003$ and $r= 0.48$, $p= 0.0006$, respectively).
Conclusion: Circulating miR-99a-5p and miR-100-5p are significantly associated with liver fibrosis progression in subjects with HIV-1/HCV co-infections, even before liver fibrosis is detectable. This study demonstrates the potential of miRs as biomarkers in the progression of liver injury in HIV-infected subjects. Levels of miR-99a-5p and miR-100-5p may be suitable markers of liver fibrosis amelioration in HIV-1/HCV co-infected patients treated with HCV DAAs and cured of HCV infection.

553 HEPATIC FIBROSIS DETERMINED WITH MRE SIGNIFICANTLY PREDICTS COGNITIVE IMPAIRMENT

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Background: Liver disease is a leading cause of morbidity and mortality among people living with HIV (PLWH), and has been associated with neurocognitive impairments (NCI) in PLWH, even in the absence of viral hepatitis. Yet, co-infection with HCV is associated with greater NCI irrespective of cirrhosis or substance abuse. Associations have been reported between indirect measures of liver fibrosis and NCI in PLWH. However, studies using more sensitive markers of liver fibrosis are needed. Magnetic resonance elastography (MRE) is currently the most accurate non-invasive measure of liver fibrosis.
Methods: Cross-sectional analysis of 211 HIV mono-infected (HIV+), 74 HCV mono-infected (HCV+), 76 HIV/HCV coinfected and 265 HIV/HCV uninfected individuals from the Miami Adult Studies on HIV (MASH) Cohort. NCI was determined with the Mini Mental State Examination (MMSE). Neurofilament light chain (NFL), a biomarker of neurodegeneration, was tested in plasma of 26 individuals. Substance use was assessed by questionnaire and urine drug screen. Liver fibrosis indicative of liver disease was determined as liver stiffness (LS) via MRE.
Results: LS was negatively correlated with MMSE scores (rho=-0.11, p=0.008) and directly correlated with NFL (rho=0.46, p=0.017). LS >2.9 kPa (fibrosis) was more prevalent in HCV+ not virally suppressed than those virally suppressed (56.9% vs 29.2%, p=0.002). HCV infection was associated with 3.42 (1.97-5.94) and 1.72 (0.99-2.99) the odds for inflamed or fibrotic liver (LS >2.5 kPa) compared to HIV+ and uninfected participants, respectively ($p<0.0001$). HIV infection was associated with decreased odds for LS >2.5 kPa (adjusted OR 0.71 [0.46-1.08], p=0.007) compared to HIV/HCV uninfected individuals. In PLWH, use of prescription opioids increased the odds for inflamed or fibrotic liver (adjusted OR: 1.62 [0.80-3.24], p=0.008) compared to opioid non-users. Hepatic fibrosis was associated with an adjusted odds ratio of 2.43 (1.28-4.59, p=0.006) for NCI (MMSE ≤24) compared to no fibrosis. In PLWH, cocaine use increased the odds for NCI compared to non-use (adjusted OR: 1.32 [0.67-2.61], p=0.036).
Conclusion: Hepatic fibrosis is associated with NCI irrespective of HIV and/or HCV infection. Substance abuse may contribute to liver disease and cognitive impairments in PLWH. Longitudinal studies with comprehensive neuropsychological testing are needed.

554 CHANGES IN LIVER CANCER SURVIVAL IN HIV INFECTION AFTER MANAGEMENT OPTIMIZATION

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Background: Hepatocellular carcinoma (HCC) has been an important cause of morbidity and mortality in HIV-infected patients during the last twenty years. Previous studies have shown that the survival after HCC diagnosis in HIV-infected patients is extremely low, mainly as a consequence of late diagnosis and a low rate of treatment. This scenario may be changing in recent years, partly due to the systematic HCC surveillance program implementation in this population. Because of this, we assessed changes in the HCC management and its impact on survival of HIV-infected patients.
Methods: Multicenter cohort study (1999-2019). HCC cases diagnosed in HIV-infected patients from the GEHEP-002 cohort were included. The cohort was divided into 2 time periods, according to the year of HCC diagnosis (1999-2009 vs

2010-2019) and the characteristics of the cases were compared between these two periods, including the survival after HCC diagnosis.
Results: 373 patients were included, 120 (32%) in the 1999-2009 period (1st period) and 253 (68%) in 2010-2019 (2nd period). In the 1st period, HCC diagnosis after SVR occurred in 12 (10.5%) patients compared with 66 (27%) in the 2nd period ($p < 0.001$). There was a greater proportion of HCC diagnosis by screening in the 2nd period [1st period, 46 (38%) patients vs 2nd period, 129 (51%); $p = 0.02$]. Likewise, there was a greater frequency of early diagnosis (BCLC stage 0-A) in the 2nd period [1st period, 25 (21%) patients vs 2nd period, 95 (37.5%); $p = 0.001$]. Sixty-four (53%) patients received some treatment strategy for HCC in 1999-2009 period, whereas 186 (73.5%) patients were treated for HCC in the 2nd period ($p < 0.001$). Furthermore, the proportion of curative therapies was higher in the 2nd period [1st period, 28 (23%) vs 2nd period, 109 (43%); $p < 0.001$]. The median survival (Q1-Q3) after HCC diagnosis was 6 (2.93-9.07) months in 1999-2009 and 16 (9.9-22.1) months since 2010 ($p = 0.035$).
Conclusion: The HCC clinical management in HIV-infected patients has improved in the last decade in Spain. Thus, the proportion of early diagnosis has increased, possibly due to an increasing rate of HCC detection by surveillance, resulting in a greater number of curative therapies. Consequently, the HCC survival in HIV-infected patients has considerably lengthened in recent years.

555 LIVER PATHOLOGY IN HIV-POSITIVE SUBJECTS UNDERGOING LIVER TRANSPLANTATION

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Background: Liver transplantation (LT) represents the best therapeutic option for end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC). Although LT in HIV+ showed similar survival rates compared to HIV- recipients, HCV recurrence and HCC severity seem more harmful. Aim of this study is to compare pathologic features of livers explanted from HIV+ and HIV- patients.
Methods: All subjects with HCV/HBV infection who underwent LT for ESLD or HCC from 2012 were retrospectively evaluated. Demographic and clinical features as well as macroscopic and histopathologic characteristics of explanted livers were collected. Descriptive statistics and non-parametric tests (Chi-square and Mann-Whitney U, as appropriate) were used.
Results: 278 individuals, mainly men (83.1%), with a median age of 57 (IQR 52-63) years were included; 30 (10.8%) were HIV+. HCC was the indication for LT in 65.8% of cases. HIV+ subjects were younger (53 vs 58 years, $p<0.00001$), more commonly HCV+ after sustained virologic response achievement (43% vs 21%, $p=0.0199$) and less diabetic (10% vs 31%, $p=0.0146$). HIV+ subjects transplanted for ESLD showed a worse Child class (11 vs 10, $p=0.0308$) and a higher MELD score at the limit of significance (23 vs 17, $p=0.0836$), while no difference was observed for those transplanted for HCC. BCLC stage, alfa-fetoprotein level, portal vein thrombosis and previous bridging treatments were similar in the two groups. Table 1 shows features of included patients and explanted livers: HIV+ were comparable to HIV- individuals in terms of number and size of lesions, grading stage and vascular invasion. Histotype distribution resulted different, in particular for a higher presence of pseudoglandular pattern and cholangiocarcinoma in HIV- subjects. The presence of a capsule was more common in HIV- subjects, although they showed higher margin invasion. Of note, 30% of cases in both groups did not satisfy the so-called Milan criteria for LT eligibility.
Conclusion: Despite a lower presence of traditional risk factors for HCC (older age, viremic HCV, diabetes), HIV+ individuals showed several macroscopic and pathologic features similar to HIV- recipients. Although no histopathologic feature has been included in prognostic staging systems because of poor reproducibility, it is recognized that trabecular and pseudoglandular HCC are associated with different gene signature mutations, thus possible different mechanisms in tumor development in the two populations could be alleged.

Table 1. Demographic and clinical features of HIV+ and HIV- LT recipients and histopathologic characteristics of explanted livers.

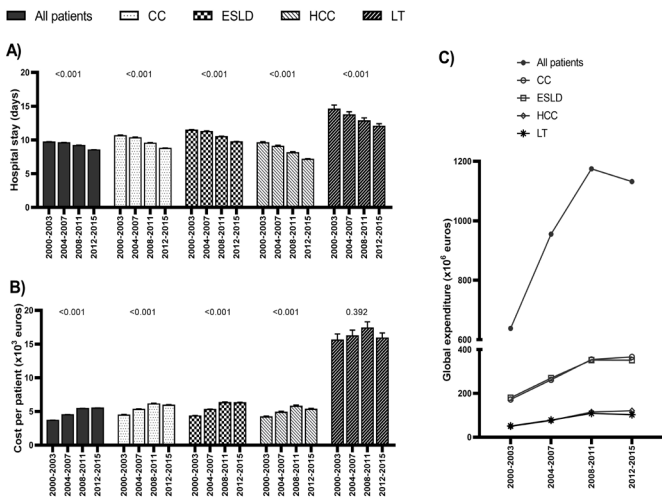
		HIV+ (N=30)	HIV- (N=248)	p
Age, years, median (IQR)		53 (50-56)	58 (52-63)	**<0.00001**
Male sex, %		83	83	0.9704
BMI, median (IQR)		23 (21-25)	25 (23-28)	0.5287
Viral hepatitis infection	HBV, %	17	23	**0.0199**
	Viremic HCV, %	40	56	
	HCV in SVR, %	43	21	
HCV Genotype	1A, %	40	14	**0.0073**
	1B, %	20	44	
	2, %	--	7	
	3, %	24	27	
	4, %	18	8	
Child-Pugh Class in ESLD cases, median (IQR)		11 (10-12)	10 (9-11)	**0.0308**
Child-Pugh Class in HCC cases, median (IQR)		7 (5-9)	6 (5-8)	0.5961
MELD score in ESLD cases, median (IQR)		23 (18-31)	17 (16-24)	**0.0836**
MELD score in HCC cases, median (IQR)		13 (9-17)	12 (9-15)	0.4354
Alfa-fetoprotein, ng/dL, median (IQR)		5.4 (3.6-13.1)	7 (3.5-18.7)	0.3221
Portal vein thrombosis, %		20	13	0.3187
Time in waiting list, months, median (IQR)		18.4 (8.7-33.0)	18.1 (7.9-35.9)	0.6965
Diabetes, %		10	31	**0.0146**
Number of bridging treatments^, mean		2.3	1.7	0.4368
BCLC Stage	A, %	56	55	0.2293
	B, %	39	22	
	C, %	6	23	
	D, %	--	1	
Weight of explanted liver, mg, median (IQR)*		1481 (1280-1700)	1300 (1003-1500)	**0.0111**
Classification according to the evidence of lesions in explanted liver	No HCC, %	37	28	0.4631
	Unexpected HCC, %	3	5	
	Cured HCC, %	13	11	
	HCC Milan-IN, %	13	29	
	HCC Milan-OUT, %	33	31	
Number of lesions, median (IQR)		3 (1-7)	2 (1-4)	0.2671
Cumulative size of lesions, cm, median (IQR)		4.6 (0.7-6.1)	2.9 (1-4.7)	0.3125
Grading	G1, %	21	15	0.5433
	G2, %	42	58	
	G3, %	16	22	
	Missing, %	21	13	
Architectural pattern and histotypes	Trabecular, %	28	30	**0.0004**
	Pseudoglandular, %	--	2	
	Mixed trabecular/pseudoglandular, %	--	16	
	Cholangiocarcinoma, %	--	4	
	Missing, %	72	52	
Cytological pattern: clear cells, %		5	10	0.6091
Capsular structure	Capsular, %	25	25	**0.0223**
	Pseudocapsular, %	63	71	
	No capsule, %	12	4	
Capsular invasion, %		38	72	**0.0384**
Vascular invasion, %		42	29	0.2236

BMI: body mass index; IQR: interquartile range; SVR: sustained virological response; ESLD: end-stage liver disease; HCC: hepatocellular carcinoma; BCLC: Barcelona clinical staging classification.
^ including trans arterial chemoembolization, radiofrequency ablation/microwave ablation, surgical excision.
* confirmed after adjusting for sex and BMI.

556 EPIDEMIOLOGICAL TREND OF CHRONIC HEPATITIS C IN SPAIN (2000-2015): NATIONWIDE STUDY

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Background: Chronically Hepatitis C infected patients are at risk of progression to liver disease, developing liver fibrosis, compensated cirrhosis (CC), end-stage liver disease (ESLD), hepatocellular carcinoma (HCC), and finally dying, or need for liver transplantation (LT). The management of those patients generates a substantial economic cost on the National Health Services.
Objective: To analyze the epidemiological trends of hospital admissions, intra-hospital deaths, and costs related to chronic hepatitis C (CHC) taking into account four major clinical stages: CC, ESLD, HCC and LT during the 21st century in Spain.
Methods: Retrospective study in patients with CHC and a hospital admission in the Spanish Minimum Basic Data Set (2000-2015). The outcome variables were hospital admission, death, length of hospital stay (LOHS) and costs. ICD-9-CM codes were used for HCV diagnosis and HCV chronical clinical stages : CHC (070.44, 070.51, 070.54, 070.7x, or V02.62); compensated cirrhosis (571.2 or 571.5); end stage liver disease (572.2, 572.3, 572.4, 456.0 – 456.21, 530.7, 530.82, 578.X, 789.5, 567.23, 572.8, 54.9, 42.91, 44.91, 96.06, 573); hepatocellular carcinoma (155.x, 155.0, 155.1, 155.2); liver transplantation (996.82, V42.7, 50.5x).
Results: 868,523 hospital admissions with CHC (25.5% CC, 25.3% ESLD, 8.6% HCC, and 2.5% LT) were identified. Overall rates of hospital admission and mortality increased from 2000-2003 to 2004-2007, but as of 2008, these rates stabilized and/or decreased. We found an upward trend for hospitalization percentage in CC (from 22.3% to 30%; $p<0.001$), ESLD (from 23.9% to 27.1%; $p<0.001$), HCC (from 7.4% to 11%; $p<0.001$), and LT (from 0.07% to 0.10%; $p=0.003$). We also found an upward trend for case fatality rate, except in ESLD ($p=0.944$). Gender and age influenced the evolution of hospitalization rates and mortality differently. LOHS showed a significant downward trend in all strata analyzed ($p<0.001$) (Fig1A). Cost per patient had a significant upward trend ($p<0.001$), except in LT, and a decrease from 2008-2011 to 2012-2015 in CC ($p=0.025$), HCC ($p<0.001$), and LT ($p=0.050$) was found (Fig1B). Global expedienture amounted up to 1200x106 euros in 2008-2011, decreasing slightly in 2012-2015 (Fig 1C).
Conclusion: The initial upward trend of the disease burden in chronic hepatitis C has changed during the 21st century (2000-2015) in Spain, improving in many parameters after 2004-2007, particularly in the last calendar period (2012-2015)



557 HEPATITIS C COINFECTION AND EXTRAHEPATIC CANCER INCIDENCE AMONG PEOPLE WITH HIV

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Background: Hepatitis C virus (HCV) coinfection may contribute to the elevated risk of cancers among people with HIV infection through increased inflammation or immune activation. Although HCV coinfection is a known risk factor for liver cancer, HCV may also be associated with an increased risk of extrahepatic cancers among people with HIV infection. However, few studies have explored the risk of extrahepatic cancers among people with HIV/HCV coinfection or the potential impact of HCV treatment using direct-acting antiviral agents (DAAs).

Methods: Our study population included adults in HIV care at a CNICS site in the U.S. during 1995-2018, excluding those with previous cancer diagnoses and those without HCV testing. We defined HCV infection by positive HCV antibody or detectable HCV RNA level up to baseline (i.e., 180 days after enrollment). Patients were followed from baseline until cancer diagnosis, death, or last HIV care visit. We used Cox regression to estimate hazard ratios (HRs) for extrahepatic cancer incidence among patients with HIV/HCV coinfection compared with those with HIV monoinfection. We used standardized morbidity ratio weights to compare extrahepatic cancer incidence among patients with HIV/HCV coinfection with the incidence we would have observed under a hypothetical scenario in which all patients with HIV/HCV coinfection were successfully treated with DAAs at baseline. To explore potential misclassification of HCV status, we conducted a sensitivity analysis classifying those who only had a positive HCV antibody as missing HCV status.

Results: Of the 21,310 adults in our analyses, 3823 (18%) were coinfected with HCV. Incidence rates of any extrahepatic cancer among patients with HIV/HCV coinfection and HIV monoinfection were 643 and 572 cases per 100,000 person-years, respectively, with a crude HR of 1.13 (99% CI: 0.89, 1.43; Table). In crude analyses, patients with HIV/HCV coinfection were at elevated risk of cancer of the kidney and lung, and of inflammation-related cancers (defined in Table footnote), compared with patients with HIV monoinfection. In weighted analyses (Table), patients with HIV/HCV coinfection remained at elevated risk of kidney cancer (HR 3.43, 99% CI: 1.06, 11.06). Results were similar when classifying those with only positive HCV antibody as missing HCV status.

Conclusion: Extrahepatic cancers driven by immune dysfunction, specifically kidney cancer, may be prevented by HCV-curative DAA therapies among patients with HIV/HCV coinfection.

Table. Crude and weighted hazard ratios for extrahepatic cancers among patients with HIV/HCV coinfection compared with those with HIV monoinfection, Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), 1995-2018

	Crude hazard ratio (99% CI)	Weighted hazard ratio (99% CI)[a]
Any extrahepatic cancer	1.13 (0.89, 1.43)	0.83 (0.63, 1.08)
Anal	0.85 (0.40, 1.79)	0.60 (0.27, 1.37)
Kidney	4.40 (1.47, 13.21)	3.43 (1.06, 11.06)
Lung	2.17 (1.26, 3.73)	1.23 (0.67, 2.25)
Non-Hodgkin's lymphoma	1.39 (0.83, 2.32)	1.09 (0.60, 1.98)
Prostate (men only)	1.71 (0.84, 3.48)	1.06 (0.49, 2.30)
Infection-related extrahepatic cancers[b]	0.93 (0.68, 1.27)	0.72 (0.50, 1.02)
Inflammation-related extrahepatic cancers[c]	2.00 (1.29, 3.10)	1.31 (0.80, 2.14)

HIV, human immunodeficiency virus; HCV, hepatitis C virus; CFAR, Centers for AIDS Research.
[a] Standardized morbidity ratio weights included age, sex, race/ethnicity, calendar era of CNICS entry, hepatitis B status, alcohol use, drug use, smoking, liver fibrosis as measured by FIB-4, CD4 count, and HIV suppression. Patients with HIV monoinfection were weighted to reflect the distribution of potential confounders among those with HIV/HCV coinfection.
[b] Infection-related cancers included anal cancer, anorectum cancer, cervical cancer, Hodgkin's lymphoma, Kaposi's sarcoma, non-Hodgkin's lymphoma, and cancers of the oral cavity and pharynx.
[c] Inflammation-related cancers included bladder cancer, colon cancer, esophageal cancer, lung cancer, multiple myeloma, pancreatic cancer, and stomach cancer.

558 SYNDEMIC OF VIRAL COINFECTIONS AND INCIDENT END-STAGE RENAL DISEASE

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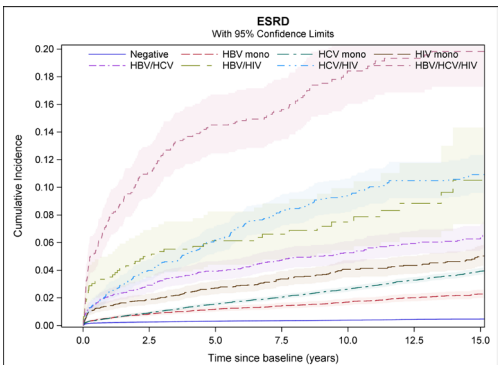
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Background: Advances in infection care and treatment have improved the life expectancy of persons living with HIV. Consequently, persons living with HIV are aging with increased risk of chronic conditions such as liver and cardiovascular diseases, lung cancer, neurocognitive impairment and chronic kidney disease (CKD). Syndemic viral infections are associated with increased risk of CKD and end-stage renal disease (ESRD). However, population-level estimates of the impact of syndemic co-infections are lacking. This study assessed the effect of HBV, HCV and HIV co-infections on incident ESRD in a large population-based cohort.

Methods: The British Columbia (BC) Hepatitis Testers Cohort includes ~1.7 million individuals tested for HCV or HIV, or reported as a case of HBV, HCV, or HIV in BC, and is linked with various administrative healthcare data. ESRD was defined through ICD-9/10 codes. Individuals tested for all three infections since 1990 were followed from the date of their last test until the earliest of 1) incident ESRD, 2) death or 3) 12/31/2015. Fine and Gray competing risk models with adjustment for age, sex, ethnicity, alcohol and injection substance use, social/material deprivation, and history of diabetes and hypertension were used to estimate sub-distributional hazard ratios (HRs) and 95% confidence intervals (CIs) for incident ESRD. Further stratified analysis was performed accounting for diabetes.

Results: Of 524,186 individuals tested, we observed 3,762 incident ESRD events (0.7%) and 24,714 deaths (4.7%) during a median follow-up of 4.1 years. The highest ESRD incidence rate (per 1,000 person-years) was observed in persons with triple HBV/HCV/HIV infection (26.7) followed by HCV/HIV (10.2), HBV/HIV (10.0), HBV/HCV co-infection (5.8), and HIV (3.8), HCV (3.0) and HBV mono-infection (1.8) (Figure). In multivariable analysis, relative to those with no chronic infections, those with triple infection had the highest relative hazard for ESRD (HR 34, 95% CI: 29-41). When stratified by diabetes status, triple infection still had the highest relative hazard for ESRD (HRs 16, 95% CI: 5-28 and 38, 95% CI: 31-46) for both persons with diabetes and those without, respectively.

Conclusion: Persons living with HIV/HBV/HCV triple infection were at highest risk of ESRD. Management of these syndemic conditions, particularly through HBV, HCV and/or HIV treatment could reduce the risk of ESRD among people with co-infections.



559 CAUSE OF DEATH AMONG THOSE DIAGNOSED WITH HEPATITIS C IN WASHINGTON, DC, 2009-2017

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Background: There has been very limited research on mortality among people diagnosed with Hepatitis C (HCV) in the District of Columbia (DC). As the opioid use crisis continues to grow both nationally and locally, knowledge of how opiate use deaths has had an impact on residents, especially among those with HCV, may be useful in strategizing intervention programs. The purpose of this analysis is to describe the differentiating causes of death among those diagnosed with HCV in DC.
Methods: Data from DC Health HCV surveillance system and Vital Statistics records were matched to identify DC residents diagnosed with HCV who died between 2009 and 2017. Bivariate analysis was performed to identify differences between opiate overdose and non-opiate overdose deaths by demographics including gender identity, race/ethnicity age at death, HIV co-infection, year of death, HCV diagnosis class and last RNA results. Standardized mortality ratios for all causes of death were calculated and adjusted for age, sex, and death year.
Results: Between 2009 and 2017, there were 4,633 deaths among DC residents diagnosed with HCV. Majority of deaths were among those who were male (68.1%), Black (60.2%) and died between the ages of 50 and 69 (76.5%). Cardiovascular disease was the leading primary cause of death (30.6%) followed by non-AIDS defining cancers (12.6%), opiate overdose (9.8%) and liver diseases (8.9%). Over the 9-year period, there was a 561% increase in opiate overdose deaths compared to a 69.1% decrease in liver-related deaths. Compared to persons who had a non-opiate related death between 2009 and 2017, HCV cases with a death due to opiate overdose were more likely to have a death age between the ages of 50-69 (84.1% vs 75.6%, p<.0001), have a year of death in 2017 (26.2% vs 13.6%, p<.0001), and have a positive/detectable result at their last RNA screening (62.1% vs 53.7%, p<.0001). There were no differences by gender identity, race/ethnicity and HIV-coinfection. Risk of dying from opiate-overdose was significantly greater than liver-related causes (p=0.0009), with the greatest excess risk in men aged 50-69 years (12.58, 5.91-26.78).
Conclusion: This analysis highlights that older adult males with hepatitis C face a higher mortality risk from continued opiate drug use than from their hepatitis infection. As local governments continue to strategize interventions around opioid overdose, it will be important to include approaches around specific subpopulations affected by HCV.

560 CAUSES OF DEATH IN PERSONS WITH AND WITHOUT HCV INFECTION

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Background: HCV is associated with a higher risk of overall mortality and several hepatic and extrahepatic consequences, including atherosclerotic cardiovascular disease (ACVD), diabetes, chronic kidney disease, hepatocellular carcinoma (HCC) and certain non-liver cancers. Whether the excess mortality is primarily due to liver-related or other causes is unknown. Knowing the most common causes of death is critically important to design targeted strategies to reduce mortality in persons with HCV infection. Our objective was to determine the most common causes of death in persons with and without HCV infection.
Methods: HCV infected and uninfected participants in the ERCHIVS cohort between Jan 1, 2002 to December 31, 2016 were included. To determine cause of death, we linked deceased ERCHIVES participants to the National Death Index (NDI) data updated to end of 2016. NDI is a part of the National Center for Health Statistics and compiles cause of death data from the death certificates obtained from state vital statistics offices. Cause of death was retrieved from the underlying cause listed on the death certificate by using ICD-10 codes. Each cause of death was categorized according to the primary organ system listed in the cause of death form. Liver-related causes included viral hepatitis and HCC, but excluded alcohol-related liver disease. Malignancy included all malignant cancers but excluded benign neoplasms and HCC. Self-harm category included suicide, intentional self-harm, intentional and unintentional drug-overdose but excluded accidental death due to external causes, e.g. road traffic accidents, homicide and falls.
Results: Among 754,670 ERCHIVES participants, a total of 182,744 deaths were recorded during the study period (113,650 in HCV+ and 69,094 in HCV-). Among persons with HCV, the five most common causes of death were: Liver related (19.6%); malignancy (18.0%); ASCVD (16.8%); self-harm (6.2%); pulmonary disease (5.6%). Among those without HCV, the five most common causes were: Malignancy (25.2%); ASCVD (23.0%); pulmonary disease (7.8%); infections (5.4%); endocrine including diabetes (5.1%).
Conclusion: Liver disease, ASCVD and malignancy are responsible for the majority of deaths HCV+ persons. Self-harm is responsible for twice as many deaths in HCV+ vs. HCV-. Targeted strategies to reduce non-liver-related causes of death are needed to reduce mortality further in HCV+ persons.

Figure. Most common causes of death overall, and by hepatitis C virus infection status in the ERCHIVES cohort.

	TOTAL		HCV+		HCV-		P-value
	N	%	N	%	N	%	
Malignancy	37877	20.7	20489	18.0	17388	25.2	<.0001
ASCVD	34985	19.1	19091	16.8	15894	23.0	<.0001
Liver-related	24522	13.4	22298	19.6	2224	3.2	<.0001
Pulmonary disease	11772	6.4	6417	5.6	5355	7.8	<.0001
Infections	9819	5.4	6087	5.4	3732	5.4	0.68
Self-harm	9432	5.2	7045	6.2	2387	3.5	<.0001
Alcohol related	7528	4.1	5100	4.5	2428	3.5	<.0001
Endocrine	7215	3.9	3698	3.3	3517	5.1	<.0001
Neurological	7117	3.9	3721	3.3	3396	4.9	<.0001
Accidental	6612	3.6	4158	3.7	2454	3.6	0.24
Genitourinary	5127	2.8	3036	2.7	2091	3.0	<.0001
Gastrointestinal	2377	1.3	1434	1.3	943	1.4	0.06
HIV infection	2130	1.2	1615	1.4	515	0.7	<.0001
Drug use	649	0.4	550	0.5	99	0.1	<.0001
Autoimmune diseases	312	0.2	159	0.1	153	0.2	<.0001
Biliary disease	153	0.1	89	0.1	64	0.1	0.3
Psychiatric Disorders	149	0.1	82	0.1	67	0.1	0.07
Other causes	14968	8.2	8581	7.6	6387	9.2	<.0001

Abbreviations: HCV, hepatitis C virus infection; ASCVD, atherosclerotic cardiovascular disease;

561 RESOLVING HCV SUBTYPES IN A BELGIAN COHORT BY FULL GENOME NEXT-GENERATION SEQUENCING

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Background: In order to reach WHOs goal of HCV elimination it has been suggested to prioritize populations that are actively propagating infection, given e.g. several outbreaks of HCV among HIV-infected men who have sex with men in the last decade. Genotyping the infecting virus is part of routine care to guide antiviral treatment, but commercial assays have been shown to occasionally report inaccurate results. In this study, we use next-generation sequencing (NGS) to increase the discriminatory power and evaluate the accuracy of genotyping in routine HCV care.
Methods: From the University Hospitals of Leuven, Belgium, 64 samples from patients with HIV/HCV co-infection were selected and matched with 86 samples from HCV mono-infected patients to exhibit a similar genotype distribution based on determinations with the VERSANT HCV Genotype Assay. For the co-infected patients, 30.4%, 66.1%, and 46.4% reported intravenous drug use, same-sex practices, and being born outside of Belgium, respectively. HCV genomes were generated using the veSeq-HCV protocol and an in-house optimized bioinformatics pipeline. Concordance between geno- and subtypes designated by VERSANT and the Hepatitis C Virus Phylogenetic Typing Tool v2.4 using the generated consensus sequence was determined.
Results: When considering only the 87 samples with an associated VERSANT genotyping record and >90% of the coding region of HCV sequenced to a depth >100, the genotype distribution following NGS was: genotype 1: 72% (42: 1b, 21: 1a), genotype 4: 15% (8: 4d, 2: 4k, 1 each: 4q, 4c, 4r), genotype 3: 9% (3: 3a) and genotype 2: 3% (1 each: 2a, 2c, 2i). Despite not all samples passing quality control thresholds, 112 samples had both a genotype determined by VERSANT and the phylogenetic typing tool. Of these, 78% had identical subtypes using VERSANT and NGS, 20% had a genotype specified into one of its constituent subtypes, one sample had a different subtype (VERSANT: 1b, NGS: 1a) and one had a different genotype (VERSANT: 1a, NGS: 4d). Based on near full-genome coverage by contigs of different genotypes generated de novo, 5 samples showed signs of mixed infection not indicated by VERSANT.
Conclusion: While the applied sequencing strategy requires further optimisation to reliably classify all geno- and subtypes across a broad viral load range, a good overall concordance was found with the genotype determined by VERSANT. The higher resolution of NGS proves capable of resolving specific subtypes and detecting cases of potential mixed infections.

562 VIROLOGIC PATTERNS OF HCV PATIENTS WITH FAILURE TO SECOND-GENERATION DAAs

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Background: Despite the excellent efficacy, direct-acting antivirals (DAA)-regimens are associated with failure in about 5% of cases. To characterize the virological patterns and the resistant-associated substitutions (RASs) in the patients with failure to second-line DAA-regimen. It may help to identify the best approach of new line DAA-regimen.

Methods: All the consecutive 63 HCV patients (pts) with failure to IFN-free regimen observed at the laboratory of infectious diseases of University of Campania, Naples from January 2018 to February 2019 were were enrolled. All the pts had been treated with DAA-regimens according HCV genotype, international guidelines and local availability. Sanger sequencing of NS3 (for genotypes 1 and 4), NS5A and NS5B (for all genotypes) was performed at failure by home-made protocols.

Results: Table 1 shows characteristics of patients enrolled and type of treatment. According to therapeutic outcome, 90.5% relapse, 4.7% breakthrough and 4.7% non-response. Among the 63 patients failed at three therapeutic regimens, 19 (30.1%) were been treated with Sofosbuvir+Velpatasvir, 11 (17.4%) with Glecaprevir/Pibrentasvir and 33 (52.4%) with Elbasvir/Grazoprevir. The duration of DAA in months, median (range) 12 (8-24), the timing of resistence test in months at the end of treatment, median (range) 5 (1-19). The NS5A-RASs were more frequent in Sofosbuvir+Velpatasvir (17/19, 89.5%) and in Grazoprevir/Elbasvir (32/33, 97%) failed patients than in Glecaprevir/Pibrentasvir (4/11, 36.7%) failed patients (p=0,002 and 0,000 respectively). According to Sofosbuvir/Velpatasvir regimen 36.4% pts showed at least 2 RASs in at least two HCV region including NS5A and 70.3% pts showed at least 2 RASs only in NS5A region. Considering Grazoprevir/Elbasvir regimen 27.3% pts showed at least 2 RASs in at least two HCV region including NS5A and 88% pts showed at least 2 RASs only in NS5A region. (p=0.00). All 21 re-treated patients with Sofosbuvir/Velpatasvir /Voxilaprevir, obtained with SVR. The re-treatment was guided by genotyping test.

Conclusion: Patients with failure to a second-line therapeutic regimens frequently present mutations above all in the NS5A region. At re-treatment all patients obtained SVR. According to our real-life experience, re-treatment with the new regimes is effective and safe.

Table 1: Demographic, virological and clinical characteristics of the patients enrolled and type of treatment

N° patients	63
Median age, years (range)	67.5 (42-81)
Males, n° (%)	38 (60)
HCV RNA, IU/ml, median (range)	2.27E+06 (9.08E+00-1.10E+07)
Patients with cirrhosis, n° (%)	21 (33.3)
• Relapser	57 (90.5)
• Non-responder	3 (4.7)
• Breakthrough	3 (4.7)
HCV genotype 1a, n° (%)	5 (8)
treated with:	
- Sofosbuvir plus velpatasvir ± ribavirin	4 (80)
- Grazoprevir plus elbasvir ±ribavirin	0
- Glecaprevir plus pibrentasvir ±ribavirin	1 (20)
HCV genotype 1b, n° (%)	41 (65)
treated with:	
- Sofosbuvir plus velpatasvir ± ribavirin	5 (12.2)
- Grazoprevir plus elbasvir ±ribavirin	33 (80.5)
- Glecaprevir plus pibrentasvir ±ribavirin	3 (7.3)
HCV genotype 2a/2c, n° (%)	5 (8)
treated with:	
- Sofosbuvir plus velpatasvir ± ribavirin	1 (20)
- Grazoprevir plus elbasvir ±ribavirin	0
- Glecaprevir plus pibrentasvir ±ribavirin	4 (80)
HCV genotype 3a/3b, n° (%)	9 (14.3)
treated with:	
- Sofosbuvir plus velpatasvir ± ribavirin	7 (78)
- Grazoprevir plus elbasvir ±ribavirin	0
- Glecaprevir plus pibrentasvir ±ribavirin	2 (22.2)
HCV genotype 4, n° (%)	3 (4.7)
treated with:	
- Sofosbuvir plus velpatasvir ± ribavirin	2 (66.6)
- Grazoprevir plus elbasvir ±ribavirin	0
- Glecaprevir plus pibrentasvir ±ribavirin	1(33.3)
Duration of DAA in months, median (range)	12 (8-24)

563 RESISTANCE-ASSOCIATED SUBSTITUTIONS (RAS) IN "UNUSUAL" HCV SUBTYPES

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Background: "Unusual" Hepatitis C virus (HCV) subtypes in patients from Africa and Asia origin have been associated with a lower sustained virological response(SVR) to DAAs. This can be ascribed to polymorphisms at relevant amino acid positions compared to the most sensitive subtype in the same genotype. Using the global SHARED network, we aimed to assess the prevalence of RAS and RAS patterns at failure among unusual HCV subtypes, defined as GT1 non1a/b, GT2 non2a/b, GT3 non3a, GT-4 non4a/d, GT5, and GT6.

Methods: We extracted data from the SHARED database of patients who did not achieve SVR. Only patients who failed DAA regimens recommended by EASL guidelines were included. Geno- and subtype were sequence-derived, and analyses grouped by subtype. RAS were analysed at positions according to the 2018 EASL guidelines.

Results: We analysed 60 unusual subtypes among DAA failures, including: GT2c(n=8), GT3b(n=6), GT3h(n=7) and GT4r(n=10) followed by GT4v(n=3), GT2q,3k,4g,4o, and 6q(n=2, each), and GT1l,2j,3g,4b,4f,4k,4q,4t, 6h, 6p,6r and 6xe(n=1, each). Patients failed; SOF/DCV(n= 14), SOF/VEL +/- RBV(n=13), and EBR/GZR(n=10), SOF/LDV +/- RBV(n=10), G/P(n=5) or other regimens(n=2). At failure, all patients harbored NS5A RASs regardless of their subtype, with a mean number of 3 NS5A RAS per sample. Interestingly, failures with GT6h/p/r/xe carried 5 to 6 NS5A polymorphisms possibly associated with reduced NS5A inhibitor susceptibility. All GT3h failures harbored a S62M RAS with unknown impact, 71% of which were combined with the Y93H/F. All GT4r failures harbored L28M/T/V RAS in association with L30R with or without L31M/F. All GT-3b and GT3g harbored the A30K+L31M+S62D/E/I combination. Additionally, among NS3 failures RAS at position 168(D168V/N/E) were observed in 50% of patients(n=6/12). Importantly, combinations of several NS3 RAS were detected in specific subtypes(GT4g with R155Q+A156T/I/V+D168N, GT6q with A156F+D168V in patients failing GZP/ELB and G/P respectively). The S282T variant in NS5B occurred in 20% of GT4r patients(n=1).

Conclusion: Unusual subtypes(mainly but not only GT3b, 3h, and 4r) may be overrepresented among failures, suggesting lower SVR rates due to the presence of polymorphisms. In-depth characterization of these subtypes is crucial, in Africa and Asia where these subtypes are common as well as in countries of immigration from these regions. Our results emphasize the need for identification of RAS in these subtypes and their in vitro drug susceptibilities.

564 TRANSMISSION OF THE NS5A-RESISTANT VARIANT M28V AMONG ACUTE HIV/HCV COINFECTED MSM

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Background: The World Health Organization (WHO) has declared to eliminate hepatitis C virus (HCV) as a global health threat by 2030. To achieve this goal, WHO recommends expanding direct-acting antivirals (DAAs), which can achieve high cure rates and thereby prevent onward transmission. Widespread use of DAAs has drastically reduced new HCV infections in the Netherlands. Unfortunately, virological failure can still occur and is associated with emergence of resistance associated substitutions (RAS). Transmission of RAS can hamper HCV elimination efforts. In Western Europe, HCV is predominantly transmitted between HIV-positive men-who-have-sex-with-men (MSM). We investigated the transmission dynamics of HCV and its specific RAS among MSM, before and after the widespread use of DAAs.

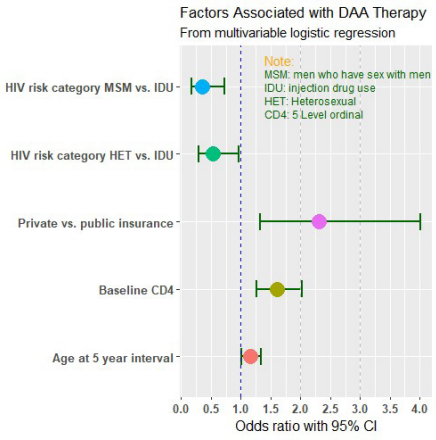
Methods: We included 90 plasma samples from 101 acute HCV genotype 1a infected HIV-positive MSM that were diagnosed in one Belgian and ten Dutch HIV-treatment centres between 2013 and 2018. Samples were subjected to Sanger sequencing or Illumina sequencing, using a 15% cut-off for variant calling. RAS were defined based on the EASL guidelines. Phylogenetic analysis was based on concatenated NS5A and NS5B sequences from the included plasma samples and from 425 publicly available sequences. Clusters were defined based on a bootstrap support of 100% and a genetic distance of <1.5% (maximum likelihood analysis GTR+G4+I).
Results: We found strong clustering of HCV sequences and distinguished five major clusters including 84% of individuals. Four clusters included at least 10 individuals that were sampled in different treatment centres. One-third of all new HCV infections (28 individuals) clustered in one large cluster, of which 96% harboured the NS5A RAS M28V. The number of clusters and the proportion of individuals belonging to a cluster remained stable in the period before and after introduction of DAAs in 2015.
Conclusion: Large clusters of acute HCV infections were detected in the years preceding as well as after introduction of DAAs, suggesting active transmission of HCV among HIV-infected MSM. A stable transmission of the RAS M28V was found, which is known to influence susceptibility to some of the NS5A inhibitors. The continuing transmission of M28V illustrates the need for resistance surveillance in populations with ongoing HCV transmission. Despite elimination efforts, most clusters persisted, highlighting the need for targeted monitoring and risk reduction strategies to achieve HCV elimination.

565 RESISTANCE ANALYSIS IN HCV-3–INFECTED PATIENTS WITHIN THE ITALIAN NETWORK VIRONET-C

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Background: This study aimed to investigate the presence and role of resistance-associated-substitutions (RASs) in HCV genotype 3 (GT3).
Methods: Within the Italian VIRONET-C network, a total of 539 GT3 infected patients (pts, 417 DAA-naïve and 135 DAA-failures, of them,13 at both baseline [BL] and failure), were analysed. Sanger-sequencing of NS3/NS5A/NS5B was performed by home-made protocols.
Results: The majority of pts were male (79%) and cirrhotic (50%). 23 pts (14%) were HIV-coinfected. Phylogenetic analysis classified sequences as GT3a-3b-3g-3h (98%-0.4%-0.2%-1.2%), respectively. Notably, 39 pts were previously misclassified as infected with GT indeterminate, non-3, or mixed (N=10/22/7, respectively). Overall, 135 GT3 pts failed an interferon-free regimen: sofosbuvir(SOF)/daclatasvir(DCV) or velpatasvir(VEL)±RBV (N=91/15) and glecaprevir(G)/pibrentasvir(P) (N=9). Moreover, 14.8% of pts were treated with suboptimal regimens for GT3: 3D±RBV (Paritaprevir/r+Ombitasvir+Dasabuvir, N=15), SOF+Simeprevir (N=1) or SOF/ Ledipasvir (LDV)+RBV (N=4). In DAA-naïve pts, overall RAS prevalence was 16% (NS5A-RAS:15.5%). At failure, 81.5% pts showed at least one RAS related to the DAA-regimen, of whom 11/25 (44%) in NS3, 109/135 (81%) in NS5A, 7/111 (6%) in NS5B SOF-failures. In NS5A-failures, Y93H was the most prevalent RAS (68.5% vs 5% DAA-naïve, p<0.001) followed by A30K (13% vs 3% in DAA-naïve, p<0.001). Interestingly, analysing the BL samples, a higher prevalence of NS5A-RASs was observed before treatment in DAA-failures (5/13, 38%) vs DAA-naïve pts (61/393, 15.5%, p=0.04). The single Y93H was detected mainly after SOF/DCV or VEL (67% and 60%) and 3D (80%) failures. By contrast, NS5A-RASs patterns (mostly A30K+Y93H) were frequently observed (55%) after G/P failure. In NS5B, RASs L159F and S282T were detected only in SOF/DCV failures (5% and 1%, respectively). Regarding DAA-naïve pts with an available outcome, 228 were treated with the following regimens: SOF/DCV or VEL±RBV (N=150/47) and G/P (N=31). Overall, 94% achieved a SVR. In particular, for pts with BL Y93H and/or A30K the overall SVR rate was 72% vs 96% for pts without NS5A RASs (p=0.002).
Conclusion: In this large cohort of GT3 infected pts, the majority of failures harbored resistant HCV variants carrying one or two NS5A RASs, the most frequent being Y93H. The presence of natural NS5A RAS before treatment was associated with failure. Further analyses are needed to confirm this observation, particularly for the new current regimens.

566 BARRIERS TO DIRECTLY ACTING ANTIVIRALS THERAPY AMONG HIV/HCV-COINFECTED ADULTS

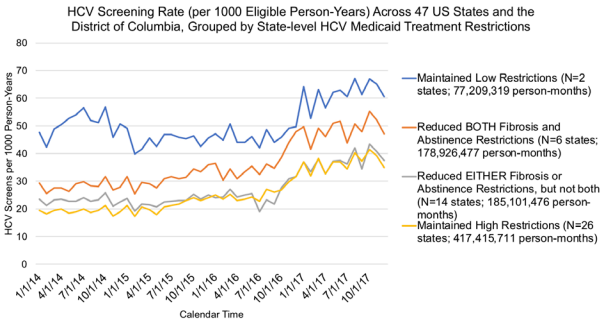
Gina M. Simoncini[1], Qingjiang Hou[2], Kate Buchacz[3], Ellen Tedaldi[1], Frank J. Palella[4], Jack Fuhrer[5], Richard M. Novak[6], Cynthia Mayer[7], David E. Koren[1], Linda A. Battalora[8], Stockton Mayer[9], Stacey Purinton[2], Jun Li[3], for the HIV Outpatient Study (HOPS) Investigators
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Background: HIV and chronic hepatitis C virus (HCV) coinfection carries substantial risk for all-cause mortality and liver-related morbidity and mortality; yet many people co-infected with HIV/HCV remain untreated for HCV infection. We explored demographic, clinical variables and social determinants of health among coinfected participants in routine HIV care that may differentiate those treated versus untreated with directly-acting antivirals (DAAs).
Methods: We analyzed medical record data as of December 31, 2018 of HIV Outpatient Study (HOPS) participants seen at 9 U.S. clinics who were diagnosed with HCV with at least one confirmatory HCV RNA viral load (VL) test or genotype test since June 30, 2010. DAA therapy was determined by medication prescription from the HOPS database. Participants treated with interferon/ribavirin along with DAA were excluded. Based on bivariate analyses, factors associated with the probability of receiving DAA therapy were further evaluated by multivariable logistic regression.
Results: Among 306 eligible participants, median age was 52 years, median duration of follow up was 3.96 years, 97 (32%) were female, and 202 (66%) were non-white, 131 (42.8%) were prescribed DAA therapy, 127 (96.9%) had at least one follow-up HCV VL and 13 (9.9%) participants remained HCV viremic 12 months after initiating DAA therapy, resulting in an overall cure rate of 90.1%. DAA treatment was not associated with patient's race and ethnicity (p=0.17), history of substance abuse (p=0.53), nor a mental health condition (p=0.43). Multivariable logistic regression analyses indicated that participants who were older (p=0.03), with health insurance (p=0.01), higher CD4 range (p<0.001), and injection drug use as the HIV risk category (p=0.03), were more likely to receive DAA therapy (Figure). Compared with the publicly insured, privately insured participants were more likely to receive DAA with an odds ratio of 2.30 (95% confidence interval: 1.32-4.12).
Conclusion: Only 42.8% of HIV/HCV-coinfected participants have been treated in the HOPS cohort. Factors associated with lower uptake of DAA therapy included younger age, sexual transmission as the HIV risk factor, lower CD4 range, and public or no insurance. Substance use, mental health diagnosis, race, and ethnicity were not associated with DAA treatment. Improved insurance coverage and expanded clinical care access to younger, presumably healthier individuals, is needed to bridge the treatment gap.



567 MEDICAID HCV TREATMENT RESTRICTIONS: SPILLOVER TO THE PRIVATE-PAYER HCV CARE CASCADE?

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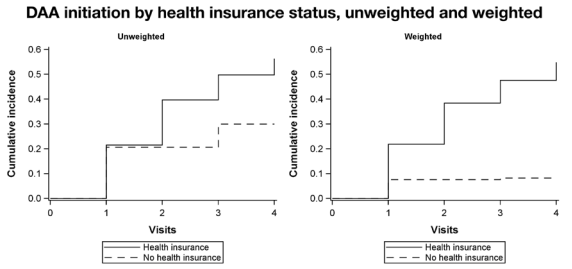
Background: Medicaid HCV treatment restrictions limit access to HCV cure. There is evidence that public insurance policies influence care more broadly, even among commercially insured patients. Further, if states limit HCV treatment access, screening may lag due to decreased provider motivation. This study investigates whether Medicaid HCV treatment restrictions 'spillover' to affect HCV testing among patients with commercial insurance.
Methods: We linked the Marketscan commercial claims database to the National Viral Hepatitis Roundtable state-by-state categorization of Medicaid HCV treatment policies. We considered any requirement for negative drug testing prior to HCV treatment to be a restrictive abstinence-based policy and any requirement that a patient have evidence of Metavir fibrosis stage F2 or greater to be a restrictive fibrosis-based policy. We categorized states into four groups: 1) maintained low fibrosis or abstinence restrictions over the study period (2014-2017), 2) relaxed both fibrosis and abstinence restrictions, 3) relaxed only one restriction type, and 4) maintained high restrictions in both domains. We analyzed HCV testing rates across these groups in 18-64-year-olds. We used negative binomial regression adjusted for calendar time and for whether policy change occurred, to estimate testing rate ratios between groups.
Results: From 2014-2017, 2,134,569 HCV tests occurred over 876,444,123 eligible person-months (29.2 tests/1000 person-years). Testing rates increased over time in all groups. States that maintained unrestrictive policies had the highest HCV testing rates, followed by states that reduced both fibrosis and abstinence restrictions. States maintaining high restrictions for one or both policies had similar rates (Figure). In regression analysis, states maintaining low restrictions had an adjusted rate ratio of 1.74 (95% CI 1.61-1.89) compared with states maintaining high restrictions. In states that relaxed restrictions, we observed a rate ratio of 1.07 (95% CI 1.00-1.14) post- vs. pre-policy change.
Conclusion: Restrictive state Medicaid HCV treatment policies are associated with decreased HCV screening rates among commercially insured individuals in the same state. Unmeasured state-level variables such as Medicaid expansion may contribute to observed differences, and we will conduct further analysis. These data suggest, however, that Medicaid HCV treatment restrictions may have spillover effects that hinder HCV elimination progress across all payers.



568 HEALTH INSURANCE AND DIRECT-ACTING HCV ANTIVIRAL INITIATION IN US WOMEN WITH HIV

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Background: Direct-acting antiviral (DAA) therapy for Hepatitis C virus (HCV) is well tolerated, yields high sustained virologic response rates, and is cost-effective, but has remained out of reach for many patients due to high cost. We evaluated the relationship between health insurance status, a key factor for the mitigation of financial barriers to medical care, and DAA initiation in an observational cohort of women living with HIV in the United States (US).
Methods: Women's Interagency HIV Study participants coinfected with HIV and HCV (RNA+) without history of DAA use were followed for DAA initiation (2015-2018). We estimated risk ratios (RRs) of the relationship between time-varying health insurance and DAA initiation, adjusting for confounders with stabilized inverse-probability-of-treatment weights. Baseline covariates were age, race, and education, and time-varying predictors in the weight models were US region of residence, annual household income, alcohol use, injection/non-injection drug use, AIDS Drug Assistance Program participation, HIV viral load, CD4 count, and advanced liver fibrosis (APRI ≥1.5 or FIB-4 ≥3.25). We also estimated unweighted and weighted cumulative incidences of DAA initiation by health insurance status.
Results: 137 women (74% Black) were followed; at baseline, median age was 55 years (interquartile range, 50-59) and 87% were insured. The majority of women (79%) lived in Northern states and had annual household incomes ≤$18,000 (85%). Advanced liver fibrosis (30%) and use of alcohol (45%) and drugs (34%) were common. At 368 subsequent biannual visits, 74 women (54%) reported DAA initiation. The weights had a mean of 0.99 and ranged from 0.12 to 8.06. Compared to no insurance, health insurance increased the likelihood of reporting DAA initiation at a given visit (RR 4.99, 95% confidence interval [CI] 1.56-16.0), an estimate markedly stronger (but less precise) than the unadjusted (RR 2.02, 95% CI 0.76-5.34). When weighted, the cumulative incidence of DAA initiation was lower (8% vs. 30%) at two years among the uninsured (Figure).
Conclusion: In an analysis accounting for financial, clinical, behavioral, and sociodemographic factors over time, health insurance had a substantial positive effect on DAA initiation. Interventions to improve insurance coverage, such as Medicaid expansion or subsidies for private plans, should be prioritized in order to increase uptake of HCV curative therapy for persons with HIV.



569 MOBILE HCV SCREENING IN AN AT-RISK URBAN POPULATION IDENTIFIES SIGNIFICANT FIBROSIS

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Background: Most people living with hepatitis C virus (HCV) remain undiagnosed, impacting HCV elimination efforts. We designed a mobile unit to bring HCV screening and liver fibrosis staging to at-risk communities in San Francisco.
Methods: A university shuttle bus was furnished with a phlebotomy station, Fibroscan®430 Mini+ and clinical exam table. Screening with the OraQuick® HCV Rapid Antibody (Ab) test was performed at: 1) community events 2) street outreach and 3) outside methadone programs. HCV Ab+ clients were offered venipuncture for confirmatory HCV RNA, liver stiffness measurement (LSM) and linkage to care. Significant fibrosis and advanced fibrosis were defined as LSM ≥7.0 kPa and ≥9.5, respectively.
Results: From 1/17/2019-9/13/2019, 428 people underwent HCV Ab screening at community events (12%), street outreach (72%) and methadone programs (15%). Median age was 53 (IQR 43-62), 67% were male, 49% reported living outdoors or in a vehicle in the past year, and 5% were HIV-positive. Overall, 156 were HCV Ab+ (36%), and prevalence varied by screening location: 17% at community events, 34% at street outreach sites, and 66% outside methadone programs (p<0.001). HCV Ab+ individuals were more likely than HCV Ab- to be white (44% vs 32%, p=0.003), have Medi-Cal insurance (80% vs 61%, p<0.001), and report ever injection drug use (IDU) (86% vs 29%, p<0.001), ever smoking

crack or speed (87% vs 64%, p<0.001), current IDU (54% vs 16%, p<0.001), current non-IDU (67% vs 50%, p=0.001), or history of incarceration (74% vs 53%, p<0.001). Among the HCV Ab+, 73% had HCV RNA testing and 38% were HCV RNA+ (Figure). Fifty-nine of the HCV Ab+ underwent LSM: 27 (46%) and 16 (27%) had significant and advanced fibrosis, respectively. Fibrosis prevalence was similarly high regardless of HCV RNA status. The majority of the HCV RNA+ had health insurance (91%) and a primary care provider (PCP) (68%). Among the 44 HCV RNA+, 25 were referred to further HCV care, including 8 who were referred to an HCV provider on the van, 4 of whom have started HCV treatment on the van.

Conclusion: HCV screening on a mobile van in a large urban center demonstrated a high prevalence of HCV Ab+ (36%) among high-risk groups, with one-fourth having advanced fibrosis. Despite the majority having insurance and a PCP, 38% of the HCV Ab+ had active HCV viremia. This underscores the need for heightened efforts to improve HCV treatment access to high-risk groups and has motivated a program offering HCV treatment on the mobile unit.

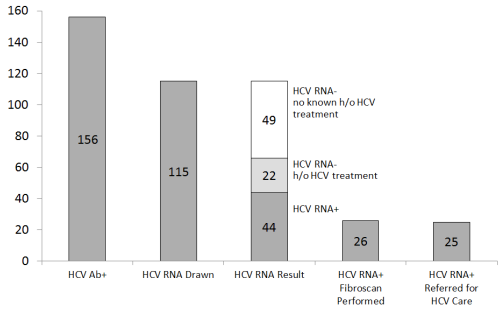


Figure. HCV care cascade for HCV Ab+

570 PROGRESS AND REAL-LIFE CHALLENGES FOR HCV ELIMINATION IN PEOPLE LIVING WITH HIV

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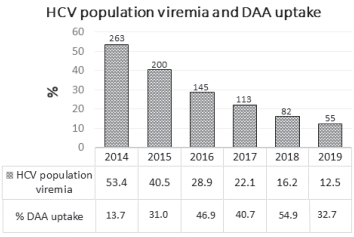
Background: The state of California has provided unrestricted access to direct-acting antivirals (DAA) since January 2018 for people living with HIV (PLWH). We aim to assess the impact of the hepatitis C virus (HCV) treatment uptake among PLWH on HCV population viremia and identify health-system areas for improvement to achieve HCV elimination.

Methods: Retrospective cohort of PLWH with active HCV infection (detectable HCV viral load) under care at UC San Diego between 2014 and June 2019. We describe the annual proportion of PLWH with active HCV who started DAA therapy and the resulting cumulative population level of HCV viremia. Our cohort was then divided into early DAA (2014-2017) and unrestricted DAA (2018-2019) era groups. We compared the difference of proportion in health system landmarks of HCV treatment referral, HCV care uptake, staged/retained/prescribed DAA therapy, DAA treatment initiation, and HCV cure between the two groups.

Results: Following DAA approval, of 3,111 PLWH in care, 493 (15.9%) had HCV Ab positive and 263 (53.4%) of whom had active HCV viremia. The proportion of viremic patients starting DAA therapy increased from 13.5% in 2014 to 41% in 2017. After the first year of unrestricted DAA access, HCV treatment uptake increased to 54.9% and then dropped to 32% in 2019. The overall HCV population viremia among those with HCV Ab positive decreased from 53.4% in 2014 to 12.5% in 2019 (figure, panel A). In comparison to the early DAA era, following unrestricted DAA access, the proportion of patients who did not initiate therapy after establishing HCV care decreased from 22% to 14%. During the early DAA era and after establishing HCV care, the main reason for not initiating DAA was lack of insurance approval. In contrast, all PLWH who did not start DAA in the DAA unrestricted era were due failure to pick up their approved DAA or lost to follow-up. Despite DAA unrestricted access in 2018, there was almost a 2-fold increase in the proportion of PLWH not linked to HCV care (figure, panel B). Among those patients with active viremia, the number of patients engaged in their HIV care decreased from 95% in 2014 to 63% after one year of unrestricted DAA access.

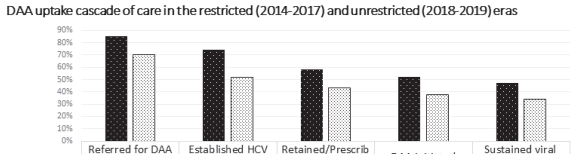
Conclusion: HCV linkage and HCV retention in care have emerged as main challenges among PLWH for HCV treatment uptake. As many of the remaining PLWH in need of DAA are not fully engaged in HIV care, DAA treatment outside conventional healths system is needed to achieve HCV micro-elimination

A



	2014	2015	2016	2017	2018	2019
HCV population viremia	53.4	40.5	28.9	22.1	16.2	12.5
% DAA uptake	13.7	31.0	46.9	40.7	54.9	32.7

B



	Referred for DAA therapy	Established HCV care	Retained/Prescribed DAA	DAA initiated	Sustained viral response
Early DAA era (n =368)	85%	74%	58%	52%	47%
Unrestricted DAA era (n =159)	70%	52%	43%	38%	34%

571 REAL-WORLD EFFECTIVENESS OF GLECAPREVIR/PIBRENTASVIR FOR HEPATITIS C VIRUS INFECTION

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Background: Glecaprevir and pibrentasvir (GLE/PIB) are direct-acting antiviral agents (DAAs) with pan-genotypic activity and a high barrier to resistance. We evaluated the effectiveness and safety of GLE/PIB in a large prospective registry HCV-infected individuals with/without coinfection by HIV and receiving DAAs for HCV infection.

Methods: RUA-VHC (Madrid Registry of Use of DAA for HCV) is a prospective registry of HCV-monoinfected (MoP) and HIV/HCV-coinfected (CoP) individuals receiving all-oral DAAs in hospitals of the Madrid Regional Health Service. RUA-VHC was created in November 2014 (Hepatology 2017; 66:344). For this study, we selected patients with chronic hepatitis C who had received once-daily treatment with 3 tablets of the fixed-dose combination of GLE/PIB (total dose: 300 mg/120 mg) and were scheduled to finish treatment on or before01/February/2019. Retreatment after all-oral DAA therapy was excluded. We assessed sustained virologic response at 12 wk by intention-to-treat (ITT) and by a modified intention-to-treat approach (m-ITT), in which non-virological failures for reasons other than discontinuation of treatment secondary to adverse events or death were not considered in the analysis.

Results: A total of 1,183 patients (1,078 MoP/105 CoP) met the inclusion criteria. Treatment duration was 8 weeks in 1,063 patients (964 MoP/99 CoP), 12 weeks in 115 patients (109 MoP/6 CoP), and 16 weeks in 5 MoP. Median age was 54 years, 51.7% were men, 9.4% had been treated previously with interferon-based anti-HCV therapies, and 7.0% had cirrhosis. Genotype distribution was as follows: G1, 70.7%; G3, 10.6%; G4, 10.2%; G2, 3.5%; Other/mixed/unknown genotypes accounted for 4.8%. Patient characteristics and treatment results overall and by treatment duration and the presence/absence of HIV coinfection are shown in the Table. Sustained virologic response rates were 97.7% (95% CI, 96.7%-98.5%) by ITT and 99.0% (95% CI, 98.2%-99.5%) by m-ITT analysis. The presence of HIV or liver cirrhosis, and genotype distribution did not influence treatment response.

Conclusion: In this large prospective real-life cohort of patients with hepatitis C, treatment with GLE/PIB led to SVR rates of almost 98%. Treatment with GLE/PIB was highly efficacious across all genotypes and in the presence of HIV infection or liver cirrhosis.

Table. Patient characteristics and treatment results overall and categorized by the presence or absence of HIV coinfection

Variable	MoP N=1,078	CoP N=105	*P*	Total N=1,183
Age, yr. – median (IQR)	55 (49 – 62)	49 (44 – 53)	<.001	54 (48 – 61)
Male sex – no. (%)	535 (49.6)	77 (73.3)	<.001	612 (51.7)
Genotype 1/2/3/4/Other – %	71.5/3.7/10.8/8.8/5.1	62.9/1.9/8.6/24.8/1.9	<.001	70.7/3.5/10.6/10.2/4.8
Previously treated – no. (%)	99 (9.2)	12 (11.4)	.451	111 (9.4)
Cirrhosis – no. (%)	80 (7.5)	3 (2.9)	.287	83 (7.0)
SVR ITT – no. (%)	1054 (97.8)	102 (97.1)	.679	1156 (97.7)
SVR ITT 95% CI	96.7 – 98.6	91.9 – 99.4		96.7 – 98.5
Relapse – no. (%)	8 (0.7)	1 (0.9)		9 (0.8)
DC due to AE – no. (%)	1 (0.1)	0		1 (0.1)
DC other reasons – no. (%)	14 (1.3)	1 (0.9)		15 (1.3)
Death – no. (%)	1 (0.1)	1 (0.9)		2 (0.2)
SVR m-ITT – no. (%)	1054 (99.1)	102 (98.1)	.343	1156 (99.0)
SVR m-ITT 95% CI	98.3 – 99.5	93.2 – 99.8		98.2 – 99.5

572 REAL-WORLD EFFECTIVENESS OF SOFOSBUVIR/VELPATASVIR FOR HEPATITIS C VIRUS INFECTION

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Background: Little is known about the real-world effectiveness of sofosbuvir and velpatasvir (SOF/VEL), a direct-acting antiviral agent (DAA) regimen with pan-genotypic activity. We evaluated the effectiveness and safety of SOF/VEL in a large prospective registry of individuals receiving DAAs for HCV.

Methods: RUA-VHC (Madrid Registry of Use of DAA for HCV) is a prospective registry of HCV-monoinfected (MoP) and HIV/HCV-coinfected (CoP) individuals receiving all-oral DAAs in hospitals of the Madrid Regional Health Service. RUA-VHC was created in November 2014 (Hepatology 2017; 66:344). For this study, we selected patients with chronic hepatitis C who had received once-daily treatment with 1 tablet of the fixed-dose combination of SOF/VEL (400 mg/100 mg) for 12 wks. The patients were scheduled to finish treatment on or before 01/February/2019. Patients who were retreated after all-oral DAA therapy were excluded. We assessed sustained virologic response (SVR) at 12 wk by intention-to-treat (ITT) and by a modified intention-to-treat approach (m-ITT), in which non-virological failures for reasons other than discontinuation of treatment secondary to adverse events or death were not considered in the analysis.

Results: A total of 1,003 patients (888 MoP/115 CoP) met the inclusion criteria. Median age was 55 y, 61.1% were men, 10.3% were previously treated, 19.7% had compensated cirrhosis, and 3.9% had decompensated cirrhosis. Genotype distribution was as follows: G1, 40.0%; G2, 11.2%; G3, 36.9%; G4, 7.6%. Other/mixed/unknown genotypes accounted for 4.4%. Statistically significant differences were observed between MoP and CoP at baseline for age, gender, and genotype distribution. SVR rates overall were 95.4% by ITT and 97.9% by m-ITT (Table). The presence of HIV or genotype distribution did not influence response to treatment. The SVR rate was lower in patients with decompensated cirrhosis than in patients without cirrhosis both by ITT (87.2% vs 96.1%, P=0.008) and by m-ITT (91.9% vs 98.5%, P=0.003).

Conclusion: In this large cohort of patients with hepatitis C, 12 wks of treatment with SOF/VEL led to SVR rates > 95%. Treatment with SOF/VEL was highly efficacious across all genotypes and in the presence of HIV. Response to treatment was significantly poorer in patients with decompensated cirrhosis than in patients without cirrhosis.

Table. Patient characteristics and treatment results overall and categorized by the presence or absence of HIV coinfection.

	MoP n=888	CoP n=115	*P*	Total N=1,003
Genotype 1/2/3/4/Other – (%)	42.3/11.3/35.0/6.9/4.5	21.7/10.4/51.3/13.0/3.5	<.001	40.0/11.2/36.9/7.6/4.4
No cirrhosis – no. (%)	646 (72.7)	95 (82.6)	.144	741 (73.9)
Compensated cirrhosis – no. (%)	182 (20.5)	16 (13.9)		198 (19.7)
Decompensated cirrhosis – no. (%)	37 (4.2)	2 (1.7)		39 (3.9)
SVR ITT	850 (95.7)	107 (93.0)	.197	957 (95.4)
SVR ITT (95% CI)	94.2-97.0	86.8-96.9		93.9-96.6
Relapse	14 (1.6)	3 (2.6)		17 (1.7)
DC due to AE	1 (0.3)	0		1 (0.2)
DC other reasons	19 (5.5)	6 (12.2)		25 (6.3)
Death	1 (0.1)	1 (0.9)		2 (0.2)
SVR m-ITT	850 (98.0)	107 (96.4)	.261	957 (97.9)
SVR m-ITT (95% CI)	96.9-98.9	91.0-99.0		96.7-98.7

573 A MULTICENTER REGISTRY IN PATIENTS WITH HIV/HCV COINFECTION ON LEDIPASVIR/SOFOSBUVIR

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Background: Switches in antiretroviral therapy (ART) to simplify and/or update regimens are increasingly common, with safety supported by randomized clinical trials. Switches in ARTs to limit drug interactions prior to initiating direct acting antivirals (DAA) for HCV are also common, although there are limited data to guide this practice and the risk of loss of HIV control is unknown. Furthermore, there are reports that ART switches may increase HCV treatment failure.

Methods: This is the final analysis of a multicenter (N=9), observational clinical registry. The study population includes patients with HIV/HCV co-infection treated with ledipasvir/sofosbuvir. Cases (ART switch prior to HCV therapy) and controls (no ART switch prior to HCV therapy) were enrolled with a targeted 1:1 ratio and a planned total 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 ART regimen, 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. Analyses include use of Fischer's exact for differences in proportions.

Results: Total enrollment was 287 and 281 had evaluable data for the primary endpoint. The cohort is predominantly male (83%), with a mean age of 55 years, and 43% Black race. Patients who switched ARTs were more commonly on protease inhibitors and/or boosted-TDF regimens (Table). Overall, a total of 17 patients, 6% in each group, met the primary composite outcome of HIV treatment failure. Nephrotoxicity events (change from baseline creatinine of ≥0.4 mg/dL, decrease in creatinine clearance <50 mL/min or new >1+ proteinuria) occurred in 26% of patients and was not associated with ART switch or boosted-TDF during DAA therapy. Nephrotoxicity was more common in patients with lower baseline creatinine clearance or baseline proteinuria. Overall, 242 patients (14% no HCV RNA available after DAA therapy) had evaluable SVR12, which was 99%.

Conclusion: In a real-world cohort of patients with HIV/HCV co-infection receiving ledipasvir/sofosbuvir, switches in ARTs were not associated with HIV treatment failure and did not prevent nephrotoxicity events. Nephrotoxicity was more common in patients with evidence of baseline renal dysfunction although it was not associated with discontinuation of therapy. HCV treatment success was independent of ART switch.

Baseline Characteristic	Overall n = 281	ART Switch n = 110	Control n = 171	p-value
Age, mean [range]	55 [48, 61]	56 [51, 62]	53 [46, 61]	0.03
Male, n (%)	234 (83)	83 (76)	151 (88)	0.008
Black race, n (%)	119 (43)	54 (50)	65 (38)	0.04
CD4, mean [range]	594 [427, 805]	554 [427, 818]	640 [427, 803]	0.38
HCV Genotype 1, n (%)	266 (95)	102 (93)	164 (96)	0.45
Antiretroviral regimen				
Boosted protease inhibitor, n (%)	92 (33)	54 (49)	38 (22)	< 0.0001
NRTI, n (%)	268 (95)	106 (96)	162 (95)	0.77
NNRTI, n (%)	98 (35)	33 (30)	65 (38)	0.20
Integrase inhibitor, n (%)	128 (46)	39 (36)	89 (52)	0.007
TDF, n (%)	188 (67)	88 (80)	100 (58)	0.0002
Boosted TDF, n (%)	54 (19)	44 (40)	10 (6)	< 0.0001
TAF, n (%)	15 (5)	3 (3)	12 (7)	0.17
Creatinine clearance, mean [range]	93 [71, 111]	91 [70, 109]	93 [72, 112]	0.89
Study Outcomes				
Composite, HIV treatment failure, n (%)	17 (6)	7 (6)	10 (6)	1.0
Virologic failure	3 (1)	2 (2)	1 (1)	0.56
ARV switch	14 (5)	5 (4)	9 (5)	1.0
AIDS	0 (0)	0 (0)	0 (0)	
Death	0 (0)	0 (0)	0 (0)	
Nephrotoxicity	72 (26)	25 (23)	47 (28)	0.40
>1+ proteinuria	38 (14)	13 (12)	25 (15)	0.59
Creatinine change > 0.4 mg/dL from baseline	18 (6)	9 (8)	9 (5)	0.33
Creatinine clearance < 50 ml/min	26 (9)	8 (7)	18 (10)	0.41
SVR12 (N = 242 evaluable)	239 (99)	94 (99)	145 (99)	1.0

574 EFFECTIVENESS OF LDV/SOF FOR HIV-POSITIVE PATIENTS WITH HCV GENOTYPE 2 INFECTION

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Background: While the fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) (LDV/SOF) is not approved in the US for the treatment of hepatitis C virus infection genotype 2 (HCV-2), it is approved in Taiwan, Japan, and New Zealand. Data regarding its use for HIV-positive patients with HCV-2 are sparse, however.

Methods: From Jan-Jun 2019, HIV-positive patients with HCV-2 seeking care at 14 designated hospitals who received LDV/SOF were included for analysis. Laboratory investigations at baseline, end of treatment (EOT) and 12 weeks off therapy (SVR12), as required by the HCV treatment program of the Taiwan National Health Insurance.

Results: Of the 101 patients (mean age, 38.4 years) initiating LDV/SOF during the study period, 99.0% were men, 76.0% men who have sex with men, 19% injecting drug users, and 3.0% heterosexuals. At the time of LDV/SOF initiation, all had estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73m_2 and were receiving combination antiretroviral therapy (cART) with TAF-containing regimen in 38.6%, TDF 13.9%, non-TDF/TAF 47.5%, NNRTI 12.9%, PI 14.9%, and InSTI 72.3% (dolutegravir 46.6% and elvitegravir 53.4%%), with 98.0% having CD4 counts ≥200 cells/mm_3 and 94.1% HIV RNA load <50 cp/mL. 8.9% of them tested positive for HBsAg, 1.0% had cirrhosis of the liver and 5.0% were HCV treatment-experienced. HCV seroconversion within one year was documented in 20.8% of the patients. Sexually transmitted HCV infection was reported in 67.7% and injection-related in 21.8%. The mean plasma HCV RNA load was 6.3 log_{10} IU/mL before LDV/SOF initiation, and 97.7% had undetectable HCV viral load at week 4 of LDV/SOF, 98.9% at the end of the treatment, and 97.4% had SVR12 with eGFR >30 ml/min/1.73m_2 in all patients. eGFR increased in 34.1% with a mean increase of 7.2 ml/min/1.73m_2, while eGFR decreased in 65.9% with a mean decrease of 12.6 ml/min/1.73m_2.

Conclusion: Similar to the reported treatment response among HIV-negative patients, LDV/SOF is effective for HIV-positive patients infected with HCV-2.

575 EFFECTIVENESS OF DAA IN HIV-POSITIVE PATIENTS WITH HCV GENOTYPE 6 INFECTION

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Background: Hepatitis C virus genotype 6 (HCV-6) is prevalent predominantly in Southeast Asia, and the data on the virologic response of HCV-6 to direct-acting antivirals (DAA) are sparse in HIV-positive patients.

Methods: From May 2017 to July 2019, HIV-positive patients coinfected with HCV-6 who initiated DAAs were included for analysis. Laboratory investigations were performed at baseline, the end of therapy (EOT), and 12 weeks off therapy (SVR12), as required by the HCV treatment program of the Taiwan National Health Insurance.

Results: Of 264 patients (mean age, 50.7 years) initiating DAAs during the study period, 84.8% were men, 83.3% injecting drug users, 15.5% men who have sex with men, and 1.1% heterosexuals. Sofosbuvir-ledipasvir (SOF/LED) was used in 52.3% of the patients, glecaprevir-pibrentasvir (GP) in 45.8%, and sofosbuvir-velpatasvir (SOF/VEL) in 1.9%. At the time of DAA initiation, all had estimated glomerular filtration rate ≥30 ml/min/1.73m_2, and combination antiretroviral therapy included regimens containing TAF in 27.3% of the patients, TDF 32.2%, non-TDF/TAF 40.5%, NNRTI 29.9%, PI 3.4%, and InSTI 68.6% (dolutegravir 55.8%, elvitegravir 39.8%, and raltegravir 4.4%), with 95.5% of the patients having CD4 counts ≥200 cells/mm_3 and 96.6% plasma HIV RNA load <50 copies/mL. 11.4% of the patients tested positive for HBsAg and 12.2% had liver cirrhosis and 0.8% hepatocellular carcinoma. 9.5% of the patients were HCV treatment-experienced. HCV seroconversion within one year was documented in 3.8%, while injection-related HCV infection was reported in 82.2% (217/264) and sexually transmitted infection in 13.6% (36/264). The mean plasma HCV RNA load was 6.2 log_{10} IU/mL before DAA initiation. Overall, 98.3% achieved undetectable plasma HCV RNA load (<15 IU/mL) at EOT and 96.6% achieved SVR12 (97.2% in patients receiving SOF/LED, 96.0% in GP, and 100% in SOF/VEL).

Conclusion: Similar to the observation in HIV-negative patients, SVR12 with DAAs is high in HIV-positive patients with HCV-6.

576LB ADHERENCE AND 007-TP DBS LEVELS IN ACTIVE DRUG USERS WITH HCV: THE INCLUD TRIAL

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Background: Active drug users may be overlooked for HCV treatment due to adherence concerns. Here, we report treatment outcomes, objective adherence data, and predictors of adherence and 007-TP in dried blood spots (DBS) (a pharmacologic measure of sofosbuvir [SOF] adherence) in active drug and/or alcohol users receiving ledipasvir (LDV)/SOF.

Methods: INCLUD was a prospective, open-label study of LDV/SOF x 12 wks in active drug users ages 18-70 yrs. Participants were randomized to wireless (WOT) by Wisepill® or video-based directly observed therapy (DOT) with miDOT (Emocha®). DBS and drug use by urine tox screen and self-report were collected every 2 wks. Two-wk adherence (adh2wk) was calculated as # doses taken/# days between visits by WOT or DOT. Generalized linear models examined risk factors for ≥1 missed dose between visits (i.e., adh2wk ≥100% vs. <100%) and mixed models identified predictors of ln-transformed 007-TP. Select covariates (n=17) were screened (p≤0.2), followed by backward selection (p≤0.1).

Results: 60 participants received ≥1 LDV/SOF dose (47 HIV/HCV, 13 HCV only; 78% male; 22% black; 25% cirrhotic). Drug use during treatment (286 person-visits) included: 20% IV drug use, 60% THC, 37% methamphetamine, 22% opioids (street or Rx), 16% cocaine, and 57% alcohol (21% binge, 20% heavy). The SVR rate by ITT was 83% (50/60). Two did not comply with study requirements and were withdrawn, 5 were LTFU, and 3 failed treatment (1 relapse, 1 reinfection, 1 unknown). As treated (≥1 LDV/SOF dose and SVR12 available), the SVR rate was 93% (50/53). Median (IQR [range]) total adherence was 96% (83-99% [1-101%]) and adh2wk was 90% (86-100% [0-107%]). As treated total adherence was 98% (87-100% [30-101%]) in cures vs. 90% [90-91% [89-92%]) in failures. HIV coinfection, black race, meth and cocaine use were associated with lower odds of adh2wk ≥100%, whereas THC use and DOT were associated with higher odds (Table). Geometric mean 007-TP (%lnCV) in DBS were 218 (20.1%), 495 (9.7%), and 665 (6.3%) fmol/punch for 0-50%, 50-80%, and ≥80% adh2wk. Higher eGFR, black race, younger age, and higher BMI were associated with lower 007-TP levels after controlling for adh2wk (Table).

Conclusion: Active drug users with HCV had good but variable LDV/SOF adherence using technology-based methods, with improved adherence using video DOT. 007-TP in DBS increased with adherence, and SVR12 rates were high demonstrating substantial PK forgiveness. These findings support efforts to expand HCV treatment to active drug users.

Predictors of adh2wk ≥100%		
Predictor	Odds Ratio [95% CI]	p-value
HIV status (yes vs. no)	0.25 [0.11, 0.58]	0.001
Race (black vs. non-black)	0.20 [0.07, 0.59]	0.003
Methamphetamine use (yes vs. no)[a]	0.38 [0.20, 0.74]	0.005
Marijuana use (yes vs. no)[a]	3.17 [1.33, 7.55]	0.009
Adherence monitoring (DOT vs. WOT)	2.32 [1.07, 5.02]	0.032
Cocaine use (yes vs. no)[a]	0.49 [0.25, 0.98]	0.042

Predictors of 007-TP in DBS		
Predictor	% Change [95% CI]	p-value
Adh2wk (per 10% increase)	11.1% [8.4, 13.9%]	<0.0001
eGFR (per 10 mL/min/1.73 m^2 increase)	-4.2% [-7.5, -0.9%]	0.013
Race (black vs. non-black)	-26.7% [-44.5, -3.3%]	0.029
Age (per year increase)	1.4% [0.1, 2.7%]	0.037
BMI (per 1 kg/m^2 increase)	-2.3% [-4.6, 0.1%]	0.055

[a] Drug use defined as positive urine toxicology screen or self-reported use over previous 2 weeks. Binge alcohol use defined as >4 drinks/day for females and >5 drinks/day for males; heavy alcohol use was defined as 8 drinks/week for females and >15 drinks/week for males.

577 OVERALL SURVIVAL IN HIV-POSITIVE LIVER TRANSPLANT RECIPIENTS AND THE ROLE OF DAAs

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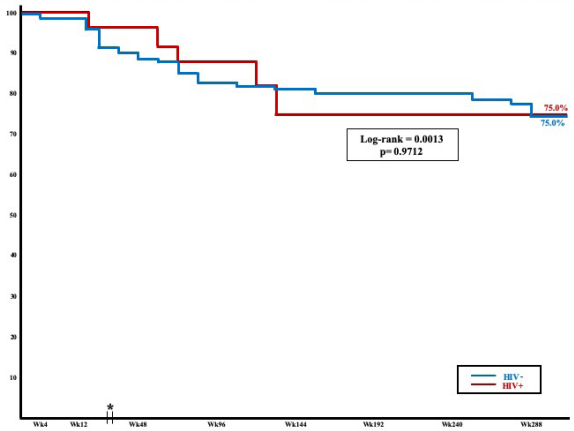
Background: Liver transplantation (LT) represents the best therapeutic option for end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC). In recent years, LT in HIV+ recipients showed similar survival rates compared to HIV-, even though the risks of rejection and infection seem higher. Direct-acting agents (DAAs) are widely available in Italy from 2015: few data are available on their impact on mortality in this special population. Aims of this study: evaluate the rate of overall survival and HCC recurrence; define the causes of death; describe the impact of DAAs on mortality.

Methods: All subjects with HCV/HBV infection who underwent LT for ESLD or HCC from 2012 were retrospectively evaluated. Descriptive statistics and non-parametric tests (Chi-square and Mann-Whitney U, as appropriate) were used; KM probability curves were calculated.

Results: 278 individuals, mainly men (83.1%), with a median age of 57 (IQR 52-63) years were included; 30 (10.8%) were HIV+. HCC was the indication for LT in 65.8% of cases. HIV+ subjects were younger (53 vs 58 years, p<0.00001), more commonly HCV+ after Sustained Virologic Response (43% vs 21%, p=0.0199) and infected by HCV genotype 1a (40% vs 14.1%, p=0.0073). HIV+ subjects transplanted for ESLD showed a worse Child class (11 vs 10, p=0.0308) and a higher MELD score at the limit of significance (23 vs 17, p=0.0836), while no difference was observed for those transplanted for HCC. BCLC stage, alfa-fetoprotein level, portal vein thrombosis and previous bridging treatments were similar in the two groups. The overall survival after a median follow up of 42 months was 80.6% with no difference among HIV+ and HIV- (Figure 1). Mortality after DAAs availability dropped from 27% (before 2015) to 9% (since 2016, p=0.0003), with similar trajectories in both groups. In HIV+ patients HCC relapse was significantly more common (26% vs 9%, p=0.0141) and with extra-hepatic involvement (17% vs 5%, p=0.0107). Although the main reason of death was HCC recurrence in HIV+ (40%) and liver-related issues in HIV- (29%), such difference was not statistically significant, as highlighted also by similar infection-related mortality (20% vs 16%, p=0.9265).

Conclusion: Over a follow up of more than 6 years, HIV+ subjects showed survival rates comparable to what observed in HIV- LT recipients with a significant decrease in mortality after DAA availability. Even if HCC recurrence was more common in HIV+, the causes of death were similar in the two groups with no distinctive role for infective complications.

Figure 1. Kaplan-Meier overall survival curves in HIV-infected and uninfected liver transplant recipients.



578 HIV COINFECTION AND RISK OF MORBIDITY AND MORTALITY IN HCV PATIENTS TREATED BY DAA

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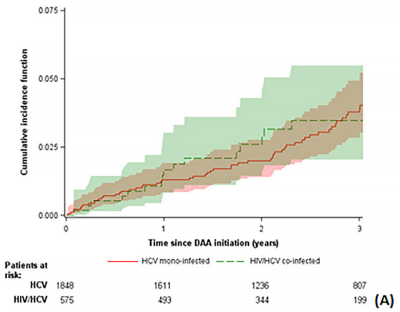
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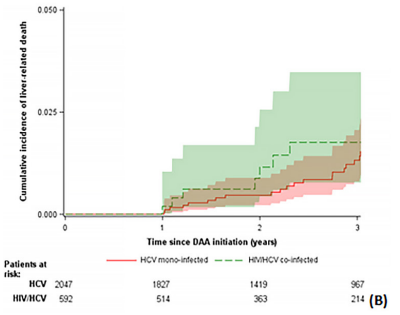
Background: HIV co-infection leads to increased mortality, liver disease progression and extra-hepatic manifestations in HCV-infected patients. DAA lead to high SVR rates and decrease the risk of disease progression. We compared risks of liver-related events, liver-related mortality and non-liver-related mortality in HIV/HCV co-infected and HCV mono-infected patients treated by DAA.

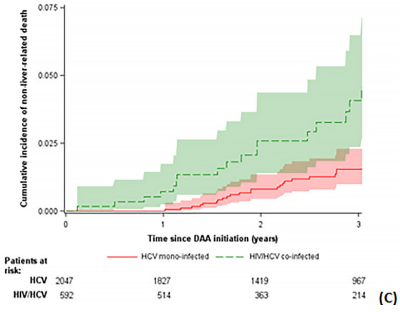
Methods: Four HCV mono-infected participants from the ANRS CO22 HEPATHER cohort were matched on age and sex to each HIV/HCV co-infected participant from the ANRS CO13 HEPAVIH cohort. All participants were treated by DAA between March 2014 and December 2017. Cox proportional Hazards models adjusted on age, sex, duration since HCV diagnosis, HCV contamination routes, HCV genotype, cirrhosis status, tobacco and alcohol consumption were used.

Results: 592 HIV/HCV co-infected and 2049 HCV mono-infected were included. Median age was 52.9 years [IQR: 49.6 ; 56.7] and 53.3 years [IQR: 49.6 ; 56.9]; 436 (73.6%) and 1498 (73.1%) were men; median duration since HCV diagnosis was 18.0 years [IQR: 12.4 ; 22.2] and 14.5 years [6.4 ; 20.8], and 159 (28.8%) and 793 (41.2%) were cirrhotic, respectively. Participants were predominantly treated by Sofosbuvir and Ledipasvir (48.8% and 34.5%, respectively) or Sofosbuvir and Daclatasvir (32.6% and 31.2%, respectively) and SVR was observed in 92.9% and 94.6% overall, respectively. After a median follow-up of 2.8 years, incidence of liver-related events was 12.4 per 1000 PY (95%CI: 7.7 ; 19.9) in HIV/HCV co-infected and 13.4 per 1000PY (95%CI: 10.5 ; 17.0) in HCV mono-infected (p=0.78). Incidence of liver-related mortality was 5.6 per 1000 PY (95%CI: 2.8 ; 11.1) in HIV/HCV co-infected and 4.9 per 1000 PY (95%CI: 3.4 ; 7.1) in HCV mono-infected (p=0.76). Incidence of non-liver-related mortality was 12.5 per 1000 PY (95%CI: 7.9 ; 19.8) in HIV/HCV co-infected and 4.9 per 1000 PY (95%CI: 3.4 ; 7.1) in HCV mono-infected (p<0.01). After adjustment, HIV co-infection was not associated with a higher risk of liver-related events (HR=0.67 95%CI: 0.27 ; 1.67) or liver-related-mortality (HR=0.94 95%CI: 0.19 ; 4.67), but the risk of non-liver-related mortality (HR=2.67 95%CI: 0.97 ; 7.37) tended to be higher in HIV/HCV co-infected.

Conclusion: After DAA treatment, SVR rates were not impacted by HIV co-infection, the risk of liver-related events and liver-related mortality were similar between HIV/HCV co-infected and HCV mono-infected but HIV co-infection tended to increase the risk of non-liver-related mortality.







579 EFFECT OF DAA REGIMENS ON MORTALITY IN HIV/HCV-COINFECTED PATIENTS WITH CIRRHOSIS

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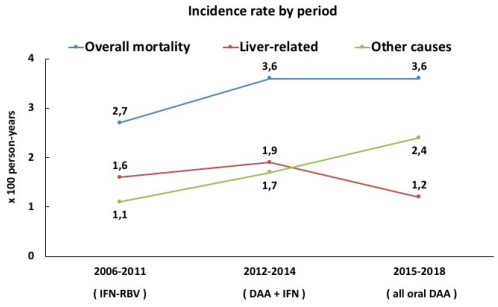
Background: Our objective was to assess the impact of all-oral direct antiviral agents (DAA) regimens on mortality in HIV/HCV-coinfected patients with cirrhosis.

Methods: 637 HIV/HCV-coinfected patients with cirrhosis prospectively recruited in the HEPAVIR-cirrhosis cohort from 2006 were followed-up until death or December 2018. The primary end-point was death of any cause and secondary end-point was liver-related death. The incidence rate (IR) (95% CI) of death of any cause in different groups were computed. Time-to-event analyses were performed to identify predictors of death.

Results: After a median (Q1-Q3) follow-up of 72 (39-104) months, 131 (21%; 95% CI: 17-23) patients died, 59 (45%) of them due to liver-related complications. IR (95% CI) of death was 3.4 (2.8-4.1) per 100 person-years (PY). 480 (75%) patients achieved sustained virological response (SVR) during follow-up, 90 after interferon (IFN)-based regimens and 390 after all-oral DAA regimens. The median follow-up after all-oral DAA was 34 (23-41) months. 28 out of the 131 deaths and 8 out of the 59 liver-related deaths occurred after SVR. IR (95% CI) of death after SVR was 1.8 (1.2-2.7) per 100 PY versus 17.7 (14.6-21.5) per 100 PY in those not achieving SVR during follow-up (p<0.0001). When only patients with SVR were considered, the IR (95% CI) of death after SVR with all-oral DAA regimens was 2.1 (1.4-3.3) per 100 PY whereas it was 1.3 (0.5-2.8) per 100 PY in those achieving SVR with IFN-based regimens (p=0.27). The respective figures for liver-related death were 0.7 (0.3-1.5) and 0.2 (0.03-12.8) per 100 PY respectively (p=0.26). Figure 1 summarizes the trends in overall and liver-related mortality according to the changes of treatment strategies for hepatitis C in the cohort. Achieving SVR with an all-oral DAA regimen during follow-up was independently associated with a lower risk of death (adjusted hazard ratio 0.04; 95% CI: 0.02-0.07; p<0.0001). The type of regimen leading to SVR (all-oral DAA vs IFN-based) had no impact on the risk of liver-related death in a competing risk model adjusted by propensity score (adjusted sub-hazard ratio 1.91; 95% CI: 0.21-17.09; p=0.56).

Conclusion: SVR with all-oral DAA regimens reduces the risk of death in HIV/HCV-coinfected patients with cirrhosis. The sum of this effect to the high uptake and SVR rates of this therapy has led to a decline in the incidence of liver-related mortality in our cohort.

Trends in overall and liver-related mortality according to the evolution of treatment for hepatitis C in HIV/HCV-coinfected patients with cirrhosis



580 ALL-CAUSE MORTALITY AND CAUSES OF DEATH IN THE SWISS HEPATITIS C COHORT STUDY

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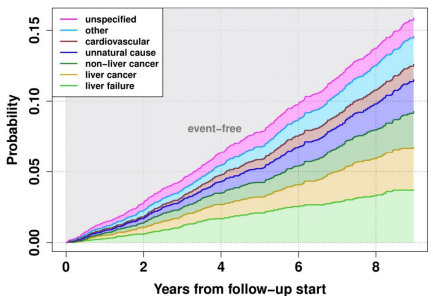
Background: Mortality rates and causes of death among persons with hepatitis C virus (HCV) infection are likely to change over time, with the introduction of direct-acting antiviral agents (DAA). However, the relatively slow progression of chronic hepatitis C may delay the emergence of such trends. To date, detailed analyses of cause-specific mortality among HCV-infected persons over time remain limited.

Methods: We evaluated changes in causes of death among the Swiss Hepatitis C Cohort Study (SCCS) participants, from 2008 to 2016. We analysed risk factors for all-cause and cause-specific mortality, accounting for changes in treatment, fibrosis stage and use of injectable drugs over time. Mortality ascertainment was completed by linking lost-to-follow-up participants to the Swiss Federal Statistical Office (SFSO) death registry.

Results: We included 4,700 SCCS participants, of whom 478 died between 2008 and 2016. Linkage to the SFSO death registry substantially improved the information on causes of death (from 42% of deaths with unknown cause before linkage to 10% after linkage). Leading causes of death were liver failure (crude death rate 4.4/1000 person-years), liver cancer (3.4/1000 p-yrs) and non-liver cancer (2.8/1000 p-yrs), with an increasing proportion of cancer-related deaths over time. Cause-specific analysis showed that persons with sustained virologic response (SVR) were less at risk for liver-related mortality.

Conclusion: Although the expected decrease in mortality is not yet observed, causes of death among HCV-infected persons evolved over time. With the progressive widening of guidelines for DAA use, liver-related mortality is expected to decline in the future. Continued monitoring of cause-specific mortality will remain important to assess the long-term effect of DAA and to design effective interventions.

Cumulative incidence of different causes of death since registration into the Swiss Hepatitis C cohort study (causes of death are in the same order in the legend and on the plot)



581 KINETICS OF EMERGENCE OF LIVER COMPLICATIONS IN HCV-INFECTED PATIENTS AFTER SVR

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Background: Despite achieving SVR with DAA-based regimens, a few HCV-infected patients still develop liver complications. Consequently, life-long surveillance for hepatic events, including hepatocellular carcinoma (HCC), is recommended among individuals with pre-treatment cirrhosis. However, there is little available evidence on the distribution over time of these liver complications' appearing after SVR. Thus, the aim of this study was to describe the kinetics of liver complications appearance in HCV-infected patients, with advanced fibrosis, who attain SVR after DAA based therapy.

Methods: Multicentric prospective cohort study, including HCV- and HIV/HCV-coinfected patients, who met: 1) Had achieved SVR with DAA-based therapy;

2) Liver stiffness prior to starting treatment≥ 9.5 kPa; 3) Had an available LS measurement at the time of SVR. SVR was considered as the baseline time-point. Overall accumulated incidence of liver complications was estimated, as well as complication-specific incidences. The median time (Q1-Q3) to the emergence of a hepatic event was assessed.

Results: 1006 patients were included, 661 (61%) coinfected with VIH. 554 (55%) showed previous compensated cirrhosis. 994 (94%) patients had achieved SVR with interferon-free regimens. After SVR, 42% of individuals (426) showed liver stiffness values above 14 KPa. After a median follow-up time (Q1-Q3) of 37 (24-42) months, 47 (4.7%) patients developed liver complications: 19 (1.9%) HCC, 15 (1.5%) ascites, 9 (0.9%) portal hypertensive gastrointestinal bleeding (PHGB) and 4 (0.4%) hepatic encephalopathy. The distribution of liver complications during follow-up is displayed in figure 1. The median time to the emergence of hepatic events was: hepatic encephalopathy 10.2 (6.6-12.6) months, ascites 12.7 (4.6-25.9) months, HCC 16.9 (12.4-32.2) months and PHGB 26.5 (16.6-40.5) months.

Conclusion: The vast majority of HCV-infected patients who develop liver complications after reaching SVR with DAA do it within two years after SVR time-point. Specifically, hepatic encephalopathy and ascites do not usually emerge after this period. Conversely, HCC and PHGB may occur in longer term, hence it is mandatory to identify patients at risk of developing these hepatic events to continue performing surveillance for them

582 LIVER STIFFNESS FOR PORTAL HYPERTENSIVE GASTROINTESTINAL BLEEDING AFTER HCV CURE

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Background: Among patients with active HCV-infection, values of liver stiffness (LS)<21 kPa identify individuals without risk of developing portal hypertensive gastrointestinal bleeding (PHGB).Thus, this LS level has been incorporated to some management algorithm of HCV-infected patients,so that upper gastrointestinal endoscopy (UGE) is safely spared in those with LS<21 kPa.However, there is no information about its predictive value among HCV-infected patients after SVR.So, the aim of this study was to assess the predictive ability of LS for PHGB in HCV-infected patients with advanced fibrosis who attain SVR with DAA-based therapy.

Methods: Multicentric prospective cohort study where HCV-monoinfected patients and HIV/HCV-coinfected patients were included if they met the following inclusion criteria: 1)Had achieved SVR with a DAA-based regimen; 2) Had LS values ≥9.5 kPa prior to treatment; 3)Had an available LS measurement at SVR time-point.Patients with PHGB episodes prior to SVR were excluded. Absolute frequencies and accumulated incidences of PHGB after SVR were calculated.

Results: In this study,991 individuals were included. 647 (65%) were coinfected with HIV. 598 (60%) patients showed cirrhosis prior to treatment and specifically 360 (36%) had LS values ≥21 kPa. The corresponding figures at SVR were: 413 (42%) individuals with LS ≥14 kPa and 227 (23%) with LS ≥21 kPa. After a median follow-up time (Q1-Q3) of 37 (24-42) months, 9 [0.9% (0.5%-1.7%)] patients developed a first PHGB episode. The cummulative incidences of PGHB in the group of patients with LS ≥21 kPa and in patients with LS ≥14 kPa, after SVR, were respectively 4.0% (2.1%-7.4%) and 2.2% (1.2%-4.1%).133 (37%) individuals with LS ≥21 kPa prior to treatment had a value below this cut-off at the time of SVR. None out of the 764 patients who showed LS <21 kPa at SVR time-point presented a PHGB event. Hence, the negative predictive value of this LS cut-off for the emergence of a first PHGB episode after SVR was 100%.

Conclusion: The predictive ability of the LS 21 kPa cut-off for a first PHGB episode evidenced in patients with HCV-active infection remains among HCV-infected individuals who attain SVR with DAA-based therapy.These results suggest that stopping surveillance of esophagogastric varices in patients with LS<21 kPa at SVR is safe.At least 133 (37%) patients with LS≥21 kPa,in whom this parameter declines below to such a cut-off with SVR, may benefit from this decision.

583 TREATMENT WITH DIRECT-ACTING ANTIVIRALS REDUCES HEALTH CARE SERVICE UTILIZATION

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Background: Empirical evidence to support cost savings of direct-acting antivirals (DAAs) in real-world populations would support wider access. We investigated the impact of successful treatment of hepatitis C (HCV) with DAA therapy on healthcare services utilization (HCSU) among people living with HIV in Canada.

Methods: We used data from the Canadian Co-Infection Cohort study that prospectively follows 1974 HIV-HCV coinfected participants from 18 centres. Data is collected through self-administrated questionnaires, chart review and blood testing biannually. Among people who initiated DAA and achieved a sustained virologic response (SVR) we used a segmented negative binomial mixed-effect models to evaluate the impact of SVR on HCSU. The model controlled for pre-treatment trends in HCSU, exposure time (offset) and time updated covariates: CD4 cell count, HIV RNA, active injection drug use, significant fibrosis (>F2) and fixed covariates: age and sex. We categorized HCSU as out-patient visits (walk-in, general (GP) or HIV practitioners, specialists); or in-patient visits (emergency room (ER) and hospitalizations). Observations were truncated 6-months before DAA initiation to account for changes in HCSU in preparation for initiating DAAs.

Results: Between 2014-2018, 455 participants completed DAA therapy, of whom 424 achieved SVR. Median age at DAA initiation was 51 years (IQR 46, 56), 75% were male, 81% had HIV RNA <50 copies/mL; median CD4 was 520 cells/mL (IQR 331, 749) and 27% had liver fibrosis. A total of 2573 visits were divided as either pre-treatment (mean of 2.3 years (SD 1.2)) or post-SVR (mean 1.8 years (SD 0.9)). Overall, out-patient visits decreased from 12.6 visits/person-year (PY) before DAA initiation to 9.4 visits/PY post-SVR. Similarly, in-patient visits dropped from 2.8 visits/PY pre-treatment to 1.4 visits/PY post-SVR. Table 1 summarizes changes in HCSU by visit type. Before DAA initiation, annual rates of ER and specialist visits increased, hospitalizations and HIV visits were stable, while GP and walk-in-clinic visits decreased over time. Reductions in ER, hospitalizations and specialist visits were seen immediately after SVR and this effect persisted over time with annual reductions of 13%, 6% and 18% respectively, controlling for pre-treatment trends.

Conclusion: We found evidence of immediate and sustained reductions of both in- and out-patient visits following SVR with DAA therapy in a real-world HIV-HCV co-infected population.

Table 1. Health care service utilization before and after oral DAA treatment in those achieving SVR (Adjusted Incidence Rate Ratio (95% CI)

	Emergency Room	Hospitalizations	Specialist	General Practitioners	HIV Practitioners	Walk-in Visits
Pre-DAA trends, per year	1.09 (1.01, 1.17)	1.00 (0.90, 1.10)	1.13 (1.06, 1.20)	0.94 (0.89, 1.00)	0.97 (0.93, 1.01)	0.92 (0.84, 1.00)
Immediate impact (post-SVR compared to pre-DAA)	0.64 (0.45, 0.91)	0.60 (0.35, 1.02)	0.82 (0.78, 1.31)	1.36 (1.06, 1.74)	1.17 (0.97, 1.43)	0.74 (0.48, 1.17)
Post-SVR trends, per year (controlling for pre-treatment trends)	0.87 (0.73, 1.03)	0.94 (0.73, 1.20)	0.82 (0.72, 0.93)	0.90 (0.80, 1.01)	0.88 (0.80, 0.97)	1.16 (0.94, 1.42)

584 HCV CURE IN HIV COINFECTION DAMPENS INFLAMMATION AND IMPROVES COGNITION

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Background: Chronic inflammation in HIV/HCV coinfection increases cognitive impairment. With new direct-acting antiviral therapies for HCV, sustained viral response (SVR) or cure is possible. Our objective was to determine if chronic

inflammation and cognitive impairment in coinfection would be decreased after HCV SVR.

Methods: We studied 41 participants before and after treatment for HCV alone or with viral controlled HIV coinfection. We measured monocyte activation and gene expression, plasma inflammation and cognitive impairment. Monocyte-derived exosomal miRNAs were studied with RNA sequencing before treatment and followed by qRT-PCR after SVR.

Results: All HCV-coinfected subjects achieved SVR but one. Blood CD16+ monocytes were significantly decreased in coinfection after HCV treatment. Plasma sCD163 and neopterin were also decreased in HCV mono and coinfected persons. Overall cognition improved 25% in coinfection with visual learning/memory the most improved. HCV SVR decreased monocyte interferon genes MX1, IFI27 and CD169 in coinfection and MX1, LGALS3BP and TNFAIP6 in HCV monoinfection. CD83, IL6 and CXCL10 monocyte gene expression correlated with cognitive impairment before therapy; only CXCL10 continued to correlate with impairment and specifically worsening executive function and attention deficits despite DAA therapy. Monocyte exosomes from coinfected persons after treatment were significantly increased in miR-19a, miR-221 and marginally miR-223, all associated with decreasing inflammation and NF-κB activation.

Conclusion: HCV SVR in coinfection brings monocyte activation markers to levels seen with HIV alone. Cognitive impairment is significantly improved with HCV cure but not better than HIV infection alone strongly suggesting that cognitive impairment was driven by both HIV and HCV. Previous reports on the high percentage of cognitive impairment in HIV may have been greatly influenced by HCV coinfection.

585 TELOMERE LENGTH OF CIRRHOTIC HIV/HCV PATIENTS INCREASES AFTER HCV CLEARANCE WITH DAAS

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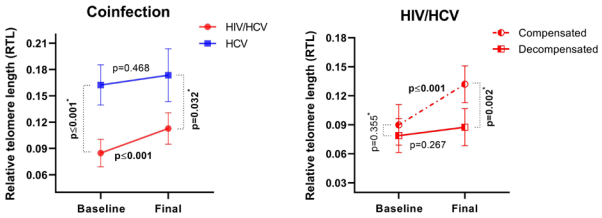
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Background: Human immunodeficiency virus (HIV) infection and cirrhosis are associated with a senescent phenotype that decreases telomere length. We evaluated the impact of hepatitis C virus (HCV) elimination on telomere length in patients with advanced HCV-related cirrhosis after sustained virological response (SVR) with all-oral direct-acting antiviral agents (DAAs).

Methods: Prospective study of 60 HIV/HCV-coinfected and 30 HCV-monoinfected patients with advanced HCV-cirrhosis (liver decompensation or liver stiffness measurement [LSM] >= 5 kPa or hepatic liver pressure gradient [HVPG] >= 10 mmHg or Child-Pugh-Turcotte (CPT) >= 7). The relative telomere length (RTL) was quantified by real-time multiplex PCR (MMqPCR) on peripheral blood mononuclear cells at baseline and 48 weeks after completing successful DAA therapy. Generalized linear models (GLMs) adjusted for the most relevant clinical and epidemiological variables and mixed GLMs were used.

Results: In comparison with HCV-monoinfected patients, HIV/HCV-coinfected patients were younger (p<0.001), had lower BMI (p=0.002), and had been exposed more frequently to interferon (p=0.011). Besides, they were more frequently men (p=0.011), smokers (p=0.005), prior IDUs (p<0.001), and alcohol abusers (p=0.005). RTL was significantly lower in HIV/HCV-coinfected patients than in HCV-monoinfected patients both at baseline (p<0.001), and at the end of follow-up (p=0.032). A significant RTL increase over time was found only for HIV/HCV-coinfected patients (p<0.001), especially in those patients with compensated cirrhosis (p<0.001) (Figure).

Conclusion: Eradication of HCV with DAAs was associated with a statistically significant increase in telomere length in HIV/HCV-coinfected patients with advanced cirrhosis, particularly in compensated patients. This finding suggests that HCV clearance may have implications in age-related conditions in this population group.



586 T-CELL AND MONOCYTE ACTIVATION CORRELATE AND DECLINE DURING HCV THERAPY FOR HCV/HIV

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Background: Immune activation predicts morbidity in HCV, HIV and HCV-HIV co-infection despite antiretroviral therapy (ART). HCV DAA therapy is associated with partial/complete normalization of soluble markers of immune activation during HCV infection. How this extends to cellular immunity during HCV-HIV infection is less clear.

Methods: We analyzed plasma and PBMC from AIDS Clinical Trials Group (ACTG) A5329, where ART treated HCV-HIV co-infected participants were treated with paritaprevir/ritonavir/ombitasvir+dasabuvir+/-ribavirin for 24 (n=36) or 12 (n=9) weeks. In a subset of participants where viable samples were available (n=21 24 week therapy and n=7 12 week therapy) we performed flow cytometric analysis of T-cells, central memory (CM)/effector memory (EM) subsets, monocyte subsets (CD14+CD16- classical, CD14+CD16+ inflammatory, and CD14-CD16+ patrolling), and cell activation (CD38 and HLA-DR expression) before (w0), during (w12) and after therapy (w36) to assess changes (Wilcoxon Signed Rank Test) pooled over the entire sample. Spearman's correlations evaluated associations between soluble immune activation markers (plasma sCD14, sCD163, IP10 and IL6) and T cell and monocyte subset/activation.

Results: CD38/HLA-DR co-expression on CD4 and CD8 memory T-cells decreased 12 weeks after initiation of DAA therapy (p<0.05, Table 1), and for some parameters at w36 (CD8 CM p=0.02, and CD4EM p=<0.001). HLA-DRhi expressing classical monocyte frequency tended to decrease at 12 weeks (p=0.06). Before therapy, HLA-DR expression on classical and inflammatory monocytes positively correlated with absolute counts of CD4 co-expressing CD38/HLA-DR (r=0.56, p=0.001), CD4CM (r=0.46, p=0.009), and CD4EM (r=0.43, p=0.02) T-cells, and CD8 CD38/HLA-DR co-expressing frequencies (CD8 r=0.38, p=0.04, CD8CM r=0.47, p=0.08 and CD8EM r=0.38, p=0.04) T-cells. Before DAA therapy IL-6 levels negatively correlated with classical monocyte frequency (r= -0.45, p=0.01), while 36 weeks after therapy initiation plasma sCD14 positively correlated with CD4s co-expressing CD38/HLA-DR (r=0.67, p=0.004) and CD4+CM (r=0.74, p=0.001) cells.

Conclusion: In this sample (n=28), memory T-cell activation associated with monocyte subset activation during HCV-HIV co-infection, consistent with related underlying mechanisms. 12 weeks following therapy initiation, monocyte, CD4 and CD8 activation was reduced. Residual memory CD4 activation after HCV therapy associated with sCD14, potentially attributable to ART controlled HIV immune activation.

Table 1: Percent CD38 and/or HLA-DR expression on CD4, CD8 T cell and monocyte cell subsets

	Median (25th, 75th %ile)			Median (25th, 75th %ile) change		P-value (Wilcoxon Signed-Rank Test)	
	Week 0 (n=28)	Week 12 (n=28)	Week 36 (n=20)	Week 0 vs 12	Week 0 vs 36	Week 0 vs 12	Week 0 vs 36
CD4+ CD38+HLADR+ (%)	8.9 (5.6, 14.4)	6.6 (4.9, 12.1)	8.0 (6.2, 11.7)	-1.2 (-3.2, -0.1)	-1.4 (-2.9, 1.7)	0.004	0.07
CD4+ CD38+HLADR+ (cells/mm^3)	60 (40,100)	48 (28,74)	53 (33.89)	-11 (-29, 3)	-12 (-35, 23)	0.003	0.26
CD4+ Central Memory CD38+HLADR+ (%)	7.2 (4.2, 11.3)	5.3 (4.3, 9.2)	6.9 (4.8, 9.8)	-1.3 (-3.5, 0.6)	-0.7 (-3.7, 1.2)	0.027	0.077
CD4+ Central Memory CD38+HLADR+ (cells/mm^3)	21 (13,29)	16 (10,24)	18 (15,26)	-2 (-9, 3)	-3 (-7, 3)	0.11	0.378
CD4+ Effector Memory CD38+HLADR+ (%)	10.6 (7.0, 15.6)	7.4 (5.1, 13.8)	9.1 (7.4, 12.1)	-1.7 (-5.1, 0.1)	-2.6 (-7.2, -0.3)	0.002	<0.001
CD4+ Effector Memory CD38+HLADR+ (cells/mm^3)	16 (9,28)	13 (5,18)	15 (12,20)	-5 (-10, -1)	-1 (-11, 4)	0.001	0.18
CD8+ CD38+HLADR+ (%)	22.9 (13.8, 29.0)	14.2 (10.9, 22.8)	13.9 (10.7, 21.9)	-4.285 (-12.0, 0.4)	-3.5 (-9.4, 1.8)	0.001	0.07
CD8+ Central Memory CD38+HLADR+ (%)	15.7 (8.3, 22.9)	11.7 (7.1, 15.6)	11.3 (9.6, 17.2)	-4.3 (-8.0, -0.7)	-4.0 (-6.2, -0.7)	0.001	0.02
CD8+ Effector Memory CD38+HLADR+ (%)	22.5 (15.3, 32.1)	15.1 (8.8, 28.1)	14.7 (9.9, 31.8)	-4.85 (-11.2, -0.01)	-5.8 (-10.2, 1.4)	0.002	0.11
CD14+CD16- HLA-DR^{hi} classical monocyte (%)	2.8 (0.60 6.0)	1.9 (1.1, 3.3)	1.9 (0.8, 6.6)	-0.3 (-2.0, 0.5)	-0.7 (-1.9, 0.4)	0.06	0.3
CD14+CD16+ HLA-DR^{hi} inflammatory monocyte (%)	19.9 (9.4, 27.8)	14.7 (7.0, 26.0)	15.8 (6.5, 29.4)	-1.4 (-9.5, 1.4)	-1.7 (-8.0, 6.8)	0.16	0.56
CD14-CD16+ HLA-DR^{hi} patrolling monocyte (%)	2.0 (1.0, 5.6)	1.2 (0.5, 4.6)	1.9 (0.5, 11.6)	-3.2 (-2.3, 2.6)	0.3 (-3.5, 2.1)	0.97	0.97

587 IMPACT OF HCV CLEARANCE ON NK CELLS AND HIV TRANSCRIPTION IN COINFECTED SUBJECTS

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Background: Hepatitis C is a frequent coinfection in people living with HIV. HCV replication and its subsequent clearance with direct acting antivirals (DAA) can potentially modify how HIV persists on antiretroviral therapy (ART). Natural killer (NK) cells are key effectors against both viruses and may be involved in shaping HIV reservoir. In this regard, we studied NK cell phenotype before and after HCV treatment with DAAs and its association with the dynamics of HIV reservoir.

Methods: In a prospective longitudinal observational study, HIV/HCV-coinfected individuals on suppressive cART (n=19) received sofosbuvir/daclatasvir alone or with ribavirin (n=7). Blood samples were obtained before HCV treatment (baseline sample, BSL), at end-of-treatment (EOT) and at 12 months after EOT (12MPT). Cell-associated (CA) HIV DNA (total, integrated, 2LTR), unspliced (US) and multiply-spliced (MS) RNA were quantified by real-time PCR. Expression of HLA-DR, CD38, NKG2D, NKp46, NKp30, CD95, CD69, CD25 on NK cells was evaluated by flow cytometry. Data was analyzed using non-parametric statistics.

Results: At 12MPT, US-RNA and US/MS ratio were significantly higher than at BSL (p=0.02 and p=0.03, respectively). No changes in CA-DNA were observed. At EOT, surface expression of HLA-DR, CD38, HLADR/CD38, NKG2D, and CD95, decreased compared to BSL (p=0.0002, p=0.006, p=0.0005, p=0.001 and p=0.001, respectively). CD95+, HLA-DR+, and HLA-DR+/CD38+ NK cells rebounded at 12MPT compared to EOT. Higher percentages of non-activated NK cells were observed at EOT (HLA-DR-/CD38- and CD25-/CD69-/CD95-) and at 12MPT (HLA-DR-/CD38-). Overall, higher levels of EOT and 12MPT NK cell activation correlated with higher 12MPT US-RNA. Particularly, EOT-expression of HLA-DR correlated with 12MPT US-RNA (r=0.57, p=0.04). Also, 12MPT CD38 expression correlated with fold change in US-RNA levels between12MPT and BSL (r=0.5919, p=0.0462).

Conclusion: Downregulation of NK cell activation was observed immediately after HCV clearance although some markers rebounded one year later, in concomitance with increased transcriptional activity of HIV reservoir. This may be reflecting the priming of NK cells by the residual HIV transcription and might point out a role for NK cells in shaping HIV persistence.

588 CHANGES IN IMMUNE-CELL SUBSETS IN HCV AND HCV/HIV PATIENTS UPON VIRALLY EFFECTIVE DAA

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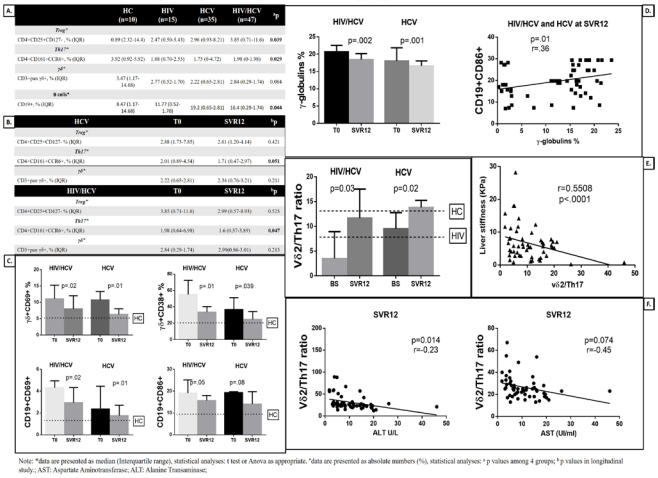
Background: Direct-Acting Antivirals (DAAs) eradicate HCV and reduce liver fibrosis by containing inflammation. Virologic response correlates with the restoration of NK and CD8, however, little is known on the effects of DAAs on gd, Th17 and Treg which all play a role in liver fibrogenesis. Further, while B-cell activation has been linked to extrahepatic manifestations of HCV, literature is lacking on the role of these cells in liver damage.

Methods: We enrolled 97 virally-infected (VI) subjects (15 HIV cART-suppressed; 35 HCV naive to HCV therapy; 47 HIV/HCV cART-suppressed and naive to HCV therapy) and 10 age-matched healthy controls (HC). All HCV-infected individuals underwent DAA therapy. At baseline (T0) and 12 weeks after End of Treatment (SVR12) we measured: (i) γδ frequency (CD3+Pan γδ+), activation (CD69/CD38), (ii) Th17-like (CD4+CD161+CCR6+); (iii) Treg (CD4+CD25+CD127-); (iv) B cell frequency (CD19+), activation (CD86/CD38); v) γ-globulin levels.vi) Fibrosis stage was determined by transient elastography (Fibroscan) Statistical analysis as appropriate

Results: At T0, VI presented lower Th17 and higher Treg versus HC (Fig1A). DAA led to a further contraction of Th17 and no changes in Treg frequency (Fig.1B). While total γδ were comparable in VI and HC both prior to and following treatment (Fig.1B), activated γδ subset decreased upon DAA (Fig.1C). Compared to HC, VI also featured higher B-cell frequencies and activation which both decreased during DAA (Fig1C). Accordingly, γ-globulin concentrations also diminished in HCV mono and co-infection following DAA and correlated with B-cell activation (Fig1D). In VI, a low vδ2/Th17 ratio, known to predict liver damage, increased from baseline to SVR12, yet remained lower than HC (HIV/HCV vs HC: p=.04; HCV vs HC: p=.03) and negatively correlated with liver stiffness (Fig.1E) and serum ALT and AST (Fig.1F) Further, also γ-globulin levels were positively linked to liver fibrosis indexes following DAAs (r=0.6, p<.0001). No differences in B and T cell phenotypes were registered (Fig1A).

Conclusion: Effective DAA in both HCV- mono and HIV/HCV co-infected subjects resulted in decreased B- and γδ cell activation, with recovery of vδ2/Th17 ratio. These changes are linked to the reduction of hepatic necrosis and stiffness, suggesting that DAA-mediated lightening of the pro-inflammatory liver insult may limit organ damage.

Figure 1. B and T Immunophenotype in Virally-infected Patients pre e post DAA treatment



Note: *data are presented as median (Interquartile range), statistical analyses: t test or Anova as appropriate. †data are presented as absolute numbers (%), statistical analyses: ° p values among 4 groups; ¶ p values in longitudinal study.; AST: Aspartate Aminotransferase; ALT: Alanine Transaminase;

589 LIVER FIBROSIS HINDERS NORMALIZATION OF SYSTEMIC INFLAMMATION AFTER HCV ERADICATION

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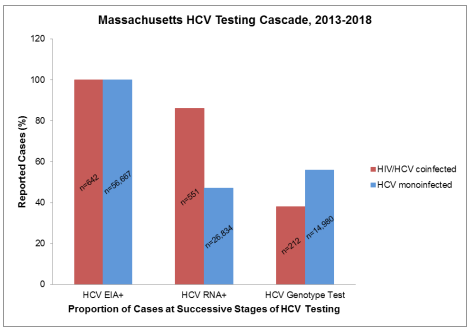
Background: HCV co-infection significantly impacts on inflammation, endothelial activation and coagulation function parameters leading to several comorbidities among people living with HIV (PLWH). The new direct-acting antivirals (DAAs) therapy achieves eradication of HCV in the majority of patients. However, the early effect of HCV eradication on these parameters on PLWH has been scarcely explored. We have analyzed the effect of HCV on systemic inflammation and endothelial/coagulation function in PLWH and its evolution after HCV eradication with DAAs.

Methods: Twenty five HIV/HCV coinfected (HIV/HCV group),25 HIV-infected (HIV group) and 20 healthy controls (HC) were included. All patients were on ART and HIV suppressed. Parameters of systemic inflammation, endothelial activation and coagulation were measured on plasma samples using Human Custom ProcartaPlex kit (Invitrogen,Thermo Fisher Scientific) and acquired on a Luminex analyzer (Bio-Plex 200 System by Biorad). Cross-sectional and longitudinal (comparing baseline vs 12 weeks after end of treatment in HIV/HCV group) analyses were performed. Non-parametric tests were used to establish inter and intra-group differences.
Results: No significant differences between HIV and HC groups were observed for any of the parameters analyzed. In contrast, at baseline HCV/HIV group showed increased levels of IL-18 (p=0.028), IP-10 (p<0.0001), VCAM-1 (p<0.0001) and ICAM-1 (p=0.045) compared to HC and HIV groups. Interestingly, the highest levels of these markers were observed in HCV/HIV patients with significant liver fibrosis (>F2, n=10), with significant differences between <F2 and >F2 HIV/HCV patients for IL18 and IP10 (p=0.007 and p=0.015, respectively). Of note, after HCV eradication, levels of VCAM-1 remained significantly increased compared to HIV and HC groups (p=0.006) with a similar profile in patients with (>F2) and without (<F2) liver fibrosis (p=0.034 and p=0.033 respectively), whereas levels of IP-10 remained significantly increased only in patients with liver fibrosis (p=0.032).
Conclusion: Both HCV co-infection and presence of liver fibrosis significantly impacts on markers of systemic inflammation and endothelial activation in PLWH. Normalization of these parameters is not completely achieved after HCV eradication, especially in patients with liver fibrosis. These data prompts HCV treatment in all HIV/HCV coinfected patients at the earliest stages of liver damage to enhance normalization of systemic inflammation and endothelial activation.

590 HEPATITIS C TESTING OF INDIVIDUALS WITH HCV/HIV COINFECTION, MASSACHUSETTS 2013-2018

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Background: Current CDC guidelines recommend routine hepatitis C virus (HCV) screening for people living with HIV (PLWH) and that HCV testing should follow a testing cascade. Tests should be initiated with an anti-HCV antibody test and, if reactive (EIA+), should be followed with an HCV RNA test, and genotype tests to guide treatment decisions. Here we use state-level reports to model the HCV testing cascade to serve as a proxy for access to care for PLWH coinfected with HCV and those monoinfected with HCV.
Methods: The Massachusetts Department of Public Health receives electronic reports of laboratory tests for HIV and HCV in residents of the state. We analyzed demographic and laboratory data from all individuals diagnosed and reported as living with HIV in Massachusetts as of December 2016 and coinfected with HCV 2013-2018. PLWH were matched to HCV laboratory data reported 2013-2018 to characterize HCV testing after an HCV EIA+ test. We also analyzed HCV test results from those uninfected with HIV for the same period. Outcomes included type of (nucleic acid or genotype test) HCV tests received after HCV EIA+ test. The proportion of cases at each step in the cascade was calculated as a conditional proportion. Variables examined included sex, birth cohort, risk history, and race/ethnicity.
Results: As of December 2016, there were 642 PLWH who tested HCV EIA+ in Massachusetts. Among PLWH, the majority of HCV seroconversions occurred in males (71%), people who reported injection drug use (46%), and people diagnosed with HIV before 2013 (77%). Compared to HIV-uninfected HCV EIA+ persons, a greater proportion of PLWH received viral load testing (86% vs. 47%). A greater proportion of monoinfected HCV persons were reported to have a subsequent genotype test (56% vs. 38%).
Conclusion: While only 47% of HCV EIA+ cases reported to the state had a positive HCV RNA test reported, a majority (87%) of PLWH who tested HCV EIA+ were confirmed with HCV infection. This discrepancy may reflect that PLWH are more likely to be engaged in ongoing care, including HCV. Our findings on genotype testing require further investigation in the context of pan-genotypic direct acting antivirals. Effective surveillance is critical for success in evaluating and promoting HCV elimination among PLWH. Improved surveillance capture of demographic and behavioral information, such as injection drug use, is needed to help public health agencies ensure equity in HCV diagnosis and linkage to HCV care for PLWH and non-PLWH.



591 COST-SAVING OF POOLED HCV RNA TESTING TO DIAGNOSE ACUTE HCV IN HIGH-RISK POPULATIONS

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Background: Acute HCV infection has emerged as a sexually transmitted disease (STD) in MSM. With highly effective direct acting antivirals (DAAs) against HCV, timely diagnosis and treatment of acute HCV infection can curb further transmission. Given the cost concerns about HCV RNA testing, we assessed the cost-saving strategy with the use of pooled sera for HCV RNA testing to diagnose acute HCV infection in high-risk populations.
Methods: We enrolled HIV-positive patients without HCV infection who presented with STDs or elevated aminotransferases within 6 months, HIV-positive patients with spontaneous HCV clearance or achievement of sustained virologic response (SVR) with HCV treatment, and PrEP users without HCV infection. A total of 20 specimens were combined into a pooled specimen for HCV RNA testing. STD screening was performed for HIV-positive patients or PrEP users with STDs. All of the 20 patients would be considered free of HCV if a pooled specimen was tested negative for HCV RNA. For any pooled specimen tested positive, every 5 specimens of the 20 specimens would be combined into a sub-pooled specimen for HCV RNA testing. For a sub-pooled specimen tested positive, each of the 5 specimens would be retested individually to identify the one with HCV.
Results: From Jun 25 to Sep 19, 2019, 322 individuals were enrolled, including 304 (94.4%) HIV-positive patients and 18 (5.6%) PrEP users, with 99.1% being MSM. Patients were enrolled because of STDs in 228 (75.0%), follow-up of HCV status after SVR in 79 (26.0%) or spontaneous HCV clearance in 9 (3.0%), and elevated aminotransferases in 8 (2.6%). Chlamydia infection was identified in 23.4% (49/209) of HIV-positive patients and 44.4% (4/9) of PrEP users, while gonorrhea was diagnosed in 11.5% (24/209) of HIV-positive patients and 22.2% (2/9) of PrEP users. Acute HCV infection was diagnosed in 8 (2.5%) patients (3 with STD, 2 STD/SVR, 3 elevated aminotransferases) at the first determination and 1 at the second determination 3 months later, with negative anti-HCV antibody in 2. Instead of 340 tests, a total of 89 HCV RNA tests were needed to identify the 9 individuals with acute HCV infection by the pooled-serum approach, and we were able to save 73.8% of the total cost required if all the specimens had been tested individually.
Conclusion: Pooled HCV RNA testing is cost-saving to diagnose acute HCV infection in high-risk populations.

592 PERSISTENT HIV CONTROLLERS ARE MORE PREDISPOSED TO SPONTANEOUSLY CLEAR HCV

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Background: HIV-controllers have the ability to spontaneously maintain viremia at low or undetectable levels in absence of antiretroviral treatment. Furthermore, HIV controllers seem to have superior capacity to spontaneously clear hepatitis C virus (HCV) coinfection compared to non HIV-controllers. Some of these subjects eventually lose HIV-controller status (transient controllers), in contrast with HIV-controllers with persistent natural HIV control (persistent

controllers). It is unknown whether persistent controllers have superior capacity to spontaneously clear HCV coinfection compared to transient controllers.
Methods: HIV-controllers with available data for antibodies to HCV (anti-HCV) were recruited (n=744). Factors associated with HIV spontaneous control in relation to HCV coinfection were analyzed in persistent and transient HIV-controllers with anti-HCV positive (n=202 and n=138, respectively) in comparison with 1700 anti-HCV positive non HIV-controllers. In addition, the factors related to the loss and time to lose HIV-controller status were explored (n=744).
Results: A higher frequency of HCV spontaneous clearance was found in persistent HIV-controllers (25.5%) compared to non-controllers (10.2%). After adjusting for potential confounders as sex, age, HIV transmission risk, CD4+ T-cell nadir and time of follow up, HCV clearance was independently associated with persistent HIV spontaneous control (p=0.002; OR (95% CI)= 2.573 (1.428-4.633), but not with transient spontaneous control (p=0.119; 1.589 (0.888-2.845). Furthermore, persistent HIV-controllers were more likely to spontaneously clear the HCV in comparison with transient controllers (p=0.027; 2.650 (1.119-6.276). Finally, no loss or a delayed time to lose HIV-controller status was independently associated with HCV spontaneous clearance (p= 0.010; 1.990 (1.177-3.364).
Conclusion: This study shows an association between spontaneous persistent HIV-control and HCV spontaneous clearance. Our results support common mechanisms involved in spontaneous persistent HIV control and HCV clearance. These results suggest persistent but not transient HIV-controllers as a good model of functional HIV cure.

593 HPTN 078: HIGH INCIDENCE OF HEPATITIS C VIRUS INFECTIONS AMONG MSM

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Background: Annual hepatitis C virus (HCV) testing is recommended in HIV-infected (HIV+) men who have sex with men (MSM) due to sexual transmission risk. While there is no HCV testing guideline for HIV-uninfected MSM, incident HCV infections have been noted. More data on incident HCV infection in MSM are needed.
Methods: HPTN 078 assessed the efficacy of an integrated strategy to achieve HIV viral suppression; MSM were screened using respondent driven sampling and direct recruitment to identify HIV+ MSM who were not in care in Atlanta, Birmingham, Baltimore and Boston. At screening, demographic and behavioral questionnaires were completed, along with HIV and HCV testing. To identify subjects with recent HCV infection, HCV antibody (Ab) and RNA+ samples were tested using a modified Green Cross antibody avidity assay. Incidence rate was calculated using the Assay-Based Incidence Estimation Model. Phylogenetic analysis was used to assess clustering. Univariable logistic regression was used to evaluate associations with recent HCV infection.
Results: This study included 1041 HCV Ab- MSM and 96 HCV Ab+/HCV RNA+ MSM who were tested for recent infection. Of the 96, 16 had a recent infection (12 HIV+), so further analyses were restricted to these 16 plus the 1041 HCV Ab- MSM. Of these 1057 men, median age 38 years, 70% Black, 83% insured, 38% employed, and 69% HIV+ (Table 1). The overall HCV incidence rate was 5.0/100 person-years (PYs) (95% confidence intervals [CI]: 2.0-8.0/100 PYs), with rates of 5.5/100 PYs (1.8-9.2/100 PYs) in HIV+ MSM and 4.0/100 PYs (-0.4-8.5/100 PYs) in HIV-uninfected MSM (P=0.38). The median lifetime number of male sexual partners was 16 (interquartile range [IQR]: 6, 50) in HCV Ab- MSM and 100 (19, 150) in MSM with recent HCV (P<0.01). The proportion of men who had substance use counseling was significantly greater in those with recent HCV compared to those who were HCV Ab- (44% vs. 16%, P<0.01). These associations were similar in the HIV+ group. Recent infections were mainly genotype 1; 3 genotype 3; none clustered together.
Conclusion: Although recent HCV infection was more common in HIV+ than in HIV-uninfected MSM, it was higher in both groups than in other studies. This suggests that HCV risk counseling should be considered in both HIV+ and HIV-uninfected MSM, particularly in those with a high number of lifetime sexual partners and substance use. Integrating HCV prevention into substance use counseling should be explored.

Table 1. CHARACTERISTICS OF HCV ANTIBODY NEGATIVE AND RECENT HCV INFECTIONS IN MSM SCREENED FOR HPTN 078

Characteristic	Total N=1057	HCV Ab Negative N=1041	Recent HCV N=16	p-value
Age, years Median (IQR)	38 (29, 50)	38 (29, 50)	42 (29, 54)	0.60
Black Race (N,%)	744 (70.4)	734 (70.5)	10 (62.5)	0.49
Education (<High school diploma) (N,%)	137 (13.0)	134 (12.9)	3 (18.8)	0.49
DC-RDS (N,%)	570 (53.9)	564 (54.2)	6 (37.5)	0.18
Employed (N,%)	404 (38.2)	398 (38.2)	6 (37.5)	0.95
Insured (Public, Private) (N,%)	876 (82.9)	861 (82.7)	15 (93.8)	0.25
Income (<$5,000)(N,%)	284 (26.9)	280 (26.9)	4 (25)	0.41
Lifetime Male Sexual Partners (IQR)	16 (6, 50)	16 (6, 50)	100 (19, 150)	<0.01
Age at first time sex with a man, years (IQR)	17 (15, 20)	17 (15, 20)	17 (15, 20)	0.70
Exchange sex (N,%)	229 (21.7)	224 (21.5)	5 (31.3)	0.38
HIV-infected (N,%)	730 (69.1)	718 (69.0)	12 (75.0)	0.25
Syphilis (Active)(N,%)	230 (21.8)	226 (21.7)	4 (25)	0.46
Substance Use Counseling (N,%)	174 (16.5)	167 (16.0)	7 (43.8)	<0.01
Unstable Housing (N,%)	67 (6.3)	65 (6.2)	3 (18.8)	0.31
Unable to get healthcare when needed in the past 6 months (N,%)	120 (11.4)	117 (11.2)	2 (12.5)	0.45

594 SEX, NOT DRUG USE, IS DRIVING HCV REINFECTION AMONG HIV-INFECTED MSM IN NEW YORK CITY

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Background: HCV reinfection rates are high among HIV-infected MSM in Western European cities as well as in New York City (NYC). We have previously shown that the two behavioral risk factors for primary HCV infection in NYC were receipt of semen into the rectum with receptive anal intercourse (semen in rectum), and sex with use of crystal methamphetamine (sex on CM). Behavioral risk factors for HCV reinfection in this population, however, have not been studied.
Methods: We performed a prospective cohort study in NYC to determine the behavioral risk factors for reinfection after primary HCV among HIV-infected MSM. Reinfection was defined as new HCV viremia after successful therapy (SVR 12) or spontaneous clearance (SC). Clinical visits for surveillance for reinfection were performed between Jan 2006 and Dec 2018, starting at the end of therapy, or the first undetectable VL for SC. Participants were queried about engagement in the two previously demonstrated risk factors for primary HCV in NYC, semen in rectum and sex on CM, and, additionally, about injection use of CM. Cox proportional hazards models analyses with these three behaviors as time-dependent variables, adjusted for age, race, ethnicity, and year of HCV clearance, were used to identify the behavioral risk factors for 1st HCV reinfection.
Results: Among our full cohort of 305 men with cleared HCV, 37 had 1st reinfections (rate 4.4/100 PY). We had adequate behavioral data from 244 (80%) men, of whom 29 (78% of 37) had 1st reinfections (rate 4.5/100 PY). Median age was 44 years, 21% were black, 78% white, and 20% Latino, which mirrored the full cohort, as did HIV and HCV parameters. Over 647 PY (median 2.13 [IQR 0.78, 3.66]) there were 1,286 visits (median 4 [IQR 2, 6] per participant). While all three risk factors were significantly associated with 1st HCV reinfection in univariable Cox proportional hazards models (Table, 1st column), in the multivariable Cox proportional hazards model, only semen in rectum was significantly associated with 1st HCV reinfection (HR=3.96 [95% CI 1.43, 10.96], p=0.008) (Table, 2nd column).
Conclusion: Sex, with receipt of semen into the rectum, rather than drug (methamphetamine) use, was the behavior driving HCV reinfection in HIV-infected MSM. Taken together with previous research demonstrating HCV in semen, and as condom use has not been successful as an HCV prevention strategy, our results suggest the need for novel interventions to prevent seminal HCV from causing trans-rectal HCV infection.

Table. Cox proportional hazards model analysis of behavioral risk factors for 1st HCV reinfection among HIV-infected MSM in New York City, 2006 to 2018 (N=244)

Univariable analysis [a]		Multivariable analysis [b]	
HR (95% CI)	p-value	HR (95% CI)	p-value
Receipt of semen into rectum with receptive anal intercourse			
4.12 (1.82, 9.33)	< 0.001	3.96 (1.43, 10.96)	0.008
Sex while high on methamphetamine			
3.32 (1.24, 8.89)	0.02	0.79 (0.18, 3.50)	0.75
Injection use of methamphetamine			
4.02 (1.36, 11.86)	0.01	2.24 (0.53, 11.35)	0.25

[a] Univariable Cox proportional hazards models were run with each of the 3 listed behavioral risk factors as the single time-dependent variable, with 1st HCV reinfection as the outcome, and adjusted for age, race, ethnicity, and year of HCV clearance.

[b] The multivariable Cox proportional hazards model included all of the 3 listed behavioral risk factors as time-dependent exposure variables, with 1st HCV reinfection as the outcome, and adjusted for age, race, ethnicity, and year of HCV clearance.

595 HCV REINFECTION AMONG HIV PATIENTS AFTER DAA THERAPY IN THE COUNTRY OF GEORGIA

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Background: In 2015, in partnership with US CDC and Gilead Sciences, Georgia launched national hepatitis C elimination program. All HCV patients, including HIV co-infected persons, have free access to direct acting antivirals (DAA). We report rates of HCV re-infection among HIV-infected persons in real-life settings.

Methods: Analysis included HIV patients treated with DAAs during 2015-2017 and who achieved sustained virologic response (SVR), defined as undetectable HCV RNA after 12 weeks after completing treatment. Patients were followed until August 2019. Risk-based approach was used to screen for HCV re-infection, which included history of injection drug use (IDU), high risk sexual behavior, recent history of invasive procedures and elevated liver enzymes. Reinfection was defined as detectable HCV RNA after confirmed SVR.

Results: During the study period 420 patients achieved SVR and 274 (65%) were screened for HCV reinfection. Among 274 persosns tested for HCV reinfection the median age was 46 (IQR: 40-51) years, 242 (88.3%) were men and 201 (73.4%) had history of IDU. HCV genotypes included: 103 (37.6%) genotype 1, 84 (30.7%) genotype 3, 83 (30.3%) genotype 2 and 4 (1.5%) genotype 4. With regard to DAA regimens, 142 (51.8%) were treated with ledipasvir/sofosbuvir ± ribavirin, 58 (21.2%) – with sofosbuvir/ribavirin and 74 (27.0%) – with sofosbuvir/ribavirin + pegilated interferon. Patients were followed for median 1.8 (IQR: 1.1-2.5) years contributing to 507 person-years (PY) of follow-up. In total, 12 (4.4%) persons had HCV re-infection with an overall incidence of 2.4 per 100 PY. All reinfected patients were men with history of IDU. The median time to reinfection was 1.5 (IQR: 0.9-2.2) years. Genotype switch was documented in 7 (58.3%) cases. Rate of reinfection among persons with history of IDU was 3.3/100 PY. Among 201 persons with history of IDU only 32 (15.9%) were engaged in opioid substitution treatment (OST). Reinfection rate among persons on OST was 1.5/100 PY (1 reinfection) vs. 3.7/100 PY (11 reinfections) among those not receiving OST. No statistically significant differences were observed in rates of reinfection by baseline HCV genotype and treatment regimen.

Conclusion: HIV positive IDUs are at high risk for HCV reinfection following successful DAA therapy. Greater engagement in OST programs are required to prevent reinfections and achieve elimination targets.

596 HCV REINFECTION AFTER DAA TREATMENT AMONG PEOPLE LIVING WITH HIV IN SAN DIEGO

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Background: Previously, we reported the HCV reinfection rate in San Diego from 2000 to 2014 among HIV-infected men who have sex with men (MSM) during the interferon era was 2.89/100 PYFU. Herein, we report the HCV re-infection rates in all groups of people living with HIV (PLWH) treated with interferon-free direct-acting antivirals (DAA) in San Diego, California

Methods: Retrospective cohort analysis of adult PLWH treated with DAA at the University of California, San Diego between 2014 and April 2019. PLWH with documented sustained virologic response (SVR), and at least one subsequent HCV RNA measurement before September 2019 were included. HCV re-infection was defined as new HCV viremia after documented SVR. Follow up time was calculated from the date of SVR documentation until the first subsequent positive HCV RNA or the last negative HCV RNA. Clinical onset of re-infection was defined as the date of the first noted HCV RNA. Person-time incidence rates [95% C.I.] per 100 years-at-risk (PYFU) were estimated using the Poisson distribution

Results: There were 204 PLWH with documented SVR. Their median age was 52 years (95% CI: 50-53.4), 83.3% were male, and 21.6% were non-white. HCV genotypes distribution were 1a in 139 (68.1%), 1b in 20 (9.8%), 3 in 27 (13.2%) and other in 18 (8.8%). The median CD4 count in cells/uL was 503 (95% CI: 464-562) and 188 (92.2%) had undetectable HIV viral load. HCV risk factors were MSM in 54.9%, of which 40.2% also had a history of intravenous drug use (IVDU), and IVDU as the only risk factor in 39.2%. Six men acquired a new HCV infection over 321.7 PYFU. The HCV reinfection incidence rate overall was 1.87 and in MSM non-IVDU 3.54 per 100 PYFU. The median time from end-of-DAA-treatment to reinfection was 54 weeks (range 7-95.4 weeks). Of the six reinfected patients, three had a change in genotype and one had cirrhosis with documented SVR a year after finishing DAA before his reinfection. The table shows reinfection rates by HCV risk category, gender, ethnicity, and age. There were no reinfections among females. Five reinfected patients were-treated successfully, with one pending retreatment with DAA

Conclusion: The overall reinfection rate in San Diego among PLWH in the DAA era is low, and is highest among MSM but comparable to previously observed in the interferon era. This result may help guide future interventions to prevent HCV reinfection in PLWH at risk in San Diego

HCV Re-infection rates based on HIV risk factor, race/ethnicity, age, and gender

	Reinfection rate (per 100 PYFU) (95% CI)	Person-Years of Follow-Up
HIV/HCV Risk factor (n)		
All (204)	1.87 (0.69-4.06)	321.70
MSM only (67)	3.54 (0.96-9.06)	113.12
MSM+IVDU (45)	2.33 (0.06-12.98)	42.95
IVDU only (80)	0.66 (0.02-3.67)	152.05
Heterosexual only (5)	0.00	4.89
Other/Unknown (7)	0.00	8.68
Biologic Gender (n)		
Female (32)	0.00	44.07
Male (172)	2.16 (0.79-4.71)	277.62
Race/Ethnicity (n)		
White (160)	2.03 (0.66-4.75)	245.99
Non-white (44)	1.32 (0.03-7.37)	75.70
Age in years (n)		
<30 (10)	0.00	10.71
30-39 (25)	7.49 (0.91-27.07)	26.70
40-49 (43)	1.49 (0.04-8.29)	67.24
50-59 (90)	1.94 (0.40-5.65)	155.16
>59 (36)	0.00	61.88

597 HCV INCIDENCE AMONG HIV-INFECTED MSM IN FRANCE: RESULTS FROM THE FHDH-ANRS CO4 COHORT

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Background: Despite the availability of highly effective directly acting antivirals (DAAs), sexual transmission of hepatitis C virus (HCV) in men who have sex with men (MSM) is still ongoing, associated with high-risk sexual behaviors. The objective of this study was to estimate the incidence of primary HCV infection among HIV-positive MSM in France in the post-DAA era.

Methods: We used data from a large French hospital cohort of HIV-positive individuals (FHDH-ANRS CO4) prospectively collected between 2014 and 2017. HCV infection rates were calculated using person-time methods, among HIV-positive MSM with a negative anti-HCV test at cohort entry and subsequent HCV tests. HCV negative status was assigned to individuals never testing HCV positive throughout follow-up, discontinued on December 31th 2017. Incident HCV infection was based on any positive HCV test (RNA and/or antibodies) during follow-up; the date of HCV infection was the midpoint between the last negative and first positive test. Individuals were considered lost to follow-up if they had no clinical visit for 18 months; follow-up was ceased 6 months after last clinical visit.

Results: A total of 15,692 HIV-positive MSM were included. Their median age was 45 years (interquartile range (IQR): 35-52). The median number of HCV serology tests during follow-up for each individual was 3 (IQR: 2-4), with a median testing interval of 1.25 years (IQR: 0.85-1.93) between two tests. Overall, 330 incident HCV infections occurred over 45,866 person-years

(py) of follow-up. Incidence of first HCV infection decreased significantly (p-trend=0.04) over time during the study period: 0.98/100py (2014), 0.82/100py (2015), 0.67/100py (2016) and 0.45/100py (2017). The stronger decrease occurred in 2017 (33% reduction from 2016 to 2017). In sensitivity analyses, similar trends were observed when the date of first positive HCV was used as a proxy for the time of infection, or when follow-up was ceased at the date of last clinical visit or 12 months after for patients lost to follow-up.

Conclusion: The observed decrease in primary HCV infections among HIV-infected MSM may be related to a concomitant and continuous scaling-up in DAA use, which was especially marked in HIV-HCV coinfected individuals. The declining trend may also be considered in parallel with the rising incidence of HCV infection recently reported among HIV-negative MSM receiving preexposure prophylaxis (PrEP), suggesting a transfer of the epidemic from the former to the latter.

Year	Person-years	Number of infections	Incidence/100py [95% CI]
2014	10 308	101	0.98 [0.81-1.19]
2015	11 455	94	0.82 [0.67-1.00]
2016	12 100	81	0.67 [0.54-0.83]
2017	12 003	54	0.45 [0.35-0.59]
Overall	45 866	330	0.72 [0.65-0.80]

Man-Kendall trend test: p=0.04

598 LARGE HEPATITIS C TRANSMISSION CLUSTER IDENTIFIED AMONG HIV-POSITIVE MSM IN BANGKOK

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Background: A rapidly emerging HCV outbreak has recently been observed among HIV-positive men who have sex with men (MSM) living in Bangkok, Thailand. Little is known regarding the transmission networks among this population.

Methods: MSM with both acute (Feibig stages 1 to 5) and chronic HIV infection and with incident HCV infections were identified in research cohorts at the Thai Red Cross AIDS Research Centre. Incident HCV infections were defined as seroconversion from anti-HCV antibody negative to positive after initiating ART. NS5B regions of the HCV genome (404 and 471 bps) were amplified using nested-PCR and sequenced. Phylogenetic inference was constructed by Maximum Likelihood methods in MEGA X.0.5 software with 1000 bootstrap samplings. Clusters were identified using ClusterPicker with support and genetic distance thresholds of 85% and of 4.5%, respectively.

Results: A total of 48 (25 acute HIV and 23 chronic HIV) MSM with incident HCV infection and amplifiable NS5B sequences were included in the analysis. Median (interquartile range, IQR) HCV RNA was 6.3 (5.3-6.9) IU/mL. HCV genotype (GT) was 85% GT 1a and 15% GT 3a or 3b. Median age at HCV diagnosis was 34 (IQR, 28-41) years. 83.3% (40/48) had history of syphilis infection and 36% (16/44) reported crystal methamphetamine use. Only 2 (4%) reported ever injecting drugs, both crystal methamphetamine. Six (12.5%) were HBV co-infected, all of whom had chronic HIV. In the phylogenetic clustering analysis, 83% belonged to one of two clusters: one large (n=36, 75%) and one small (n=4, 8%) cluster (Figure). All clusters were GT 1a. Overall mean genetic distance was 0.10 (SE=0.02). Participants with acute HIV infection were more likely to be in a cluster (92%) than those with chronic infection (74%).

Conclusion: Phylogenetic analysis showing a high degree of clustering confirms that the HCV epidemic in the HIV-infected MSM community in Bangkok is recent and rapidly expanding. This epidemic is independent of past HCV transmission among people who inject drugs in Thailand, which was largely GT 3. Crytal methamphetamine use is high in participants with HCV infection, and previous reports have identified chemsex and group sex parties as factors associated with HCV transmission. HCV antibody testing should be regularly performed for MSM on ART in Bangkok, and direct-acting antivirals being offerred to all MSM with HCV infection might contain this HCV epidemic from spreading further.

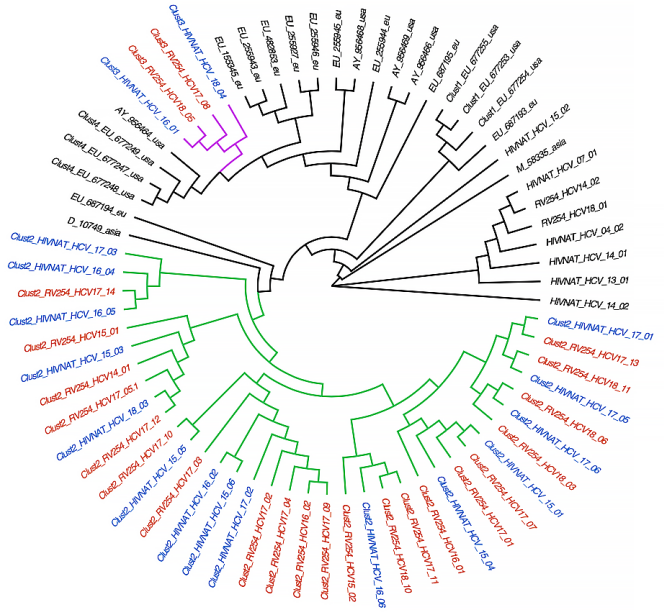


Figure. Cladogram showing phylogenetic clustering of 48 HCV NS5B sequences inferred by Maximum Likelihood methods in MEGA X.0.5 with 1000 bootstrap sampling. Reference sequences of MSM and IDU population from Asia, Europe and USA were included. Clusters were identified using ClustePicker software with support and genetic distance thresholds of 85% and of 4.5%, respectively. Participants with acute and chronic HIV infection are denoted with red and blue tip label colors. NS5B sequences from annotated transmission cluster 2 (branch label color: green) and 3 (purple) are all HCV genotype 1a.

599 ORAL PRESCRIPTION OPIOID USE AS A HIGH-RISK INDICATOR FOR HCV INFECTION

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Background: The opioid epidemic across the U.S. poses an array of public health concerns, especially HCV transmission. HCV is now widely-curable, yet incident rates are increasing due to the opioid epidemic. Despite the established trajectory from oral prescription opioids (OPOs) to opioid use disorder (OUD), OUD to injection drug use (IDU), and IDU to HCV, we have found no studies or guidelines establishing OPOs as a defined risk factor (RF) for HCV infection. In this study we observed HCV testing and antibody reactivity (HCVAb+) in patients receiving OPOs, hypothesizing that they should be considered an HCV RF, critical in the global effort toward HCV elimination.

Methods: The study was conducted on all patients with any OPO reported in the EHR at a large regional US healthcare system between January 2017 and December 2018. Chi-square and Student t-tests were used for univariate comparisons; multivariate logistic regression was used for independent variable associations. Statistical significance was defined as p<0.05; Epi Info and SAS v 9.4 were used for statistical analyses; IRB approval was received.

Results: 115,415 persons received any OPO (Table 1); 8.6% (932) were HCVAb+ when tested and not previously diagnosed (10,900); 3.4% (3,893) had an OUD diagnosis, 20.6% (803) of whom were HCV tested. Of those HCVAb+ (1,421), 25.4% (361) had an OUD diagnosis. In the Birth Cohort born between 1945-65 (BC), black race (ORadj 2.22, CI95 1.90-2.59), male (2.45, 2.12-2.82) and OUD (6.97, 5.60-8.67) were independent predictors of HCVAb+; white race (1.68, 1.32-2.13) and OUD (9.65, 7.46-12.48) in the non-BC.

Conclusion: These results offer three applicable conclusions: 1) in a large population prescribed oral opioids, HCVAb+ was 8.6%, higher than our previously published data (2.5%) and US rate (1.7%); thus, OPOs should be incorporated as a defined RF for HCV counseling and retesting; 2) although OUD may lead to known HCV RFs, only 20% of patients diagnosed with OUD were tested; thus, efforts should be increased to improve HCV RF awareness; and, 3) although the trajectory from OPOs to OUD to IDU to HCV would predict that a majority of HCVAb+ patients have OUD, only 25% of those HCVAb+ were

classified with OUD; therefore, new strategies need consideration for reporting OUD, which will also increase HCV RF identification. These recommendations should be adopted as the natural next steps in global HCV elimination.

Table 1. Characteristics of patients prescribed Oral Prescription opioids (OPOs) in MSH, January 1, 2017 — December 31, 2018

Characteristics	OPO	HCV Ab test (%)	HCV Ab+ (%)	p-value [a]	OR_{adj} (CL_{95}) [a]
Total	115,415	11,464 (9.9)	1421 (12.4)		
Age in years, mean ± standard deviation	57.9 ± 16.7	55.6 ± 14.8	58.0 ± 11.6	*NS*	
Sex					
Male	43,276 (37.5)	4,397 (10.2)	778 (17.7)	*p<0.0001*	2.0 (1.7-2.2)
Female	72,113 (62.5)	7,066 (9.8)	643 (9.1)		
Race					
Black	42,840 (38.6)	6,031 (14.1)	838 (13.9)	*p<0.0001*	1.5 (1.3-1.7) [b]
White	60,478 (54.5)	4,448 (7.4)	512 (11.5)		
Other	7,609 (6.9)	811 (10.7)	58 (7.2)		0.8 (0.6-1.1) [b]
Birth Cohort	55,616 (48.0)	6,467 (11.6)	1,041 (16.1)	*p<0.0001*	2.4 (2.1-2.9) [c]
Newly Reported HCV ICD10**	1,296 (1.1)	522 (40.2)	462 (88.5)		
Opioid Use Disorder†	3, 893 (3.4)	803 (20.6)	361 (45)	*p<0.0001*	8.5 (7.2-10.1) [c,d]
Newly Reported HCV ICD10**	417 (0.4)	176 (42.2)	164 (93.1)		
HCV Diagnosis					
Prior ICD10 HCV Dx Reported*	2,059 (1.8)	564 (27.4)	489 (86.7)		
Newly Reported ICD10 HCV Dx**	1,809 (1.6)	724 (2.5)	635 (87.7)		
HCV Testing (Excl. ICD10 Dx)	111,547 (96.6)	10,176 (9.1)	297 (2.9)		
Newly Reported Dx + HCV Testing	**113,356 (98.2)**	**10,900 (9.6)**	**932 (8.6)**		

[a] HCVAb positivity in those tested was compared using multiple logistic regression, adjusting for age, sex, race, BC designation and OUD
[b] Comparisons against white patients as reference category
[c] Comparisons against all excluded patients (i.e. BC vs. non-BC, OUD vs. non-OUD)
[d] BC with OUD OR was 7.0 (5.6-8.7) versus BC non-OUD; non-BC with OUD OR was 9.7 (7.5-12.5) versus non-BC non-OUD
*Any reported diagnosis **before** the beginning of the study period, January 1st, 2017, based on an ICD9/10 code indicating HCV infection
** Any reported diagnosis **during** the study period, between January 1st, 2017 and December 31st, 2018, based on an HCV ICD9/10 code
† Any currently reported diagnosis based on an OUD ICD9/10 code

600 SYNDEMIC OF HCV, PRESCRIPTION OPIOID USE, AND PSYCHIATRIC ILLNESS: A NOVEL FRAMEWORK

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Background: The concept of "syndemic" or synergistic epidemic, was coined by medical anthropologists to describe the clustering of two or more diseases within a population, and their biologic, social, cultural, economic and social interaction. While many definitions have been proposed, three core principles are 1) clustering of two or more conditions in a specific population; 2) their synergism in producing adverse outcomes; and 3) precipitation and propagation by large scale social, cultural, and economic forces. We propose that the confluence of hepatitis C virus (HCV) infection, prescription opioid use (POU), and psychiatric illness (PI) constitutes a syndemic with critical individual and societal consequences. Our objective was to define the epidemiology of SHOPS as a first step towards understanding its impact on individual and population outcomes.

Methods: We used the ERCHIVES cohort to identify persons with each component of SHOPS individually and in all combinations. ERCHIVES includes all HCV diagnosed Veterans from 2001 onwards, who are identified based on a positive HCV antibody test and demographically matched HCV uninfected controls. HCV infection was defined based on a positive HCV antibody and at least one positive HCV RNA. POU was described as prescription of any approved opioid drug for >31 continuous days (to exclude short term use for surgical or dental procedures or after acute trauma). PI was defined by the presence of > 1 inpatient or > 2 outpatient ICD-9/10 codes for any of the following conditions: major or minor depression; bipolar disorder; schizophrenia; post-traumatic stress disorder. Treatment for each condition was determined by prescription of any approved pharmacotherapeutic agent for the condition.

Results: Among 781,271 ERCHIVES participants between 2001-2018, 238,506 had chronic HCV only, 28,226 had POU only, and 99,681 had PI only. Other combinations of these conditions are listed in the figure. Overall, 205,473 had POU and 385,356 had PI. While 51.7% of those with HCV, 23.9% with POU and 84.2% with PI received any treatment for those conditions, only 17.8% of persons with all three syndemic components received treatment for all components.

Conclusion: Co-occurrence of HCV, POU and PI is common, with treatment offered less frequently among those with multiple syndemic components. Next steps are to determine the clinical consequences of SHOPS and impact of treatment singly and in combination.

Year	Person-years	Number of infections	Incidence/100py [95% CI]
2014	10 308	101	0.98 [0.81-1.19]
2015	11 455	94	0.82 [0.67-1.00]
2016	12 100	81	0.67 [0.54-0.83]
2017	12 003	54	0.45 [0.35-0.59]
Overall	45 866	330	0.72 [0.65-0.80]

Man-Kendall trend test: p=0.04

601 THE PERFECT ICE STORM: THE MIX OF METH AND HIV SPREADS HEPATITIS C IN THAI MSM

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[1]*Thai Red Cross AIDS Research Center, Bangkok, Thailand*

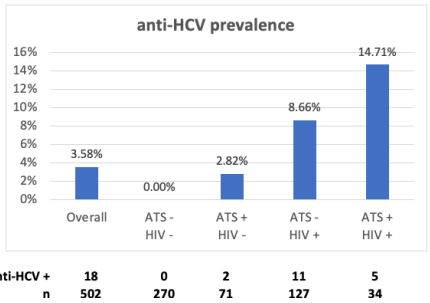
Background: Recent oubreaks of hepatitis C infection (HCV) have been reported among men who have sex with men (MSM) in multiple countries. We report on factors associated with baseline HCV prevalence in a study of the use of amphetamine-type stimulants (ATS) in Bangkok, Thailand.

Methods: MSM and transgender women (TW) who presented for routine HIV testing at the Thai Red Cross Anonymous Clinic (TRCAC) were recruited into a longitudinal study of ATS use. Recruitment was stratified to over-sample for HIV infection and ATS use within the previous 6 months. Baseline assessment included HIV serology, anti-HCV antibody, sexually transmitted infection (STI) screen (syphilis, gonorrhea, chlamydia), and a computer-assisted self interview covering sexual and substance use risk behavior.

Results: Enrollment included 470 MSM (93.6%) and 32 TW (6.4%), of whom 161 (32%) were HIV-positive. Median age was 28 (IQR 24-35). Most (69%) had a bachelor degree or higher, and 95% were employed or in school. 94% reported ever having anal sex, 21% had group sex, and 54% of group sex events involved illicit drug use. Consistent condom use was only 38% for receptive and 41% for insertive anal sex. ATS use was reported by 131, most frequently crystal methamphetamine (METH) (n=122) followed by ecstasy (n=43) and oral amphetamines (n=18). HCV prevalence overall was 3.6%, and was associated with ATS use, HIV infection, or both (Figure, P<0.001). Over one-third (n=45) of METH users reported injecting the drug intravenously in the previous 6 months. However, only a minority (28%) of those with HCV reported injection drug use. STI were common: 16% had syphilis, 16% chlamydia, and 8% gonorrhea. On multivariable analysis, factors independently associated with HCV were HIV infection (OR 16.15; 95% CI 3.3-78.99), being mainly the receptive partner in anal sex (OR 4.3, 1.1-16.71), ever used METH (OR 9.13, 3.3-78.99), ever used oral amphetamine (OR 9.48, 1.63-55.03), and any STI (OR 5.98, 1.54-23.2).

Conclusion: HCV infection is spreading rapidly among MSM with HIV in Bangkok, and is closely associated with the use of METH. Injection use of METH is also increasing rapidly in Thai MSM. However, most cases of HCV appear to be transmitted by anal sex, possibly potentiated by the presence of STIs and rough or prolonged sex in the context of illicit drug use. Harm reduction, and HCV treatment with direct-acting antivirals, are needed to address this newly emerging epidemic.

Figure: anti-HCV prevalence by ATS use and HIV status (p<0.001)



602 HEPATITIS C VIRUS INFECTION AND COINFECTION WITH HIV AMONG PWID IN 10 US CITIES

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Background: Understanding the burden of acute and chronic hepatitis C virus (HCV) infection and HIV/HCV co-infection among persons who inject drugs (PWID) is important for informing HIV and HCV elimination efforts. We measured HCV infection and HIV/HCV co-infection among PWID in 10 U.S. cities.

Methods: In 2018 National HIV Behavioral Surveillance, PWID were recruited using respondent-driven sampling and offered a behavioral survey, HIV testing, and HCV antibody and RNA testing in Chicago, Dallas, Houston, Los Angeles,

Miami, New York City, Philadelphia, San Francisco, San Juan, and Washington DC. We examined prevalence of acute (anti-HCV non-reactive/RNA detected) and chronic (anti-HCV reactive/RNA detected) HCV infection and HIV/HCV co-infection. We obtained adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) to assess characteristics associated with current HCV infection (RNA detected vs. not detected) and HIV/HCV co-infection (vs. no HIV/HCV co-infection).

Results: Overall, 62.4% (3239/5,190) had a reactive anti-HCV result, 44.2% (1678/3795) had HCV RNA detected, and 4.0% (153/3,779) had HIV/HCV co-infection. Of those with both antibody and RNA test results, 3.9% (149/3795) had acute and 40.3% (1529/3795) had chronic HCV infection. Acute infection was highest among PWID who were male (4.3%), ages 25-34 (4.2%), black (4.5%), HIV-positive (4.6%), injecting ≤5 years (4.3%), injected >1 time/day (4.2%), injected heroin most often (4.3%), and were from Miami (17.6%) or Philadelphia (5.3%). Current HCV infection was higher among PWID who were male (aPR 1.2, 95% CI 1.1-1.3), white (aPR 1.3, 95% CI 1.1-1.5), injecting >5 years (aPR 1.5, 95% CI 1.2-1.8), injected >1 time/day (aPR 1.5, 95% CI 1.3-1.7), and shared syringes (aPR 1.2, 95% CI 1.1-1.3) or injection equipment (aPR 1.3, 95% CI 1.1-1.4) in the past year. HIV/HCV co-infection was higher among participants who were transgender (aPR 6.3, 95% CI 2.8-14.5), injecting >5 years (aPR 2.1, 95% CI 1.3-3.1), injected speedball (heroin and cocaine injected together) (aPR 2.1, 95% CI 1.4-3.0) or stimulants (aPR 1.8, 95% CI 1.1-2.9) most often (vs. heroin), and were from Miami (aPR 2.3, 95% CI 1.3-3.9).

Conclusion: Acute and chronic HCV prevalence was high among a sample of U.S. urban PWID. Nearly one in two PWID had current HCV infection and one in 25 had HIV/HCV co-infection in our sample. HCV and HIV elimination efforts should focus on providing treatment and reducing risk behaviors among PWID to prevent further transmission.

603 HEPATITIS B VIRUS VACCINATION IN A CURRENT-ERA HIV CLINIC

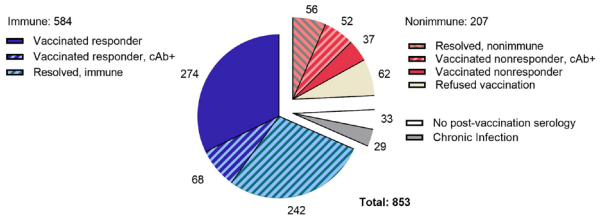
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Background: Hepatitis B virus (HBV) infections remain a global health issue with complications including liver cirrhosis and hepatocellular carcinoma. Individuals co-infected with Human Immunodeficiency Virus (HIV) and HBV have increased liver-related morbidity and mortality compared to those with HBV mono-infection. Vaccination is a potent intervention to prevent HBV infection, but certain critical populations including people living with HIV are less likely to achieve seroprotection after vaccination. Seroprotection (antibody to hepatitis B surface antigen titer ≥10 IU/mL) was historically poor, with trial rates ranging from 34 to 88% and improving with immunologic reconstitution and viral suppression. We hypothesized that the seroprotection rates (SPR) in a clinic population of Veterans would reflect the improving immunologic status of the cohort.

Methods: We reviewed the HBV serologies and vaccination records of Veterans with HIV engaged in care at the Baltimore Veterans Affairs Infectious Disease Clinic over the past 20 years to assess the ultimate seroprotection status of the cohort.

Results: The overall seroprotection status is in line with previous data, with 79% of clinic patients showing serologic response to vaccination. Of the patients who remain nonimmune, 43% (89 of 207) have been vaccinated without seroprotection. Importantly, over half the clinic population is HBV core antibody positive, reinforcing the overlapping risk factors for HIV and HBV acquisition. In the two decades surveyed, the percentage of virally suppressed patients improved from 22.5% of 507 in 2000 to 50.7% of 554 in 2009 and to 86.6% of 261 in 2019. The median CD4 count improved from 394 (IQR 212-593) in 2000 to 532 (IQR 342-772) in 2010, and to 630 (IQR 417-833) in 2019. Despite the improved immunologic status of this cohort, the SPR after 2009 showed no significant improvement compared to the prior decade: 56.7% compared to 57.0%. The apparently static response rates may reflect the aging of the cohort (median age increased from 50 to 57) and declining renal function (from 39% of patients with glomerular filtration rate >=90 to 16%). Response rates in the second decade may further reflect intrinsic immunologic anergy seen in re-vaccination attempts of prior non-responders.

Conclusion: Despite lower than anticipated SPR, consistent vaccination standards have contributed to seroprotection for a majority of the cohort, and revaccination of nonresponders with CpG-adjuvanted HBV vaccine is ongoing.



604 IMMUNIZATION RESPONSE IN INFANTS BORN TO HBsAg+ HBeAg+ MOTHERS RECEIVING TDF

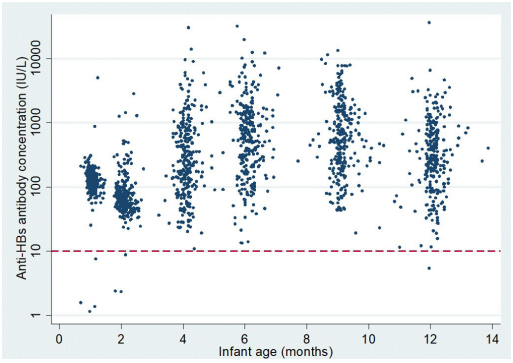
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Background: It is unknown whether maternal antiviral prophylaxis could affect the response to vaccine in infants receiving hepatitis B (HB) immune globulin (HBIg) born to mothers infected with HB virus (HBV). We analyzed the infant immunization response in a randomized clinical trial in Thailand (iTAP-1, NCT01745822).

Methods: iTAP-1 was an RCT assessing TDF prophylaxis (vs placebo) in HBsAg+ HBeAg+ women from 28 weeks' pregnancy to 2 months postpartum. All infants received HBIg and HB vaccine (monovalent at birth and 1 month, as part of a multivalent vaccine at 2, 4 and 6 months). Antibody titers were measured using the Monolisa Anti-HBs Plus kit Blood at visits scheduled at 1, 2, 4, 6, 9 and 12 months. All infants were included in this analysis, except 3 (placebo group) confirmed HBV infected. Comparisons were made using the Wilcoxon rank sum test.

Results: 315 infants (162 TDF, 153 placebo) participated in the analysis: 166 male and 149 female. At birth, median (IQR) weight was 3.0 kg (2.8-3.4) and length 50.3 cm (49.0-52.0). Median (95% CI) anti-HBs geometric concentrations at 1, 2, 4, 6, 9 and 12 month visits were: 123 IU/L (115-132), 71 (66-77), 268 (228-315), 556 (477-648), 595 (512-691), 294 (253-342), respectively (see Figure: anti-HBs geometric concentrations according to actual age at assessment). All infants had anti-HBs titers > 10 IU/L at all visits, except 4 of 311 (1.3%) at 1 month, 3 of 303 (1.0%) at 2 months, and 1 of 274 at 12 months. At 6 months and thereafter, there were no significant differences in anti-HBs titers between treatment arm (TDF versus placebo), according to maternal bodyweight before delivery, gestational age at delivery, birth weight, sex, infant length, or durations from birth to vaccine birth dose or to HBIg administration.

Conclusion: Maternal antiviral prophylaxis had no effect on the infant response. HBIg masked the response until 2 months, then titers increased until 9 months (3 months after last vaccine administration). Immunization was effective in >99% of the infants aged 4 to 12 months, a higher percentage than in most 'real world' cohorts where the birth dose is followed by 2 or 3 doses. The difference may be related to the different vaccine schedules or implementation issues in real world.



605 EFFECTIVENESS OF THE NOVEL ADJUVANTED HEPATITIS B VACCINE AMONG HIV AND HCV PATIENTS

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Background: People living with HIV or chronic hepatitis C virus (HCV) have diminished immune responses to hepatitis B virus (HBV) vaccination. The

current HBV vaccine has a positive response rate upwards of 85% in the general population, but that same vaccine series only provides immunity for 20-70% of people living with HIV and 40-60% for the HCV population, emphasizing the need for advancement. A novel, adjuvanted HBV vaccine, HepB-CpG, demonstrated improved immune response (>90%) in non-HIV and non-HCV cohorts. Yet, the effectiveness in HIV and HCV patients in unknown. This study evaluated the immune response to HepB-CpG among HIV and HCV patients at an outpatient virology clinic.

Methods: We evaluated HIV and HCV patients who received at least one dose of HepB-CpG beginning October 1, 2018. HBV vaccination and serology were performed in conjunction with routine clinical appointments. An HBV surface antibody ≥10 mIU/ml was considered a positive immune response. Population characteristics and overall effectiveness were evaluated using descriptive statistics and represented as n(%) or median(IQR) as appropriate.

Results: Among 130 individuals, 41 (32%) were living with HIV and 89 (68%) with HCV. Most were white (110, 85%) and non-diabetic (112, 86%). The median age was 53 (38-61). Viral load was <20 copies/mL in 26 (63%) HIV patients at the time of first vaccination, and the majority had CD4 counts greater than 500. Two-thirds of HIV patients had received at least one full HBV vaccine series previously, whereas the same was true for only one-third of HCV patients. Of the 11 HIV patients tested for immunity after series completion, 82% had a positive HBV antibody. Interestingly, an additional 6 patients became immune after just one dose, bringing the total positive response rate to 88%. HCV patients responded similarly, with 78% immune after completing the series and an additional 3 patients immune after one dose. No patients reported adverse events.

Conclusion: Our analysis shows an overall immune response to HepB-CpG of 84%, which is considerably higher than historical data using the non-adjuvanted vaccine. As part of a robust immunization program to protect HIV and HCV patients, HepB-CpG should be considered as an assuring alternative to the traditional HBV vaccination series.

	HIV (n=41)	HCV (n=89)	TOTAL (n=130)
MALE	24 (59)	64 (72)	88 (68)
WHITE	23 (56)	87 (98)	110 (85)
AGE	50 [46-60]	54 [37-60]	53 [38-61]
WEIGHT, kg	81 [71-96]	85 [74-100]	83 [74-100]
DIABETIC	5 (12)	13 (15)	18 (14)
SMOKER	7 (17)	48 (54)	55 (42)
UNDETECTED HIV VIRAL LOAD	26 (63)	-	26 (63)
ABSOLUTE CD4 COUNT	581 [376-798]	-	581 [376-798]
CD4%	32 [21-39]		32 [21-39]
TESTED FOR IMMUNITY	17 (42)	26 (29)	43 (33)
IMMUNE	15 (88)	21 (81)	36 (84)

606 TIMING OF ANTI-HBs ANTIBODIES DECAY IN VACCINATED PLWH/A: A LONG-LASTING RESPONSE

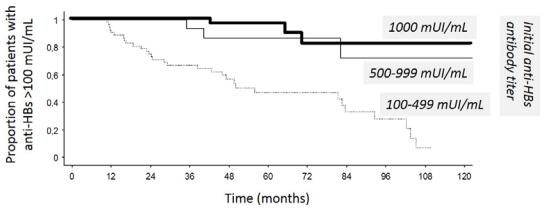
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Background: It is widely recommended to immunize people living with HIV/AIDS (PLWH/A) against hepatitis B virus. A regular monitoring of anti-HBs antibody titers is generally performed during the following year to assess the need for vaccine boost, but the timing of the decay of these antibodies is poorly known. We analyzed the waning over time of anti-HBV seroprotection in PLWH/A in our center.

Methods: We included all PLWH/A with at least 2 measurements of anti-HBs antibodies between the years 2001 and 2018; subjects positive for anti-HBc antibody or HBs antigen were excluded. We analysed the variation for each pair of successive measurements, excluding the pairs where the first measure was under 10 mUI/mL, or if an HBV vaccination was realized between the two dates, or if the rise between 2 dates was over 100 mUI/mL (as this may reflect an uncharted vaccination).

Results: We analyzed 887 couples of successive titrations in 372 patients. The delay between the 2 measurements was <10 months for 23.9%, 10-14 months for 43.6%, between 15-27 months for 18.3%, and >27 months for 14.2%. The mean and the median decrease of the anti-HBs titer were 2.6±10 mUI/ml and 0.29 [interquartiles 25-75: -0.02; 1.9] mUI/ml per month, respectively. This decay represents 0.7±3% (mean) or 0.6% (median) [interquartiles 25-75: 0.1; 1.8] per month of the initial titer. There was no statistically significant association between the slope of antibody decay and the nadir of CD4 T cells, the age at the first antibody titer, gender, or CMV serostatus. The absolute value of monthly decay was positively correlated with the initial antibody titer (rho=0.198, p<0.0001), but not the relative value. In a Kaplan-Meier analysis of the 130 patients with anti-HBs titer above 100 mUI/mL (median of follow-up: 43 months), the median time to a titer under 100 mUI/mL was 102 months; in particular, it was 56 months for those with an initial ani-HBs antibody titer between 100 and 500 mUI/mL, and was not reached for those over 500 (figure).

Conclusion: The rate of decrease of the anti-HBs antibody titer in PLWH/A suggests that measurements do not need to be performed more than every 3 to 4 years, and even longer periods for those over 500 mUI/mL.



607 HIGH INCIDENCE OF HBV INFECTION IN HIV-COINFECTED PATIENTS ACCESSING ART CARE

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Background: Hepatitis B virus (HBV), Human Immunodeficiency virus (HIV) and Tuberculosis (TB) are common infections in South Africa. HBV vaccination has been included in the country's childhood immunization schedule since 1995; however, less is known of the current burden of HBV in adults. We utilized the opportunity of care provision or HIV-TB co-infected patients to determine the magnitude of, and the relationship between HIV and HBV, and identify risk factors for HBV infection in HIV infected patients with and without TB in urban and rural KwaZulu-Natal, South Africa.

Methods: This retrospective cohort analysis was undertaken in 2018. In-care HIV infected patients were included in the analysis. Results from clinical records were analysed to determine the prevalence, incidence, persistence and factors associated with HBV infection in HIV infected patients with or without TB co-infection.

Results: A total of 4292 HIV infected patients with a mean age of 35 (SD: 8.8 years) were included. The baseline prevalence of HBV was 8.5% (363/4292) [95% confidence interval (CI): 7.7 to 9.3] and 9.4% (95%CI: 8.6% to 10.3 %) at end of follow-up. The HBV incidence rate was 2.1/100 person-years (p-y). Being male was associated with a two-fold higher risk (HR 2.11; 95% CI: 1.14 -3.92) of incident HBV infection while severe immunosuppression was associated with a two-fold higher risk of persistent infection (adjusted risk ratio 2.54; 95% CI 1.06-6.14; p=0.004). Active TB at enrolment was associated with a two-fold higher risk of incident HBV infection (aHR 2.38; 95% CI: 0.77 to 7.35).

Conclusion: The provision of HIV care and treatment in high HBV burden settings provide a missed opportunity for HBV screening, immunization and care provision.

608 CHARACTERIZING HBV INFECTION AMONG PERSONS LIVING WITH HIV IN CARE IN URBAN SENEGAL

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[1]University of Bern, Bern, Switzerland, [2]CHU de Fann, Dakar, Senegal, [3]Hopital Principal de Dakar, Dakar, Senegal, [4]University Hospital of Bern, Bern, Switzerland

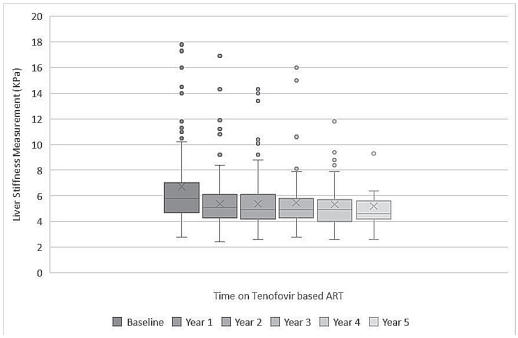
Background: Chronic hepatitis B virus (HBV) infection affects 10% of the general population and is the leading cause of liver cirrhosis and cancer in West Africa. Despite current recommendations, HBV infection is generally not tested for in clinical routine in the region. We investigated the HBV infection status of HIV-infected individuals in care at an outpatient clinic in Dakar, Senegal, and determined the proportion of HIV/HBV-coinfected individuals with viral replication despite antiretroviral therapy (ART).

Methods: We tested all HIV-infected individuals presenting for routine clinical care between March and July 2019 for the presence of HBsAg using a one-step lateral flow assay rapid test (NovaTest®). All individuals with a positive result underwent an HIV viral load (VL) and HBV VL (COBAS/ TaqMan® HBV/HIV Test) measurement. Liver stiffness measurements (LSM) were conducted by a single investigator, using transient elastography. We compared the main characteristics between individuals previously tested for HBV and the others using Chi-square and Mann-Whitney tests. We determined the proportion of

HBsAg-positive individuals who had current HBV replication (>20 IU/ml) on ART and/or who were on an inadequate ART regimen.
Results: Of 1.219 HIV-infected patients in active follow-up at Fann University Hospital, 873 had never been tested for HBsAg before our intervention. Their median time on ART was 9 years, and when compared with individuals previously tested, they were more likely to be female (67.7% vs. 55.5%: p<0.001) and to have a CD4 >350 cells/µL at enrollment (37.6% vs 29.5%, p=0.01). Of 449 patients tested during our intervention, 50 (11.1%) were HBsAg-positive, of whom 24 (50.0%) were female. Their median CD4 cell count at ART initiation was 153 cells/µL (interquartile range 57-234) and 2 (5.7%) had significant liver fibrosis (LSM >7 kPa). Seven (14.0%) individuals had a detectable HBV VL, of whom five were HIV suppressed. Four individuals were on ART including lamivudine and zidovudine as a backbone, and had to be switched to a TDF-containing regimen.
Conclusion: In our referral HIV clinic, the majority of patients on ART had never been tested for HBV. 15% of HIV/HBV-coinfected individuals had a positive HBV VL despite HIV suppression, and 10% were not receiving a TDF-containing regimen. Considering the high risk of liver-related complication in individuals with HBV replication, HBV testing should be performed routinely during HIV clinical care.

609 LIVER FIBROSIS CHANGES OVER 3 YEARS OF TENOFOVIR-BASED ART IN HIV-HBV COINFECTION

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Background: Although tenofovir-based therapy can potently reduce HBV DNA and can reverse hepatic fibrosis in HBV monoinfection, its long-term impact on clinical outcomes in HIV-HBV coinfection is not well-established and some data suggest hepatic inflammation and fibrosis persists. In Zambian HIV-HBV coinfected adults treated with antiretroviral therapy (ART), we analyzed normalization of ALT and changes in liver fibrosis, based on transient elastography (TE).
Methods: We analyzed data from an active cohort of Zambian adults (18+ years) who were HIV-positive, hepatitis B surface antigen-positive, and started tenofovir-based ART. At ART start and yearly during therapy, we measured CD4, HBV DNA, ALT, and liver stiffness (LSM; based on TE). LSM were categorized as no-minimal fibrosis (<7.9 kPa; F0-1), significant fibrosis (7.9-9.5; F2-3), and cirrhosis (>9.5; F4). HBV viral suppression (VS) was defined as ≤20 IU/ml and ALT elevation was >19 U/L for women and >30 for men. We included in analysis any cohort participants with LSM at ART start and ≥1 follow-up measure. We described on-therapy HBV VS, normalization of ALT among those with baseline elevation, and regression and progression of fibrosis and cirrhosis.
Results: Among 358 HIV-HBV coinfected patients enrolled, 234 were analyzed (median age, 34 years; 60.8% men). At ART start, median CD4 count was 198 cells/mm$_3$, median HBV DNA was 5400 IU/ml, 81 of 183 tested (44.3%) were HBeAg-positive, 102 (47.9%) had ALT elevation, 16 (6.8%) had significant hepatic fibrosis, and 23 (9.8%) had cirrhosis. Median follow-up was 2.6 years (interquartile range, 1.7-3.8). HBV DNA suppression at 1, 2, and 3-5 years was 62.7%, 80.3%, and 84.5%. Among the 102 with ALT elevation at ART start, 50 (49.5%) had persistent elevation at their last assessment. During ART, 13 of 16 (81.2%) with significant fibrosis and 18 of 23 (78.3%) with cirrhosis experienced regression to a lower category. Five patients progressed from no-minimal to significant fibrosis (n=4) or cirrhosis (n=1) and 1 progressed from significant fibrosis to cirrhosis. The majority of patients with disease progression had evidence of both HIV and HBV VS.
Conclusion: Regression of liver fibrosis and cirrhosis was common during tenofovir-based ART. Persistent ALT elevation was seen in ~20% of HIV-HBV coinfected patients, likely due to non-HIV, non-HBV-related causes such as alcohol abuse.



610 LONG-ACTING TENOFOVIR AND NITAZOXANIDE FORMULATIONS SUPPRESS HBV REPLICATION

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Background: To eliminate HBV infectious complete suppression of progeny virus coordinate with the elimination of infected cells must be achieved. These events can be facilitated by enhancing innate and adaptive immune responses given with antiviral therapy. We offer a new therapeutic prospective by increasing the potency of nitazoxanide (NTZ), a broad-spectrum antiviral and immune stimulating agent and tenofovir (TFV), a nucleoside reverse transcriptase inhibitor. This drug combination was transformed into hydrophobic prodrug nanocrystals, then stabilized into aqueous nanosuspensions. The modifications led to extended apparent drug half-lives, increased drug potency and improved distribution to liver cell viral compartments.
Methods: NTZ and TFV prodrugs (M1NTZ and M1TAF) were synthesized and nanoformulated creating NM1NTZ and NM1TAF. Cellular drug uptake and retention was determined in human monocyte-derived macrophages (MDM). The HBV-producing human hepatocellular carcinoma HepG2.2.15 cell and humanized liver TK-NOG mice evaluated antiviral activity. HBV infected mice received a single 75 mg/kg intramuscular injection of the drugs. HBV DNA, cccDNA and HBe/sAg were monitored for 48 h and for 10 weeks in cells and animals, respectively.
Results: NM1NTZ and NM1TAF had average particle sizes of 250-350 nm, polydispersity index of <0.2 and drug loading capacity of > 70%. Both formulations were taken up by MDM with sustained drug levels for 30 days; whereas native drugs were eliminated in one day. Suppression of HBV DNA release by (NM1TAF by 50%) and cccDNA pools (NM1NTZ by 88% and NM1TAF by 60%) were recorded. The combination long acting prodrug therapy reduced HBV DNA in plasma of humanized mice to undetectable levels in 2/4 animals tested at four weeks with readily detected human cells (Fig). The remaining two animals showed > log decrease in plasma viral load at equivalent times. Animals were monitored for 10 weeks to measure viral rebound.
Conclusion: Long-acting TFV and NTZ prodrugs sustained antiviral activity in humanized mice for a month after a single dose. These data sets support the potential of monthly NM1TAF and NM1NTZ dosing for treatment of HBV infections.

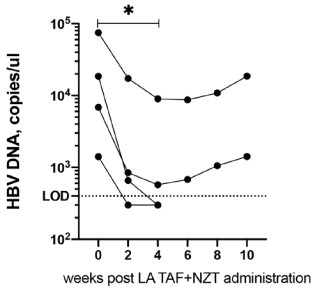


Figure. Evaluation of NM1TAF and NM1NTZ combination regimen in HBV infected humanized liver TK-NOG mice. Animals were infected with 10^6 GE HBV and tested 2-months post infection; a single intramuscular injection of the combination therapy was administered at 75 mg/kg of native drug equivalents for each prodrug formulation. Reduction of HBV DNA in two animals below limit of detection (LOD) was found. These animals were euthanized to measure liver drug concentrations. * P values obtained by t-test.

611 A RHESUS MACAQUE MODEL OF CHRONIC HBV INFECTION FOR CURE RESEARCH

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Background: Chronic HBV infection (CHB) is a major global health concern, affecting 247 million individuals worldwide and causing 887,000 deaths annually. CHB induces various degrees of liver damage and is strongly associated with the development of liver cirrhosis and hepatocellular carcinoma. Chimpanzees were the gold standard for primate HBV research, but are no longer available. Indeed, one of the major obstacles to the discovery of an HBV cure is the lack of a physiologically-relevant primate model. Based on our previous work showing that expression of the HBV receptor, human Na+-taurocholate co-transporting polypeptide (hNTCP), on rhesus macaque (RM) hepatocytes facilitates in vitro and in vivo HBV infection, we hypothesized that RM can be chronically infected with HBV.

Methods: We treated three infant RM (<1-year-old) with an immunosuppression regimen consisting of daily tacrolimus and semi-monthly belatacept injections. Following initiation of this immunosuppression, we intravenously administered high-dose adenovirus expressing hNTCP. Seven days later we challenged all three RM intravenously with HBV (1 x 109 virions). Immunosuppression was tapered after 18 weeks of HBV infection. We have followed HBV infection in the blood and liver in these RM by qPCR, ELISA, and immunofluorescent microscopy over the course of 42 weeks.

Results: We found persistently high levels of HBV plasma viremia (>1 x 105 copies/ml) accompanied by high levels of HBV surface (HBsAg) and envelope (HBeAg) antigens in blood for more than six months, the clinical definition of chronic HBV infection. In addition, high frequencies of HBV core antigen (HBcAg)- and HBsAg-positive hepatocytes were detected longitudinally in liver biopsies. Following immunosuppression tapering, two of the three animals maintained ongoing viral replication, indicating HBV immunotolerance. The set point HBV loads in these two animals correlated with the level of hNTCP expression in the liver by qPCR, indicating that hepatocyte target availability is the restricting factor in this model.

Conclusion: Our data indicate that RM can be chronically infected with HBV and represent a promising model for the testing of emerging HBV curative therapies.

612 CYTOKINE PROFILES IN ASYMPTOMATIC ACUTE HEPATITIS B

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Background: Hepatitis B Virus (HBV) co-infection occurs in 5-20% of HIV-infected individuals globally. Prior studies found elevated proinflammatory cytokines are associated with spontaneous control (SC) of symptomatic HBV, but the majority of acute HBV infections are asymptomatic. A better understanding of cytokine profiles in early asymptomatic HBV will provide insight into immune responses important for natural resolution of infection, and may suggest immune targets for curative HBV therapies. Using men enrolled in the Multicenter AIDS Cohort Study (MACS) with asymptomatic incident HBV, we compared cytokine profiles between men who either had SC or developed chronic hepatitis B (CHB).

Methods: Incident HBV occurred in 186 MACS men between 1985-2006 with available plasma samples. SC or CHB was determined by serological testing at 9-12 months after incident infection. Plasma samples at visits immediately before and after incident HBV (visits 1 and 2, respectively) were tested for 24 cytokines by electrochemiluminescence assay (Mesoscale Discovery, Rockville, MD), according to manufacturer's instructions. Non-parametric rank sum analyses were used to compare cytokine concentrations and intrasubject changes (visit 2/ visit 1).

Results: Of 186 men, 18 were black (9.7%), 68 (37%) were HIV-infected (+)(8 on anti-HBV treatment at visit 1), and median age was 32 years (IQR=26-39). Twenty-four (12.9%, 14 HIV+) progressed to CHB, and 162 (87.1%, 54 HIV+) had SC. HIV infection was associated with greater odds of CHB (OR 2.8, P=0.02). At visit 1, HIV infection was associated with increased cytokine concentrations, including IL10, TNF, IP10, MIP1b, and IL18.

Median time from incident HBV to visit 2 was 13.2 weeks. Overall, increased odds of CHB was significantly associated with elevated visit 2 levels of (OR per 10-fold increase in concentration): IL10 (OR 6.7, P<0.001), MIP1a (OR 25, P<0.001), IP10 (OR 8.3, P=0.001), MIP1b (OR 3.8, P=0.04), and IL18 (OR 7.7, P=0.04). In HIV-uninfected individuals, intrasubject increases (visit 2 fold-change over visit 1) in IL10, IP10, IL18, IL37, and MIP1a were significantly higher in those who developed CHB. In HIV-infected individuals, intrasubject increases in IL18 and TNF were higher in those who developed CHB (see Table).

Conclusion: In contrast to previous reports, elevated cytokine profiles are not associated with SC in asymptomatic incident HBV, suggesting they are not major determinants of HBV SC.

Intrasubject Changes (visit 2/ visit 1) in Circulating Cytokines during Incident HBV Infection

	HIV-uninfected			HIV-infected		
Analyte	SC	CHB	p	SC	CHB	p
IL-8	0.99 (0.63-1.70)	1.59 (1.09-2.30)	0.07	1.06 (0.59-1.30)	1.22 (0.98-1.69)	0.1
IL-10	**1.00 (1.00-1.26)**	**9.49 (1.28-12.77)**	**0.007**	1.06 (1.00-1.34)	1.88 (1.04-2.94)	0.06
IL-18	**1.07 (0.91-1.31)**	**2.85 (1.26-3.07)**	**0.003**	**1.05 (0.91-1.18)**	**1.19 (1.06-1.79)**	**0.049**
IL-37	**1.00 (0.95-1.02)**	**1.14 (1.00-1.49)**	**0.03**	1.00 (0.94-1.00)	1.00 (0.88-1.00)	0.49
TNF	1.06 (0.91-1.45)	1.50 (1.24-1.82)	0.06	**1.12 (0.78-1.25)**	**1.23 (1.11-2.25)**	**0.03**
IP10	**1.12 (0.86-1.38)**	**4.71 (1.10-7.96)**	**0.03**	1.05 (0.60-1.48)	1.22 (0.90-1.73)	0.27
MIP1α	**1.08 (0.87-1.33)**	**2.45 (1.35-3.20)**	**0.001**	1.06 (0.80-1.21)	1.14 (1.01-2.02)	0.07
MIP1β	1.04 (0.74-1.89)	1.57 (1.01-3.12)	0.1	1.00 (0.80-1.33)	1.34 (0.99-1.96)	0.09

SC-spontaneous control: CHB-chronic hepatitis B
Data reported as Median (IQR). Bold indicates P<0.05
Additional cytokine tested but not significant(data not shown): Eotaxin, MCP1, MCP4, MIP1β, CCL17, IFNγ, IFNα, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, IL-13, IL-15, LTα

613 HBV-RELATED INFLAMMATION IS LINKED TO THE LEVEL OF GENETICALLY INTACT HIV PROVIRUSES

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Background: Hepatitis B virus (HBV) coinfection increases overall and liver-related mortality in people living with HIV, even with the availability of HBV-active ART. HIV can persist in individuals in both defective and intact forms and both can contribute to persistent inflammation. We assessed the relationship between HIV proviral genomes and markers of inflammation in people living with HIV-HBV coinfection.

Methods: HIV-HBV coinfected and HIV monoinfected participants, naïve to ART, were recruited in Bangkok, Thailand as part of a prospective observational cohort study. HIV subtype AE proviruses were sequenced from peripheral blood (PB) CD4+ T-cells using full-length individual proviral sequencing, covering 92% of the genome. Circulating markers of inflammation and microbial translocation were quantified by ELISA and bead arrays. Spearmans rank correlations tests were performed to determine associations.

Results: 1008 and 222 HIV proviruses were sequenced from 18 HIV-HBV coinfected and 6 HIV monoinfected individuals respectively. The coinfected cohort had a significantly higher HIV viremia (p=0.03) and lower CD4+ T-cell count (p=0.007) than the monoinfected. A strong trend towards more intact proviruses (22-1000 copies/10^6 cells, p=0.055) was observed in the coinfected individuals. For the HIV-HBV cohort, the levels of soluble CD14 (sCD14), LPS and CXCL10 in the blood, markers of immune activation and/or inflammation, were significantly correlated with the frequency of intact HIV proviruses (p<0.01, p=0.04, p<0.01 respectively). sCD14 and CXCL10 were also correlated with the genetic diversity of the intact proviruses (p=0.03, for both). AST levels in blood, a marker of liver inflammation, and HIV DNA levels in the liver were also significantly correlated with the frequency of intact HIV proviruses in PB CD4+ T-cells (p=0.04, p=0.05 respectively). However, intact proviruses alone did not correlate with the number of PB CD4+ T-cells (p=0.2) but the inclusion of defective forms revealed a significant correlation with PB CD4+ T-cells (p=0.03).

Conclusion: During HIV-HBV coinfection, the levels of PB CD4+ T-cells may be influenced by the amount of intact and defective proviruses they contain. However, the frequency and genetic diversity of the intact proviruses within blood-derived cells from the HIV-HBV coinfected individuals appears to be linked to inflammation and liver damage.

614 LIVER DISEASE PROGRESSION IN HIV-HBV COINFECTION ON ART IS ASSOCIATED WITH HMGB1

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Background: In HIV-HBV co-infection, liver disease progression is accelerated, and liver related mortality increased, including in those on antiretroviral therapy (ART). Systemic inflammation and gut permeability are increased in HIV infection and may drive accelerated liver disease. We investigated liver disease progression in HIV-HBV co-infected individuals on ART, and its relationship with inflammatory cytokines and products of microbial translocation.

Methods: HIV-HBV co-infected adults on ART were recruited in Australia and Thailand and followed prospectively for 3 years with 6 monthly visits for clinical assessment and blood collection. Liver fibrosis was measured at baseline and yearly using transient elastography (Fibroscan®, Echosens) in kilopascals (kPa). Liver disease progression was defined as (1) an increase in Metavir grade (defined by kPa grade equivalent ranges defined in HIV-HBV infected individuals) or (2) at least 20% or a 2kPa increase in kPa with at least one value > 5.9kPa. Comparisons were made using Wilcoxon rank-sum test for continuous data and chi-square test or Fisher's exact test for categorical data at baseline and later timepoints.

Results: 67 participants (57 male) were enrolled. The mean age was 51 years and median time since HIV diagnosis was 14.8 (interquartile range (IQR) 11.4-18.7) years. Median nadir CD4+ T cell count was 25 (IQR 35-225) cells/mL. 21/69 were HBeAg+. 11 participants were classified as progressors by fibrosis grade and 7 by kPa. 6 were progressors by both definitions.

Progressors had similar baseline characteristics to non-progressors but progressors had significantly higher levels of high mobility group box 1 protein (HGMB1), a marker of cell death, using either definition (definition 1 (p=0.011) and 2 (p=0.041)). Nadir CD4 count was significantly lower in progressors than non-progressors when defined by kPa change (27 and 145 cells/mL respectively; p=0.018). No significant differences were seen between the two groups in other parameters including lipopolysaccharide, soluble CD14 or inflammatory markers including CXCL-10, monocyte chemotactic protein-1 or tumour necrosis factor-a.

Conclusion: In the setting of ART, 20% of HIV-HBV co-infected individuals have progressive liver fibrosis. Liver disease progression was associated with higher HMGB1 and lower nadir CD4 count. Interventions to prevent liver disease progression on ART require further investigation.

615 HEPATITIS B VIRUS MUTATIONS ASSOCIATED WITH HEPATOCELLULAR CARCINOMA IN BOTSWANA

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Background: Hepatitis B virus (HBV) resulted in 887,000 deaths in 2015 due to hepatocellular carcinoma (HCC) and cirrhosis. In sub-Saharan Africa, HCC has been reported in younger individuals, compared to other regions. Mutations within the HBV core, precore, and X regions may lead to rapid progression to HCC. Our aim was to identify HBV mutations associated with progression to HCC in HIV/HBV co-infected adults in Botswana.

Methods: This was a retrospective, cross-sectional study utilizing archived plasma samples from a study conducted at the Botswana Harvard AIDS Institute Partnership (2009-2012). A total of 100 samples from HIV/HBV infected adults were available of which 28 were hepatitis B surface antigen (HBsAg) positive, while 72 were HBsAg negative but HBV DNA positive (occult HBV infections). HBV regions were amplified using a semi-nested polymerase chain reaction. Sequences from Botswana were then compared to GenBank references to identify clinically relevant mutations.

Results: Of the 100 samples, 60 could be amplified and sequenced. Thirty six (60%) samples belonged to genotype D, while 24 (40%) were genotype A. Fifteen samples (25.0%) had 29 mutations which have been previously associated with HCC. Eleven HCC-associated mutations were detected in genotype A, while 18 HCC mutations were detected in genotype D samples. W28* mutation was seen in more than one participant and also occurred as a dual mutation. E64D and L65V were the most common mutations, occuring in 3 participants each. Other common mutations were I127L which also was found in 3 participants followed by K130M and V131I which were seen found in 2 participants. K130M and V131I appeared as a dual mutation.

Conclusion: This is the first study to report on the presence of mutations linked to HCC in Botswana. As participants with these mutations might be more prone to rapid disease progression, they may require additional clinical monitoring. Other polymorphisms were also detected but have not been functionally characterized; thus, future in vitro studies on these mutations are warranted.

Table 1. HBV mutations associated with HCC in the precore, core and X regions

Region	Mutation	Genotype
Precore	M1L W28*	A
Precore	V17F W28* G29D	D
Core	P50A E64D L65V T67N A131P	A
Core	P50H	D
X	T36A I127T K130M V131I	A
X	H94Y I127L K130M V131I	D

616 HEPATOCELLULAR CARCINOMA SCREENING AMONG HIV/HBV-COINFECTED INDIVIDUALS IN ZAMBIA

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Background: Chronic hepatitis B virus (HBV) infection is the single most important cause of hepatocellular carcinoma (HCC) in sub-Saharan Africa (SSA). Six-monthly abdominal ultrasound (AUS) screening allows the early diagnosis of HCC and reduces related mortality. However, very few HCC screening programs exist in the region to date. We took advantage of a cohort of HIV/HBV-coinfected individuals in Zambia to pilot an AUS-based screening program in primary care clinics.

Methods: We enrolled HIV/HBV-coinfected adults on antiretroviral therapy (ART) at two outpatient clinics in Lusaka, Zambia. In line with international recommendations, we performed AUS imaging every 6 months in all participants and collected data using a standardized case-report form. All patients had yearly liver stiffness measurements using transient elastography (TE; Fibroscan 402®), HBV viral load, HBV serology, and alcohol consumption assessments using the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C). We summarized the findings of the first AUS examination for the cohort.

Results: Of 306 HIV/HBV-coinfected patients included, 59.5% were male and the median age was 34 years (interquartile range 28-39). Their median CD4 count was 234 cells/µL (108-336), 36.8% had WHO clinical stage 3 or 4, and 140 (45.8%) reported hazardous alcohol consumption, defined as AUDIT-C >3 for women and >4 for men. HBV DNA >2000 IU/mL was observed in 54.7% of participants and 43.3% were HBeAg-positive. At ART initiation, significant fibrosis (>7.0kPa; equivalent to Metavir score ≥F2) was seen in 15.4% of patients and cirrhosis (>9.4kPa; F4) in 8.0%. On AUS, 84 (27.5%) participants had hepatomegaly, 71 (23.2%) peri-portal fibrosis, whereas 5 individuals (1.6%) had signs of cirrhosis, including surface nodularity, coarse and heterogeneous echotexture, atrophy or segmental hypertrophy, and 4 (1.3%) had liver steatosis. Of nine patients with a hyperechoic or hypoechoic lesion, 7 (77.8%) were male, 8 (88.9%) showed elevated levels of ALT prior to ART initiation, 2 (22.2%) were HBeAg-positive and 1 had HBV DNA levels >2,000 IU/mL. Four patients with a lesion had significant fibrosis, of whom one had cirrhosis, according to TE.

Conclusion: We report results from one of the first HCC screening programs in SSA. At their first assessment, 9 of 306 HIV/HBV-coinfected individuals had a liver lesion, indicating the need for further diagnostic testing. Our data also suggest AUS under-estimates cirrhosis.

617 SUBOPTIMAL IMMUNITY TO HEPATITIS A AMONG NYC MSM INITIATING PrEP OR PEP, 2016-2019

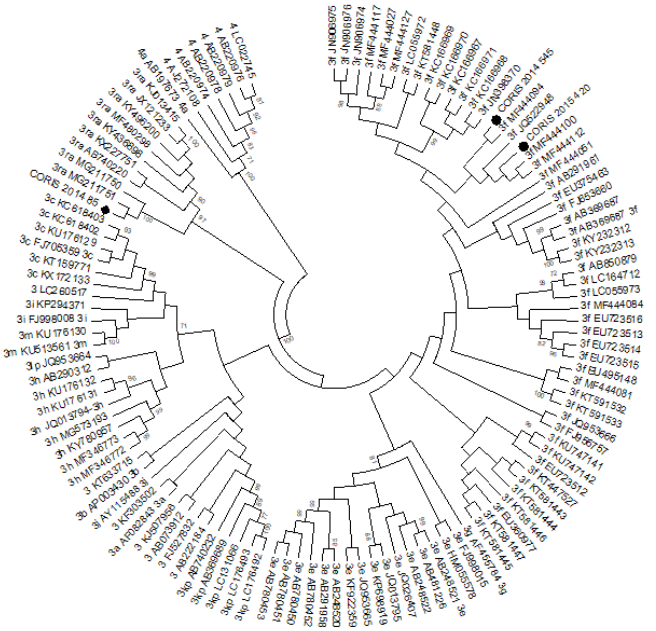
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Background: Recent outbreaks of hepatitis A virus (HAV) infection among men who have sex with men (MSM) have occurred globally, nationally, and in New York City (NYC). An estimated critical immunity threshold against HAV is ≥ 70% to prevent outbreaks in MSM populations. National HIV Pre-exposure prophylaxis (PrEP) and post exposure prophylaxis (PEP) guidelines do not recommend HAV serology testing (ST) among MSM for PrEP/PEP initiation. At NYC sexual health clinics (SHC), all patients initiating PrEP or PEP receive HAVST. This analysis aims to determine the prevalence of HAV immunity among MSM initiating PrEP/PEP at SHC and determine subsequent HAV vaccine uptake.
Methods: Electronic medical record (EMR) data was extracted for HIV-negative MSM PrEP/PrEP patients who had HAVST for the first time at SHC from September 2016 to March 2019, with a follow up through July 2019. We examined demographics, immunization history and EMR administered vaccines. Patients reactive for HAV IgG were considered immune. Patients were considered vaccinated against HAV if they received at least one dose of HAV vaccine (Havrix™) or two doses of hepatitis A/B combination vaccine (Twinrix™) at SHC (or self-reported vaccination at other clinics).
Results: Overall, 4233 MSM initiated PrEP/PEP and had HAVST. Median age was 28 years (IQR 25-33); 32% were Hispanic, 31% were non-Hispanic (NH) white, and 21% were NH Black. Foreign-born were 37% (n=1574). At time of PrEP/PEP initiation, 26% were diagnosed with bacterial STI's. Sixty five percent were HAV immune (n=2733). Of 1500 patients not immune, 50% (n=743) received ≥1 dose of Havrix™ (n= 453) or Twinrix™ (n=290) within a year after HAVST. A total of 2437 (58%) patients self-reported receiving hepatitis A vaccination at non-NYC SHC settings; 37% (n=897) were not immune.
Conclusion: HAV immunity among this NYC MSM cohort was below the critical immunity threshold against HAV. Subsequent vaccination of this cohort likely increased their immunity to ≥ 70%. HAVST identified a significant number of HAV non-immune patients, despite self-reported hepatitis A vaccination. HAVST for MSM initiating PrEP/PEP and subsequent hepatitis A vaccination of non-immune patients is an effective intervention to prevent future HAV outbreaks.

618 HEPATITIS E RABBIT GENOTYPE INFECTION IN HIV-INFECTED PATIENTS

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Background: Among the population in which hepatitis E virus (HEV) infections may have a worse prognosis, HIV-infected subjects represent a high-sensitivity population because of underlying immunosuppression. Our aim was to assess the prevalence and incidence of HEV in HIV-infected patients in a national cohort and describe the viral strains.
Methods: We included HIV-infected patients recruited in the cohort of adult HIV-infected patients of the AIDS Research Network (CoRIS) in follow-up at 26 Spanish hospitals with available serum samples from the centralized BioBank in 2014 and 2015. All samples were tested for HEV IgG and IgM by ELISA (Pharmacy Enterprise© LTD, Beijing, China) and for RNA by qPCR. Samples with detectable HEV viral loads were genotyped following European HEVnet recommendations. Prevalence and incidence of HEV infection were calculated.
Results: A total of 845 individuals were included in the study. Seven hundred and fifty-one (88.9%) were male and had a median age of 36.9 years (30.7-45.2 years). At baseline, 101 patients were positive for HEV IgG antibodies (11.9%), none had HEV IgM antibodies, and 2 presented detectable HEV RNA (0.23%). Of the 744 patients with negative HEV IgG antibody at baseline, 733 samples were available for testing during follow-up. Forty-two seroconverted for IgG, supposing a cumulative incidence of 5.7%. One patient was positive for IgM (0.13%), and 2 showed detectable HEV RNA (0.27%)., Viral strains were consistent with genotype 3f. Interestingly, in one patient, the isolated viral strain was consistent with genotype 3ra (Figure 1).
Conclusion: Our study found a relatively high prevalence and incidence of HEV infection in HIV-infected individuals from Spain. We identified one case of infection with the HEV 3ra genotype, the main host of which is rabbit, showing a potential zoonotic role of this emerging genotype in Spain.



619 THE ROLE OF E6/E7 mRNA DETERMINATION FOR ANAL CANCER SCREENING IN HIV-POSITIVE MSM

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Background: To assess High-grade Squamous Intraepithelial Lesions (HSIL) screening strategies that include biomarkers as E6/E7 oncogenes mRNA detection (E6/7-mRNA test) and human papillomavirus (HPV) DNA determination to triage candidates for High Resolution Anoscopy (HRA).
Methods: HIV-infected Men who have Sex with Men (MSM) from the ELAVI-67 cohort (NCT03357991) underwent anal smear and HRA with biopsy of suspected dysplasia areas. Anal smear samples were tested by anal liquid-based cytology (aLBC), HPV DNA detection performed by both Linear Array (LA) (37 HPV genotypes) and Hybrid Capture®2 (HC2) (13 High-Risk HPV (HR-HPV) genotypes), and E6/7-mRNA test using Aptima® (14 HR-HPV genotypes). We evaluated two screening strategies that combined aLBC and biomarkers to triage candidates for HRA: 1) aLBC Atypical Squamous Cells of Undetermined Significance (ASCUS) or worse and/or positive biomarker; 2) aLBC HSIL and ASCUS that cannot rule out HSIL (ASC-H) always and aLBC ASCUS and Low-grade SIL (LSIL) only if the biomarker results positive.
Results: 354 participants were included, mean age 45.3, mean CD4 count 802.3 cells/mm$_3$, 87.3% undetectable viral load. aLBC results: 2.5% inadequate, 49.4% benign, 16.4% ASCUS, 15.8% LSIL, 13% ASC-H and 2.8% HSIL. HRA results: 54% benign, 24.9% LSIL and 21.2% HSIL (HSIL prevalence: 23.7%). Positive result of HPV DNA tests: 90.4% LA, 46.9% LA for the 14 HR-HPV genotypes included in the E6/7-mRNA test, 23.4% LA for HPV-16, 35% LA for HPV-16, -18 and -45 and 40.7% HC2. Positive result of E6/7-mRNA test: 51.7% for all 14 HR-HPV, 16.4% for HPV-16 and 20.3% for HPV-16,-18 and -45. aLBC with a threshold of ASCUS showed 80% sensitivity and 59.3% specificity for biopsy-proven HSIL (AUC=0.617). Sensitivity and specificity of biomarkers alone and in both combined strategies are shown in the table. Comparing the AUC of aLBC with the other AUC showed in the table, a $p<0.05$ was only found with E6/7-mRNA test in the second combined strategy.
Conclusion: E6/7-mRNA test could be considered for triage as an alternative to aLBC with the advantage of being a more objective and reproducible test. The second combined strategy using E6/7-mRNA test only if the aLBC result is ASCUS

or LSIL seems to be the best strategy to triage candidates for HRA, with the highest AUC and the advantage of saving biomarker and HRA performance.

	Biomarker alone			First combined strategy: biomarker and/or aLBC			Second combined strategy: biomarker if aLBC ASCUS/LSIL		
	Se	Sp	AUC	Se	Sp	AUC	Se	Sp	AUC
LA HPV DNA test	94.7%	25.1%	0.604	98,7%	20,0%	0,593	76%	63.7%	0.701
LA HPV DNA test for the 14 HR-HPV genotypes included in the E6/7-mRNA test	92%	34.1%	0.636	97,3%	25,6%	0,614	74.7%	66.7%	0.709
LA HPV DNA test for HPV-16	46.7%	82.8%	0.642	84,0%	52,6%	0,683	44%	85.9%	0.646
LA HPV DNA test for HPV-16, -18 and -45	56%	70.6%	0.628	85,3%	48,1%	0,667	52%	78.3%	0.654
HC2 HPV DNA test	74.3%	68%	0.707	88,0%	48,1%	0,681	67.6%	76.2%	0.716
E6/7-mRNA test	84.7%	58.6%	0.711	92,0%	41,9%	0,669	73.6%	72.4%	0.730
E6/7-mRNA test for HPV-16	41.3%	90.3%	0.664	82,7%	56,7%	0,697	40%	89.3%	0.654
E6/7-mRNA test for HPV-16, -18 and -45	41.3%	90.3%	0.655	82,7%	55,2%	0,689	42.7%	86.7%	0.655
p-value for AUC comparisons	<0.05 only comparing LA HPV DNA test with HC2 HPV DNA test and E6/7-mRNA test.			<0.05 only comparing LA HPV DNA test with E6/7-mRNA test for HPV-16 and for HPV-16, -18 and -45.			>0.05 for all comparisons in this strategy.		

[Sensitivity (Se), Specificity (Sp) and Area Under the ROC Curve (AUC) for each biomarker alone and in two combined triage screening strategies]

620 ANAL CANCER SCREENING: IS IT TIME FOR CYTOLOGY AND HIGH-RISK HPV COTESTING?

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Background: Anal cancer screening targets cancer precursors, defined as high-grade squamous intraepithelial lesions (HSIL). Current guidelines suggest an anal cytology (AC) severity grade of atypical squamous cells of undetermined significance or greater (≥ASCUS) as referral threshold for high-resolution anoscopy (HRA). This study sought to determine whether co-testing AC for high-risk human papillomavirus (hrHPV) improves screening performance and to compare the efficiency of two novel HRA referral thresholds to current clinical practice. Novel algorithm A sets the threshold for HRA referral at any hrHPV or AC with low-grade squamous intraepithelial lesion or greater (≥LSIL); algorithm B was recently proposed by Sambursky et al.

Methods: Anal swabs were obtained simultaneously or within 3 months of HRA-guided biopsies and used for AC and Cobas® hrHPV DNA co-testing. Using biopsy-proven HSIL as an endpoint we calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) as well as relative risk (RR) of HSIL for various AC/HPV co-testing combinations. Test characteristics were then compared between screening strategies using an efficiency frontier method.

Results: 1,947 paired AC and hrHPV results from 1,268 individual patients were analyzed (89% HIV-positive, 90% MSM and 9.5% women). Adding hrHPV testing to the current AC referral threshold of ≥ASCUS increased sensitivity from 80.4% to 95.9% (p<0.001). Requiring HPV16/18 positivity for referral markedly improved specificity but decreased sensitivity. For each AC category, the RR of HSIL was substantially greater when any hrHPV was detected. When comparing screening strategies, sensitivity for the current guideline approach, algorithm A and B was 80.4%, 96.4%, and 86.9%, while specificity was 37.6%, 22.4%, and 35%, respectively (see table). When calculating number of missed HSILs versus number of unnecessary HRAs for a hypothetical cohort of 10,000 persons with 30% HSIL prevalence, all strategies including co-testing were found to be more efficient than those without.

Conclusion: Co-testing AC for hrHPV improves the sensitivity to detect anal HSIL for all AC categories. Positivity for any hrHPV, especially types 16/18, implies a significant risk for anal HSIL. Algorithm A, combining ≥LSIL AC and reflex hrHPV testing for benign and ASCUS cytology results, may improve efficiency of anal cancer screening.

	Outcome: HSIL		
Anoscopy Referral Threshold	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Relative Risk (95% CI)***
Cytology alone			
ASCUS or Greater	80.4 (77.6-82.9)	37.6 (34.8-40.5)	8.0 (4.1-15.6)
LSIL or Greater	43.6 (40.4-46.9)	76.1 (73.5-78.6)	9.3 (4.7-18.3)
HSIL or Greater	11.1 (9.1-13.3)	97.9 (96.9-98.7)	13.5 (6.8-26.5)
Cytology and HPV co-testing			
Benign or Greater Cytology and any hrHPV	95.9 (94.5-97.1)	23.2 (20-8-25.8)	7.0 (4.0-15.5)
Benign or Greater Cytology and HPV 16/18	51.7 (48.4-54.9)	73.8 (71.1-76.3)	9.7 (4.9-18.9)
ASCUS or Greater Cytology and any hrHPV	77.5 (74.7-80.1)	48.6 (45.6-51.5)	8.6 (4.4-16.8)
ASCUS or Greater Cytology and HPV16/18	47.4 (44.1-50.8)	80.5 (78.0-82.8)	10.4 (5.3-20.5)
Novel Algorithm A**	96.4 (94.99-97.6)	22.4 (19.9-25.01)	7.8 (4.0-15.3)
Novel Algorithm B (Sambursky et al.)***	86.9 (84.5-89.1)	35 (32.2-38.0)	8.2 (4.2-16.0)

* Compared to reference category of benign cytology AND negative high-risk HPV
** Any hrHPV or LSIL or Greater Cytology
*** Strategy described in Dis Colon Rectum 2018; 61: 1364–1371

621 LOW ADHERENCE TO TREATMENT AND SURVEILLANCE OF HPV-RELATED ANAL PRECANCER

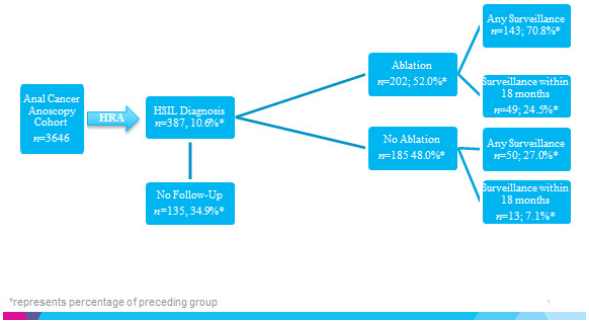
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Background: Persons living with HIV (PLWH) have nearly 20-fold elevated risk of anal cancer compared to the general population. Several guidelines recommend annual anal cancer screening using anal cytology, high-resolution anoscopy (HRA) guided biopsies, and treatment of high grade intraepithelial lesions (HSIL), the precursors to anal cancer. Untreated HSIL can progress to invasive cancer and frequently recurs after treatment (>50%) necessitating longitudinal surveillance. Using data from our large screening cohort, we evaluated rates and predictors of adherence to surveillance HRAs following a diagnosis of anal HSIL.

Methods: The Mount Sinai Anal Dysplasia Program is an HRA referral site for a large urban population of PLWH and HIV-uninfected MSM. We collected data on demographics, HIV clinical variables, and HRA attendance and outcomes from 2009-2019. We identified patients who were diagnosed with HSIL on first HRA and measured the following outcomes: (1) adherence to any follow-up, including repeat HRA or ablation, at any time after initial HSIL diagnosis; (2) follow-up examination within 18 months of HSIL diagnosis; (3) return for HSIL ablation within 6 months; (4) surveillance HRA following ablation. We also evaluated the predictors of these outcomes.

Results: 3,646 unique patients underwent at least one HRA during the study. 387 patients (11%) had HSIL or cancer on initial HRA. Of this group, median age was 45, 92% were PLWH, 90% were male, 88% MSM, with diverse race/ethnicity: 30% White, 23% Black, and 30% Hispanic. 202 patients (52% of the HSIL cohort; see Figure) underwent ablation. Median time to ablation from HRA was 49 days (10% were ablated >180 days). Of those who received ablation, 71% followed up at any time. Among those not receiving ablation, 27% followed up at any time. Among HSIL patients the only significant predictor of adherence to surveillance was Hispanic ethnicity (p=.02). 35% of patients diagnosed with HSIL never returned. Compared to Whites (69%), Hispanics were more likely to return (73%, p=.04), while Blacks (54%, p=.02) and PLWH with viremia (57%; p=.05) were less likely to return after HSIL diagnosis.

Conclusion: Adherence to treatment and surveillance following an initial diagnosis of anal HSIL was poor in a large, urban anal cancer screening cohort. Future research to understand barriers and facilitators could inform interventions to improve adherence to anal cancer screening.



622 ANAL PRECANCER SCREENING AMONG MSM: WHAT IS THE BEST STRATEGY?

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Background: Risks of non-AIDS defining cancers has increased among people living with HIV since the advent of potent ART. Anal cancer is rare in the general population, but men who have sex with men (MSM) have elevated risk. We evaluated three screening strategies (single anal cytology [aCyt], sequential aCyt, and co-testing [aCyt plus oncogenic HPV]) and their ability to predict anal precancer (anal histological high-grade squamous intraepithelial grade 2+ [hHSIL/AIN2+]) among MSM.

Methods: 1027 MSM from the Multicenter AIDS Cohort Study (MACS) had repeated aCyt and HPV testing. Men with abnormal aCyt and a subset with normal aCyt were referred for high-resolution anoscope (HRA). All men had HRA (N=430) within 5 years of their aCyt, 72% of HRAs performed in Pittsburg and LA study sites. Multivariable logistic regression models evaluated risk of AIN2+ within 5 years of screening using the three screening strategies adjusted for age, race, HIV status, number of anal sex partners, and study site. Sensitivity and specificity were calculated among participants who had HRA and results were corrected for potential verification bias (in all participants who had screening tests) using Begg and Greenes's method.

Results: Among those who had HRA tests, the median age at time of HRA was 48 years, 70 % were HIV+, 81% non-Hispanic white, and 9% had CD4 cell count<350 (cells/mm_3). Prevalence of AIN2+ was similar among HIV+ MSM than HIV- MSM (31% vs 24%, p=0.13), but was higher among the subgroup with CD4<350 (41%, p=0.04). Odds of AIN2+ was significantly higher in those with abnormal screening results with an 83% increase (95% CI: 1.1-3.04) in those with a single aCyt+, a 3-fold increase (95% CI: 1.33-7.11) following two aCyt+, and more than a 4-fold increase (95% CI: 1.93-10.29) following oncHPV+/aCyt+ co-testing.

Specificity was low in single aCyt (44%) but increased with sequential aCyt testing (79%) or oncHPV co-testing (62%). Sensitivity was moderate in single aCyt+ (67%) or dual positive cotests (61%), and high in cotests where positivity on either marker was considered as positive (93%). Sensitivity was only 36% among those with sequential aCyt+ results. After correcting for potential verification bias, specificity increased but sensitivity reduced in all strategies.

Conclusion: Anal cytology screening had moderate specificity and sensitivity among HIV+ and HIV- MSM. Sequential aCyt testing or adding an HPV co-test to aCyt improved test performance.

Table. Comparison of tests characteristics for anal precancer (AIN2+) by screening strategy including: baseline aCyt test, co-testing (aCyt plus oncHPV testing), and sequential testing (two consecutive aCyt tests), before and after correcting for verification bias.

	Crude Estimation		After Verification Bias Correction*	
	Sensitivity	Specificity	Sensitivity	Specificity
Baseline aCyt positive				
All	67%	44%	43%	69%
HIV-negative	58%	50%	31%	75%
HIV-positive	72%	40%	53%	61%
Co-test: both (aCyt plus oncHPV+)				
All	61%	62%	43%	77%
HIV-negative	54%	71%	35%	84%
HIV-positive	65%	55%	50%	70%
Co-test: either (aCyt+ and/or oncHPV+)				
All	93%	17%	81%	36%
HIV-negative	85%	22%	65%	46%
HIV-positive	96%	13%	92%	27%
Sequential aCyt results (both aCyt+)				
All	36%	79%	20%	87%
HIV-negative	27%	88%	17%	93%
HIV-positive	40%	74%	28%	83%

ACyt = Anal cytology

Potential verification bias was corrected using Begg and Greenes's method.

623 NEED FOR OPTIMIZATION OF SCREENING METHODS FOR ANAL INTRAEPITHELIAL NEOPLASIA IN PLWH

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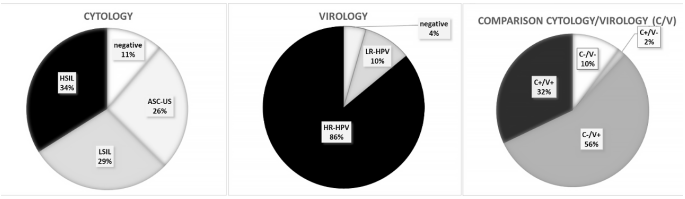
Background: The detection rate of histologically confirmed high grade anal intraepithelial neoplasia (HGAIN) and anal carcinoma by screening with anal cytological (cyto.) smears and/or human papilloma virus (HPV) typing in HIV-positive individuals (HIV+) has been examined in the TECAIN Study.

Methods: The prospective, randomized, national, multicenter TECAIN study compared the efficacy of local treatment with 85% trichloroacetic acid to electrocaustic ablation of histologically confirmed AIN in HIV+ since 2015 in Germany. Biopsies of AIN lesions, anal cyto. Swabs and HPV typing were performed at Baseline and follow-up visits. The cyto. findings were divided according to the Bethesda classification. Depending on their oncogenic potential HIV types were distinguished into high risk (HR) and low risk (LR) HPV. The consistencies between HPV types, the cyto. results and histologic findings were analysed.

Results: 292 examinations (exa.) in 184 HIV+ included during the TECAIN Study were analyzed until September 12, 2019. At Baseline the median age was 48 years, 98% of HIV+ took antiretroviral therapy and 81% were MSM. Histologically, 108 exa. (37%) showed AIN I as the highest grade HPV-associated lesion, 84 (29%) AIN II and 100 (34%) AIN III. Thus in 184 exa. (63%) HGAIN were detected. At the same time, LSIL diagnosed in 84 (29%), ASC-US in 76 (26%), HSIL in 99 (34%) and negative cyto. results in 33 (11%) cases. Virologically, in 251 cases (86%) at least one HR-HPV could be diagnosed and 28 (10%) LR-HPV. No HPV was detected in 13 (4%) exa.. A cyto. screening found no HSIL in 66.3% of all HGAIN cases. No HR-HPV was detected in 12% of all HGAIN cases. If both cytology and virology results were considered together, only 10.3% of all HGAIN cases showed no higher grade abnormalities.

Conclusion: Simultaneous screening with anal cyto. and virological smears detect HGAIN much more reliable than cytology alone (fig. 1). Comparable results in gynecology have led to an extension of routine diagnostics by the addition of HPV typing to cervical cancer screening guidelines in Germany.

Fig. 1: Results (n=292) of virological and cytological examinations of all HGAIN cases in the TECAIN RCT and detection rates in simultaneous screening of cytological (C+) and virological (V+) smears.



624 CERVICAL CANCER KNOWLEDGE AND ATTITUDES AMONG HIV-POSITIVE MEN IN MALAWI

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Background: Malawi has the greatest cervical cancer burden globally (72.9 cases and 54.5 deaths per 100,000 women), with an elevated risk among HIV-positive women. Malawian women have reported being reluctant to screen without obtaining spousal permission. This study is the first to examine Malawian HIV-positive men's knowledge and opinions of cervical cancer disease and decision-making around screening, and evaluate associations with women's screening. The goal is to develop strategies to increase women's uptake of screening.

Methods: A survey was administered at a large, free ART clinic in Lilongwe, Malawi. Male clients (≥18 years) were eligible if they were married and had ever heard of cervical cancer. The survey asked about cervical cancer awareness and perceptions, knowledge of cervical cancer screening and treatment services, and wife's experiences with screening (primary wife if polygamous). Gender attitudes were measured with the Gender Equitable Men (GEM) scale. Logistic regression was used to identify factors associated with partner screening status.

Results: A total of 125 respondents with median age of 44 years (IQR: 39-50 years) were surveyed. Just over half (58%) reported that their wife had ever received cervical cancer screening. Cervical cancer was perceived to be more dangerous than HIV by 78% of men, and 21% reported knowing someone who had died from cervical cancer. When asked who should make decisions about cervical cancer screening, 6% responded their wife only, 55% responded both partners jointly, and 39% responded himself only. Respondents correctly answered an average of 4/8 risk factor questions and 6/8 screening and treatment questions, but knowledge was not associated with whether a

respondent's wife had been screened (aOR 0.97, 95% CI: 0.77, 1.22) (Table 1). Men with more progressive gender views about sexual behaviors (higher GEM scores) were more likely to have a partner who had been screened (aOR 1.46, 95% CI: 1.00, 2.13) (Table 1).

Conclusion: Men in this study recognized the high burden and threat of cervical cancer. However, important gaps in knowledge and a strong role in decision-making may limit access to potentially life-saving services for their wives. Our findings suggest that cancer control programs should engage male partners, given their critical role in women's decisions about use of cervical cancer prevention.

Table 1: Association of male characteristics and reported partner screening behavior

	OR	95% CI	aOR[1]	95% CI
Multiple partners	0.80	0.36-1.79	1.05	0.40-2.77
Partner HIV+	2.00	0.93-4.30	1.63	0.65-4.10
Knows someone who survived or died of CC	1.81	0.77-4.25	1.38	0.50-3.75
GEM score, sex domain	1.51**	1.10-2.07	1.46*	1.00-2.13
Knowledge score	1.04	0.85-1.26	0.97	0.77-1.22

[1] Adjusted model additionally includes: respondent age, educational attainment (categorical), occupation (categorical), income sufficiency (categorical), and age difference between respondent and partner

Asterisks indicate level of significance: *p < 0.10, ** p < 0.05, *** p < 0.01

625 LUNG CANCER INCIDENCE AND RISK FACTORS DIFFER BY HISTOLOGY AMONG HIV+/– VETERANS

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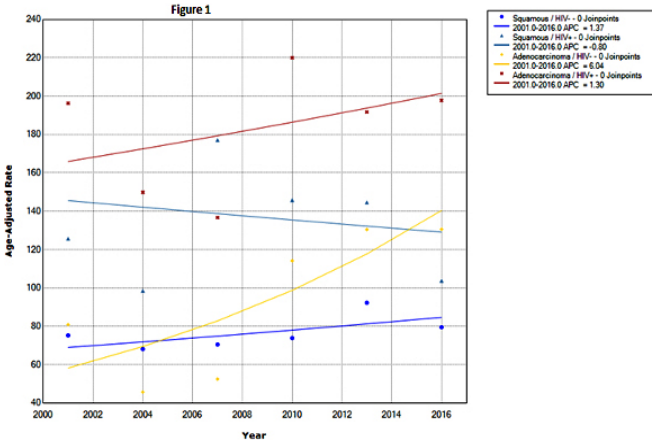
Background: People living with HIV (PWH) have high risk for developing lung cancer (LC) and poor treatment outcomes. Predominant molecular alterations and treatment algorithms differ for each of the lung cancer histologic types, which include small cell lung cancer (SCLC), and non-small cell lung cancer (NSCLC), and 2 common NSCLC histologic subtypes squamous cell (SC), and adenocarcinoma (AC). Few studies have evaluated epidemiologic differences by histology in PWH.

Methods: In a retrospective cohort study, Veterans diagnosed with HIV between 10/1/99 and 12/31/2016 were identified and matched to a 2 to 1 gender, age and year of care HIV-negative cohort. Both HIV+/- veterans were followed from index date until LC diagnosis, death or 12/31/2016. LC cases and histologic types were identified using the VA Corporate Data Warehouse and medical record review of individuals with LC ICD-9/10 codes. We identified 46604 HIV+ and 88783 HIV- veterans who met eligibility criteria. We calculated cumulative LC incidence rates by histologic types and used Joinpoint software for modeling trends. Cox regression analyses were used to identify risk factors for specific LC histologic types and subtypes among PWH. Models were adjusted for age, race, gender, year of index HIV, smoking, baseline CD4 count, and percent undetectable HIV viral load.

Results: A total of 931 incident cases of LC were ascertained among HIV+ and 1206 among HIV-. The overall incidence rate (IR) of SCLC was 20.43/100,000 among HIV+ veterans and 21.37/100,00 among HIV-, and the incidence rate ratio (IRR) was 0.96 (0.84 – 1.09). Among the NSCLC subtypes, the IRs for AC was the highest for both HIV+ and HIV- (93.52/100,000 vs 49.82/100,000, IRR was 1.88 CI: 1.75 – 2.01), and the IRs for SC were lower for both HIV+ and HIV- (67.7/100,000 vs 38.3/100,000, with an IRR of 1.77 CI: 1.63 – 1.92). Fig. 1 shows the joinpoint analysis of IRs per 3-year intervals for AC and SC for HIV+/- veterans. In multivariable analysis of PWH by LC histology, we found that baseline CD4 count >200 was not significantly protective for AC (HR 1.05 CI: 0.67 – 1.63, p=0.83) and was marginally protective for SC (HR 0.61 CI:0.35 – 1.05, p=0.08).

Conclusion: The IRs of SC and AC NSCLCs but not SCLC are higher among PWH. The IRs of AC and SC have remained stable over time for both HIV+/- veterans.

Figure 1



626 IMPACT OF UNIVERSAL ART ACCESS ON KAPOSI SARCOMA: RESULTS FROM THE ICONA COHORT

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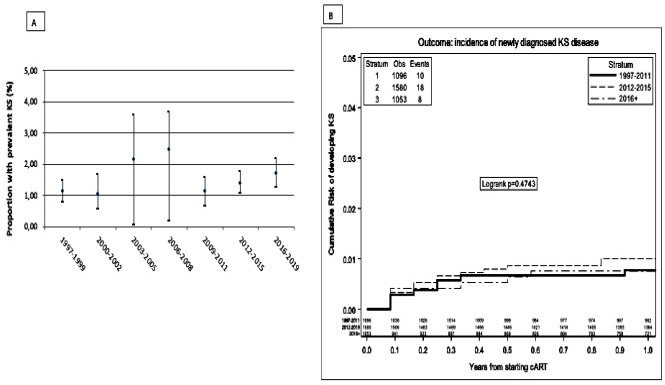
Background: The widespread introduction of effective ART reduced the burden of AIDS-related Kaposi Sarcoma (KS), even if KS does still occur also in individuals with well-controlled HIV infection.

Methods: We included naïve HIV-infected individuals (PLHIV) enrolled in the ICONA cohort over 1997-2019. Prevalent cases were PLHIV with a diagnosis of KS prior and up to 30 days after enrolment. Incident cases were defined as new KS diagnoses occurring after ART initiation. Patients' characteristics at the date of enrolment were compared by prevalent KS status and associations identified by logistic regression modelling. In the subset of people KS-free at enrolment, standard Kaplan-Meier curves were used to model time from ART initiation to development of KS and a Cox regression model to identify factors associated with this outcome. A similar analysis was performed in PLHIV with prevalent KS to identify factors associated with their risk of KS relapse or death after ART (clinical failure).

Results: Among 17,742 PLHIV enrolled in the ICONA cohort over 1997-2019, 248 prevalent KS cases and 36 incident KS cases were identified. Prevalent cases were mostly male (93%), with median age of 45 years (IQR 37-53) and median CD4+ count of 76/mmc (IQR 24-193). No significant differences in prevalence (by year of enrolment) and incidence (by year of ART initiation) of KS were observed (Figure). At multivariable logistic regression, the only factor independently associated with prevalent KS was mode of HIV transmission (MSM versus PWID, adjusted odds ratio [aOR]: 5.24 (1.35, 20,39)). In contrast, factors independently associated with the risk of incident KS were pre-ART CD4+ count (adjusted relative hazard (aHR): 0.57 (0.42, 0.77) for 100 cells/mmc higher) and mode of HIV transmission (MSM versus HS, aHR: 3.82 (1.62, 9.02)).
Over 1,316 PYFU, clinical failure after ART introduction was observed in 52 prevalent cases (29 deaths and 23 relapses) with an incidence rate of 3.9% (95% CI: 2.9-5.1). However, none of the considered factors showed an association with the risk of clinical failure.

Conclusion: Despite universal ART access, we did not observe a reduction of KS prevalence and incidence in recent years. The strong association of pre-ART CD4+ count with incidence of KS in ART-treated PLHIV strengthens the role of immune competence in KS. Further KSHV and HIV immune-virological characterization is warranted to better identify factors associated with KS occurrence in PLHIV.

Figure: Trends in prevalence(A) and incidence (B) of KS



627LB OUTCOMES AFTER PEGYLATED LIPOSOMAL DOXORUBICIN FOR KAPOSI SARCOMA IN MOZAMBIQUE

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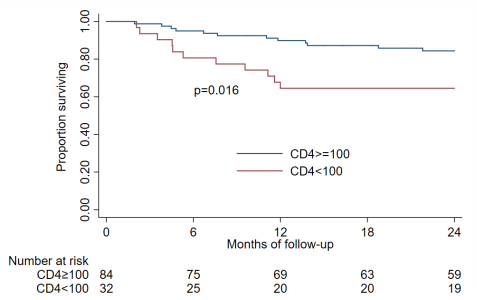
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Background: Standard care for Kaposi's sarcoma in Mozambique consists of ARV and a combination of doxorubicin, bleomycin and vincristine. Historically, patient outcomes have been poor, with Mozambique's largest case series reporting 43% death or loss to follow-up after two years. To improve outcomes and retention in care, Médecins Sans Frontières introduced pegylated liposomal doxorubicin (PLD) in 2016.

Methods: A prospective observational study was implemented between March 2016 and December 2018. Patients aged >15 years were eligible if they had T1 KS or T0 KS not responding to ≥6 months of ART with significant impact of KS on their quality of life. Exclusion criteria included prior receipt of chemotherapy and Karnofsky score <50. Patients received PLD on three-week cycles until meeting stopping criteria based on clinical response or toxicity. HIV status and KS were monitored at regular follow-up visits, and PHQ-9 and SF-12 questionnaires were administered to evaluate depression and quality of life. Adverse events were monitored passively. Primary outcomes were vital status and KS progression at 6, 12 and 24 months of follow-up. Survival was estimated using Cox proportional-hazards regression.

Results: 183 KS patients were screened and 116 participants were enrolled. At baseline, patients presented with advanced KS (72% had lymphedema) and moderately advanced immunosuppression, with 53% of patients on ART ≤6 months. 23 participants (20%) died and 15 (13%) were lost to follow-up. Participants with CD4<100 at the time of enrolment were more likely to die (HR 2.7, 95%CI [1.2-6.2], p=0.016) (Figure), as were participants with T1S1 disease at enrollment compared to those with T1S0 disease (HR 2.7, 95%CI [1.1-6.4], p=0.023). Most deaths occurred in patients with advanced immunosuppression and multiple social problems. 92 participants achieved complete or partial remission at any point during follow-up (overall response 80%), including 15 (13%) who achieved complete remission. Of those achieving CR or PR, 26 (28%) eventually restarted PLD because of recurrent disease or worsening symptoms. The most common AEs were due to neutropenia and anemia. Quality of life improved significantly after 6 months.

Conclusion: PLD was safe, well-tolerated and effective for the treatment of KS in Mozambique. The high mortality rate is likely due to advanced immunosuppression at baseline and underscores the need to provide earlier screening and referral for treatment of KS. Efforts should be made to increase access to PLD in Mozambique.



628 BREAST CANCER RISK AMONG WOMEN WITH HIV IN NORTH AMERICA (2000-2015)

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Background: Breast cancer burden is poorly characterized in women with HIV regarding incidence and risk factors. Some studies suggesting reduced risk in women with versus without HIV further support assessing breast cancer among women with HIV. We estimated breast cancer cumulative incidence and risk factors in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

Methods: We included women ≥35 years old who were prescribed antiretroviral therapy (ART), observed in the NA-ACCORD from 1/1/2000-12/31/2015, had no cancer history, and had ≥6 months of follow-up. Study entry was the latest date of: 1/1/2000, age 35, ART initiation, or NA-ACCORD enrollment. Study exit was the earliest date of: invasive breast cancer diagnosis, death, loss to follow-up (≥2-year gap after CD4/HIV RNA measurement), or administrative censoring. Standardized case validation included abstraction, linkages with cancer registries and/or record review of cancer site/pathology. With age as the time metric, we used non-parametric estimators accounting for the competing risk of death to assess breast cancer cumulative incidence. We used Fine & Gray regression to quantify breast cancer risk by time-varying HIV viral load, obesity (body mass index [BMI] ≥30 kg/m_2) at study entry, race, smoking status, and CD4 count at ART initiation. We calculated adjusted subdistribution hazard ratios (aSDHR) with 95% confidence intervals (95% CI).

Results: We included 8,242 women contributing 53 breast cancer cases with 55,113 years of follow-up. Median follow-up was 6 years (IQR: 3 to 10) and median age at study entry was 42 (IQR: 37 to 48). Median age at diagnosis was 52 (IQR: 46 to 56). Breast cancer cumulative incidence was 3.7%. Breast cancer risk was associated with smoking (aSDHR 3.0, 95% CI 1.2, 7.6) and marginally non-significantly associated with obesity (aSDHR 1.8, 95% CI 1.0, 3.2) (Table 1). Though non-significant, there was a 39% reduced risk of breast cancer per log_{10} increase in viral load (p=0.6), and 17% increased risk with lower CD4 count (p=0.6). There were no differences by race.

Conclusion: We observed breast cancer risk of 3.7% in women with HIV and compelling associations with smoking, obesity, and HIV clinical factors. Findings should be interpreted cautiously given our sample size and limited follow-up after age 65. Further investigation is merited as more follow-up is accrued incorporating traditional/reproductive risk factors and direct comparisons to the general population.

Table 1. Risk factors for breast cancer among women in the NA-ACCORD 2000-2015

Covariate	aSDHR	95% CI
Race		
White	REF	REF
Black	1.05	0.60, 1.83
Other	0.89	0.21, 3.88
Obesity (BMI ≥30 kg/m²)	1.76	0.98, 3.15
Smoking Status		
Never	REF	REF
Ever	2.97	1.16, 7.60
Unknown	1.88	0.62, 5.64
CD4 count at ART initiation (<350 versus ≥350 cells/μL)	1.17	0.61, 2.22
Per log_{10} viral load increase	0.61	0.11, 3.51

Abbreviations: adjusted subdistribution hazard ratio, aSDHR; confidence interval, CI; body mass index, BMI; antiretroviral therapy, ART.

629 BREAST CANCER RISK IN WOMEN LIVING WITH HIV IN SOUTH AFRICA: THE SAM STUDY

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Background: In the Republic of South Africa (RSA), approximately 17% of women were living with HIV (WLHIV) in 2017. Greater access to antiretroviral therapy (ART) has increased the survival of WLHIV in recent years and moved the distribution of cancer diagnoses toward non-AIDS-defining cancers, including breast cancer (BC). According to National Cancer Register South Africa (NCR SA) Report, in 2014 BC was the most commonly diagnosed cancer in women in RSA, with an age-standardized incidence rate of 33.3 per 100 000 population. However, in WLHIV, the incidence and risk factors for BC are not well understood.

Methods: The South African HIV Cancer Match (SAM) study used privacy preserving record linkage to create a large cohort of cancer in people living with HIV from national laboratory and cancer registry data. We included WLHIV aged 16 years and older with confirmed HIV status by two or more HIV related tests and with cancer diagnosed between 2004 and 2014 in the SA public health sector laboratories. We calculated BC incidence per 100 000 person-years, based on the number of WLHIV with histology-confirmed BC. We derived Cox regression model stratified by province of first HIV test to obtain hazard ratios of associations with first reported CD4 cell count, age, sex and calendar period.

Results: Between 2004 and 2014, over 8 586 130 person-years of follow-up, 4 083 incident BC cases were diagnosed in the SAM cohort of 3 137 992 WLHIV. BC incidence rate was 47.6 cases per 100 000 person-years (95% CI 46.1-49.0). The median age of WLHIV at baseline was 32 years (interquartile range (IQR): 26-40), and the median age at diagnosis was 44.9 years (IQR: 38-52.1). The median baseline CD4 cell count was 310 cells/µL (IQR: 177-477). There was general increase in CD4 cell count through calendar years. Only age was strongly associated with BC risk (Table 1).

Conclusion: We found no evidence of association between immunosuppression and BC risk in WLHIV in RSA. BC incidence in WLHIV was high and increased with age, closely similar to what is observed in the NCR SA data for the general female population. Additional analyses of trends in the stage at BC diagnosis and BC mortality are needed to inform the public health response to BC in WLHIV in RSA.

Table 1: Crude incidence rates of Breast Cancer (BC) per 100,000 person-years and hazard ratios from multivariate Cox regression analysis, stratified by province of first HIV test.

	BC cases	Incidence rates (95% CI)	Hazard ratios* (95% CI)
First CD4 count [cells/µL]			
≤200	1 458	58.4 (55.5 – 61.5)	1
201-350	1 098	44.9 (42.3 – 47.6)	0.92 (0.85-1.00)
351-500	748	42.5 (39.5 – 45.6)	1.00 (0.91-1.09)
≥501	759	40.8 (38.0 – 43.9)	1.01 (0.92-1.10)
Calendar period			
2004-2006	1 505	80.5 (76.5 – 84.6)	1
2007-2010	1 845	40.3 (38.5 – 42.2)	0.73 (0.68-0.79)
2011-2014	713	34.1 (31.7 – 36.7)	0.92 (0.83-1.03)
Age category [years]			
16-19	11	3.84 (2.13 – 6.94)	0.10 (0.05-0.18)
20-29	387	12.3 (11.2 – 13.6)	0.28 (0.25-0.32)
30-39	1 376	44.3 (42.1 – 46.7)	1
40-49	1 351	94.7 (89.8 – 99.9)	2.27 (2.11-2.45)
50-59	737	149.0 (139 – 160)	3.87 (3.53-4.23)
60+	201	193.0 (168 – 221)	5.88 (5.06-6.84)

**Multivariate analyses adjusted for the variables listed, stratified by province*

630 HIV-ASSOCIATED HEMATOLOGIC MALIGNANCIES IN PEOPLE LIVING WITH HIV IN SWEDEN

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Background: People living with HIV (PLHIV) have an increased risk of developing hematologic malignancies (HM) and in particularly non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). Despite a decline observed since the introduction of effective combined antiretroviral therapy (ART) the risk is still increased. There is no published data regarding HMs in PLHIV in the era of ART in Sweden.

Methods: A retrospective study was conducted of PLHIV receiving care at the Department of Infectious Diseases, Karolinska University Hospital, between 01/2004 and 12/2018. PLHIV diagnosed with HMs were identified and data was collected linking the InfCareHIV cohort with medical records. For incidence assessment of lymphoma, cases occurring within 30 days after cohort enrollment were excluded.

Results: During the study period, 3,484 patients received HIV care for a total of 22,903 person-years (py). HMs were identified in 43 patients (Figure 1) (31 males, 12 females). The incidence rate of lymphoma was 127,6/100 000 py, compared to 21,2/100 000 py in the general population in Sweden (Socialstyrelsen). In the early period, 2004–2010, the incidence rate was significantly higher compared to the late period, 2011–2018 (232,4 vs 73,4 per 100 000 py; p=0.003). Median follow up time was 7,6 years (IQR 3,1–9,3). Median time from HIV diagnosis was significantly shorter in patients developing NHL compared to HL (1,2 vs 8,9 years; p=0.01). Fourteen patients with HMs (33%) were diagnosed within 6 months of HIV diagnosis. Treatment with effective ART (>180 d prior to malignancy) with undetectable viral load was significantly more common in the HL group compared to NHL (89% vs 30%; p=0.005). Median CD4+ cell count at malignancy diagnosis was 190 cells/ml and a majority (86%) had a nadir CD4+ cell count <200 cell/ml. A majority of the patients (79%) received chemotherapy. Autologous hematopoietic stem-cell transplantation was conducted in three cases. Eighteen deaths occurred during the study period with a median time from malignancy to death of 0,4 years (IQR 0-1,4). The five-year survival rate for lymphoma was 55% (16/29), as compared to 74% (p=0,03) five-year survival rate for lymphoma in the general population in Sweden (Socialstyrelsen).

Conclusion: The incidence rate of lymphoma was more than 6 times higher in PLHIV and the five-year survival rate was significantly poorer when compared to general population in Sweden. The incidence declined in recent years. HL occured significantly later and were more frequent in PLHIV on effective ART.

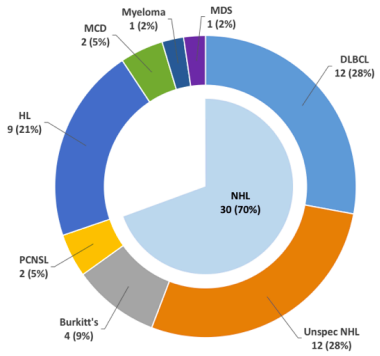


Figure 1. Hematologic malignancies identified, n=43. 30 cases of NHL (70%), nine cases of HL (21%), two cases of multicentric Castleman's disease (MCD) and one case each of myeloma and myelodysplastic syndrome (MDS).

The NHL group consisted of 12 cases of diffuse large b-cell lymphoma (DLBCL), 12 unspecified NHL, four Burkitt's lymphoma (BL) and two Primary CNS-lymphoma (PCNSL).

631 IMMUNO-VIROLOGICAL PARAMETERS IN PEOPLE LIVING WITH HIV UPON ANTI-PD-1/L-1 FOR CANCER

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Background: To characterize tolerance, immuno-virological parameters and efficacy data in people living with HIV (PLHIV) receiving Immune-CheckPoint Inhibitors (ICPi) (anti-PD1 or anti PDL1), a cohort was set up.

Methods: The ANRS CO24 ONCOVIHAC (NCT03354936) is an ongoing prospective cohort study in France enrolling PLHIV with cancer treated by ICPi. HIV RNA viral load (VL), CD4 and CD8 were collected at baseline (date of first ICPi injection) and during follow-up, as were adverse events (AEs).

Results: From January 17th, 2018 to September 21st, 2019, 43 patients were enrolled across 20 sites. Among them, 31 enrolled at least 6 months ago were included in this analysis. Median age was 59 years (IQR: 53-66) and 25 (80.6%) were males. HIV has been diagnosed in 1990 (1987–1997) and CD4 nadir was 98/µL (42–240) with 22.6% prior AIDS events. At baseline, 20 received nivolumab, 10 pembrolizumab and 1 atezolizumab for the following cancers: lung (n=15), melanoma (4), head/neck (4), bladder (3), Hodgkin (3), Kaposi sarcoma (1), anal (1), tongue (1), squamous cell carcinoma (1). All patients were under cART with a median CD4 count of 314/µL (148–642) and CD4/CD8 ratio of 0.46 (0.37–0.94) and 5 had HIV RNA >50 copies/mL with a median of 4.6 $\log_{10}$ (4.3–5.1). During a mean follow-up of 8.1 months (21.0 person-years), 101 AEs occurred in 25 pts with 28 grade 3/4 AEs in 15 pts and only 2 Immune-mediated AEs in 2 pts

(neuropathy and thyroiditis). No drug-related fatal AE occurred. Overall, 6 pts (21%, 95%CI: 8–50) discontinued ICPi: 4 for progression and 2 for SAE (epilepsy and meningoradiculitis) and 12 died (8 with lung cancer). The 8-month survival rate was 56.8% (27.5-78.1) for lung cancer and 81.3% (52.5-93.5) for the other cancers.
During the follow-up, 118 HIV RNA VL/CD4/CD8 were measured with a median of 2 per patient (IQR: 1-6). All patients with HIV VL<50 copies/mL at baseline maintained VL<50 copies/mL throughout the follow-up, while those with HIV VL≥50 copies/mL reached a VL<50 copies/mL. CD4 and CD8 T cell count significantly increased over time, respectively, +8.9/µL per month, P=0.007 and +19.4/µL, P=0.028, while CD4/CD8 ratio remained stable (-0.001, P=0.739).
Conclusion: In this ongoing French cohort of PLHIV with cancer receiving ICPi, no HIV VL rebound occurred during an 8-month follow up. An increase of CD4 and CD8 cells was observed, associated with a low frequency of serious events relative to that expected in this population.

632 T-CELL SUBPOPULATION PROFILES AND CANCER RISK FOR HIV+ AND HIV– VETERANS

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Background: Alterations in cell-mediated immunity have been associated with cancer risk for people living with HIV (PLWH). Circulating levels of T regulatory cells (Tregs), and activated and senescent T cells have been linked to cancer risk and outcomes in HIV uninfected persons but there has been limited study of T cell subset alterations and cancer development unique to PLWH. We therefore aimed to determine whether the proportions of these T cell phenotypes predicted the incidence of non-AIDS cancers that have been associated with responses to immunotherapy (lung, anus, kidney).
Methods: We used longitudinal data from 1,429 PLWH and 765 uninfected persons from the Veterans Aging Cohort Study Biomarker Cohort linked to VA cancer registry data to identify 75 incident lung, anus, and kidney cancers (the most common cancers arising in the cohort with known immunotherapy link). Subjects were followed from enrollment (2005-2006) until cancer incidence, death or were censored on 9/31/2017 (10 years of median follow-up). We measured the proportion of seven subpopulations of T cells, including Tregs (CD4+CD25+FOXP3+), activated (CD4+CD38+ and CD8+CD38+) and senescent (CD4+CD28-, CD4+CD57+, and CD8+CD28-, CD8+CD57+) CD4 and CD8 phenotypes. We used Cox proportional hazard regression to model associations between these immune cells and the risk of cancer while adjusting for age, sex, race/ethnicity and smoking status.
Results: The cohort was mostly male (95%) of median age 52 years. PLWH accounted for the majority (75%) of the cancer cases. Among PLWH, lower overall CD4 count was associated with greater proportions of Tregs, senescent CD4 and activated CD8 phenotypes. Of the included T cell subpopulations, greater proportions of circulating Tregs were significantly associated with increased incidence of the combined group of lung, anus and kidney cancers for the overall combined cohort and for PLWH only (see Table). Alterations in the proportion of subsets of CD4 and CD8 cells expressing markers of senescence or activation were not significantly associated with cancer risk during follow-up.
Conclusion: Among PWH increased circulating Tregs as a proportion of CD4 cells were associated with increased risk of lung, anus and kidney cancers. Correlation of these findings with the precancerous tumor microenvironment may provide greater insight into the role of HIV infection as an increased risk for some cancers.

Table. Adjusted regression models measuring the association of proportion of T cell subsets and cancer incidence

Cell Subset (Phenotype)	All Subjects Hazard Ratio* per SD increase (95% CI)	Persons with HIV Hazard Ratio* per SD increase (95% CI)	Uninfected Hazard Ratio* per SD increase (95% CI)
CD4+CD25+FOXP3+ (Tregs)	1.24 (1.03-1.48)	1.25 (1.03-1.51)	1.14 (0.58-2.24)
CD4+CD38+ (activation)	1.22 (0.95-1.57)	1.23 (0.93-1.63)	1.04 (0.56-1.93)
CD4+CD57+ (senescence)	0.93 (0.73-1.2)	0.96 (0.73-1.26)	0.76 (0.41-1.43)
CD4+CD28- (senescence)	1.00 (0.77-1.29)	1.02 (0.78-1.33)	0.80 (0.36-1.76)
CD8+CD38+ (activation)	1.11 (0.88-1.4)	1.2 (0.93-1.55)	0.75 (0.42-1.35)
CD8+CD57+ (senescence)	0.92 (0.72-1.16)	0.9 (0.68-1.19)	0.94 (0.6-1.47)
CD8+CD28- (senescence)	1.02 (0.79-1.31	0.99 (0.74-1.33	1.06 (0.63-1.77)

*Hazard of lung, anus or kidney cancer; adjusted for age, sex, race/ethnicity and smoking status

633 TET2 SNPs AND RISK OF CANCER IN THE START, SMART, AND ESPRIT COHORTS

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Background: Previously we have identified two groups of SNPs in the TET2 gene associated with either higher or lower HIV Viral Load (VL). These results indicated that TET2 is involved in HIV replication and the identified SNPs alter TET2 in a way that impacts that function. As TET2 also plays a role in cancer development, as a tumor suppressor gene, we hypothesized that these SNPs would also impact that function. To test this, we performed a targeted association analysis between VL-associated SNPs and risk of cancer across INSIGHT network cohorts.
Methods: We assessed associations between the 36 previously identified TET2 VL-associated SNPs with incidence of cancer (any type) in the START (NCT00867048), SMART (NCT00027352) and ESPRIT (NCT00004978) cohorts, using Cox regression models adjusting for age, gender, study arm and race (using the first 4 eigenvectors). Only SNPs with minor allele frequency (MAF) > 1% were included in the analyses. P-values are shown unadjusted and adjusted using the max(T) permutation test (10000 permutations), which accounts for correlations amongst the SNPs.
Results: In SMART, 60 (2.6%) pts were diagnosed with cancer during follow-up. Two SNPs, rs6811468 (HR=2.79, CI=1.41-5.53, p=0.003, adjusted p (Ap)=0.03) and rs72955158 (HR=3.24, CI=1.29-8.11 p=0.012, Ap=0.09) were associated with risk of cancer; the number of cancer events in pts with 0, 1 and 2 risk alleles of rs6811468 was 52/2141 (2.4%), 6/125 (4.8%) and 2/4 (50%), respectively. All 6 cancers associated with rs72955158 in SMART occurred in pts who also had rs6811468. In START, 38 participants (pts) (1.5%) were diagnosed with cancer during follow-up. One SNP, rs6811468 (HR=4.50, CI=1.14-17.76, p=0.03, Ap=0.19), was associated with risk of cancer; the number of cancers in pts with 0, 1 and 2 risk alleles of rs6811468 was 35/2412 (1.5%), 3/109 (2.8%) and 0/2 (0%), respectively. In ESPRIT, a total of 110 pts had cancer. No SNPs were associated with cancer in ESPRIT. Rs72955158 in START and both rs6811468 and rs72955158 in ESPRIT had MAF <1% and were not assessed in these cohorts. Rs6811468 associated cancers were primarily solid tumors (10/11) seen in persons of black ethnicity, with lung (n=3) and prostate (n=4) the most common cancer sites.
Conclusion: One SNP, rs6811468, was associated with consistent elevated risk of cancer in two independent HIV+ cohorts. This finding requires additional studies to confirm these results and determine whether the effect is independent of perturbed VL.

634 NEXT-GENERATION SEQUENCING TO PROFILE CANCER-RELATED GENES IN HIV+ PATIENTS

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Background: Check-point inhibitors and other antitumor drugs have become a cornerstone in cancer treatment. Now it is very important to profile cancer-related genes to understand which could be the most active drug in a specific tumor. Recently, a novel test based on massively parallel DNA sequencing to characterize base substitutions, short insertions and deletion, copy number alterations and selected fusions became available. Aim of our study was to evaluate, for the first time in HIV positive patients with cancer, the use of FoundationOne CDx, a new next-generation sequencing based assay (NGS) that identifies genomic findings within hundreds of cancer-related genes.
Methods: FoundationOne CDx, that analyzes genomic changes in 324 genes of relevant importance for tumor cells, was used on stored clinical samples that were formalin-fixed and paraffin-embedded.
Results: We analyzed 10 samples: type of cancer, genomic signatures, gene alterations and possible treatments are described in Table 1. Only one patient showed an high microsatellite instability, that suggests the possible use of check-point inhibitors. Among the 4 patients with kidney renal papillary carcinoma, gene alteration profile was markedly different, so potentially the

treatment has to be individualized, and not given on the basis of this cancer type only. Other gene alterations were present in the rest of the patients, that could thus become a possible target for check-point inhibitors or for other anti-tumor drugs, such as mTOR or tyrosine kinase inhibitors, even if these drugs are not registered or studied in these specific cancers. During the follow-up, however, none of the patients received any of these potentially active drugs.

Conclusion: FoundationOne CDx could give relevant information on treatment strategies in subjects with cancer and HIV infection, so becoming an important tool in personalized medicine. Indeed, the study of genomic signatures and gene alterations could indicate also in HIV+ patients with cancer (and not only on the basis of tumor type) the possible use of check-point inhibitors or eventually of other anticancer drugs that are registered for that specific cancer or for other cancer types.

Type of Cancer	Genomic signatures	Therapy for this tumor or clinical trials	Therapies approved for other tumors but possibly active	Gene alterations	Therapies for this tumor or clinical trials	Therapies approved for other tumors but possibly active
Head and neck squamous cells carcinoma	Microsatellite status: Stable Tumor mutation burden: low	None None		FBXW7 RICTOR	None None	Everolimus Temsirolimus None
Head and neck squamous cells carcinoma	Microsatellite status: high Tumor mutation burden: low	Nivolumab Pembrolizumab	Atezolizumab Avelumab Durvalumab	ARID1A CDKN2C TO53	None	None
Cervix squamous cell carcinoma	Microsatellite status: Stable Tumor mutation burden: low	None None		PTEN	None	Everolimus Temsirolimus
Lung non-small cell lung carcinoma	Microsatellite status: Stable Tumor mutation burden: intermediate	None Atezolizumab Durvalumab Nivolumab Pembrolizumab	Avelumab	HGF-amplification-equivocal MDM2 amplification-equivocal NRAS	None None Trametinib	None None Binimetinib Cobimetinib
Kidney renal papillary carcinoma	Microsatellite status: Stable Tumor mutation burden: low	None None	None None	BRD4	None	None
Kidney renal papillary carcinoma	Microsatellite status: Stable Tumor mutation burden: low	None None	None None	None		
Kidney renal papillary carcinoma	Microsatellite status: Stable Tumor mutation burden: low	None None	None None	TPS3	None	None
Kidney renal papillary carcinoma	Microsatellite status: Stable Tumor mutation burden: low	None None	None None	PBRM1	Nivolumab	Pembrolizumab
Breast invasive ductal carcinoma	Microsatellite status: Stable Tumor mutation burden: low	One None	None None	FGFR1 FLT3 PIK3CA	None None Everolimus	Pazopanib Ponatinib Ponatinib Sorafenib Sunitinib Temsirolimus
Liver hepatocellular carcinoma	**Microsatellite status: Stable Tumor mutation burden: low**	None None	None None	PIK3CA	None	Everolimus Temsirolimus

635 HOST GLYCOMIC DETERMINANTS OF CORONARY ATHEROSCLEROSIS DURING TREATED HIV INFECTION

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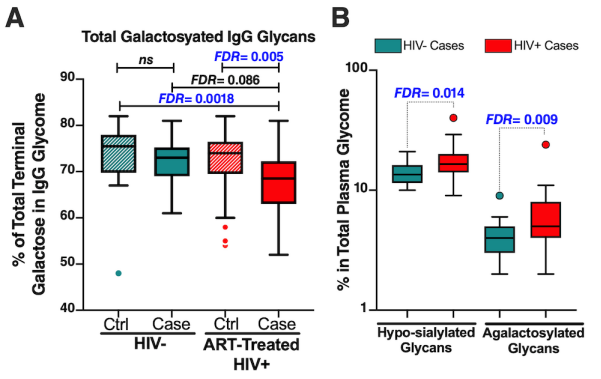
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Background: HIV-induced inflammation is associated with accelerated atherosclerosis, even after virally suppressive antiretroviral therapy (ART). In the general population, host glycomic alterations, in particular, loss of galactose and sialic acid on circulating glycoproteins (including IgG) drive inflammation and are associated with premature aging. Whether glycomic alterations contribute to the development of coronary atherosclerosis during HIV infection remains unknown.

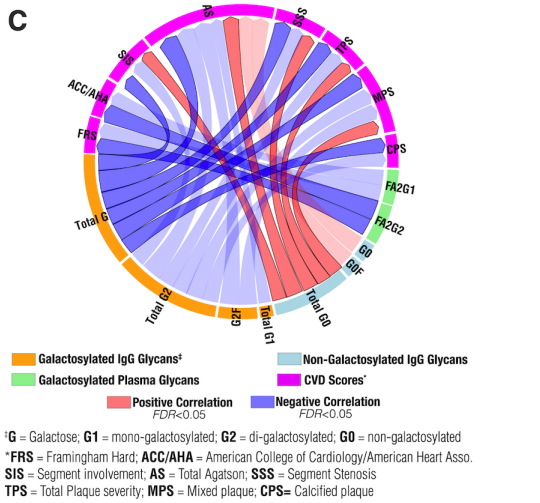
Methods: We designed a case-control study within the Multicenter AIDS Cohort Study (MACS); cases had coronary stenosis ≥50% in one or more coronary segments and controls had no coronary plaque (by CT angiography). We used a 1:1 nearest neighbor matching algorithm to select 34 HIV+ ART+ men cases / 34 HIV+ ART+ controls, and 22 HIV- men cases / 22 HIV- controls. Median Framingham Risk Score (FRS) was similar between HIV+ cases and controls (7 vs 6, p=0.8), but different between HIV- cases and controls (11 vs 7, p=0.01). Capillary electrophoresis was used to profile plasma and IgG glycomes. Kruskal-Wallis, Mann–Whitney, and Spearman's rank tests were used for statistical analyses. False discovery rates (FDR) were calculated to account for multiple comparisons.

Results: Levels of the anti-inflammatory galactosylated glycans were lower in the IgG of HIV+ cases compared to HIV+ controls (FDR=0.005; Fig. 1A). Consistently, levels of the pro-premature-aging agalactosylated glycans were higher in HIV+ cases compared to HIV+ controls (FDR<0.02). These differences were not observed between HIV- cases and HIV- controls. We also found that levels of the pro-inflammatory hypo-sialylated and agalactosylated glycans were higher in the plasma of HIV+ cases compared to HIV- cases (FDR<0.01; Fig. 1B). Examining the links between galactosylation and risk/degree of cardiovascular disease (CVD), we found that levels of several IgG and plasma galactosylated glycans associated with lower CVD scores, including FRS, segment stenosis, and plaque severity; whereas levels of agalactosylated glycans associated with higher scores (FDR<0.05; Fig. 1C).

Conclusion: Premature-aging-associated glycomic dysregulation, in particular, agalactosylation and hyposialyation, are more evident among HIV+ ART+ individuals (compared to all other groups) and are associated with the prevalence and degree of subclinical atherosclerosis. Potential HIV-promoted glycomic pathways fostering CVD warrant further investigation to examine their prognostic and functional significance.



Panel C: Circus plot highlighting the correlations between IgG and plasma glycans and CVD scores. Correlations between CVD scores and **1)** total galactosylated IgG glycans (Total G), **2)** agalactosylated IgG glycans (Total G0), and **3)** galactosylated plasma glycans (FA2G2) are highlighted.



‡**G** = Galactose; **G1** = mono-galactosylated; **G2** = di-galactosylated; **G0** = non-galactosylated
*__FRS__ = Framingham Hard; **ACC/AHA** = American College of Cardiology/American Heart Asso.
SIS = Segment involvement; **AS** = Total Agatson; **SSS** = Segment Stenosis
TPS = Total Plaque severity; **MPS** = Mixed plaque; **CPS=** Calcified plaque

636 ADVANCED GLYCATION END PRODUCTS ASSOCIATED WITH CARDIOMETABOLIC RISK ON ART

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Background: Advanced glycation end products (AGEs) are products of normal aging and are involved in the progression of different conditions such as diabetes and atherosclerosis. AGEs were recently found to be higher in people with HIV compared to uninfected controls. The effect of antiretroviral therapy (ART) on AGEs and its role in cardiometabolic complications in this population remains unknown.

Methods: In ACTG A5260s, a substudy of A5257, we compared changes in serum levels of different AGEs (methylglyoxal hydroimidazolone (MG-H1), carboxymethyl and carboxyethyl lysine (CML and CEL), 3-deoxyglucosone hydroimidazolone (3DGH), and glyoxal hydroimidazolone (GH-1)) in ART-naïve participants with HIV randomized to tenofovir disoproxil fumarate-emtricitabine (TDF/FTC) plus atazanavir-ritonavir (ATV/r), darunavir-ritonavir (DRV/r), or raltegravir (RAL) for 96 weeks. Linear regression models were used to study the associations between serum AGEs, and cardiometabolic outcomes of carotid intima median thickness (cIMT), visceral and subcutaneous adipose tissue (VAT and SAT), total fat, lean mass, BMI, homeostatic modal assessment – insulin resistance (HOMA-IR), leptin, and adiponectin, while adjusting for potential baseline confounders (age, sex, race, HIV-1 RNA, CD4+ T cell count, smoking, illicit drug use, alcohol use, and physical activity).

Results: 214 participants were included; 90% male, 48% white, non-Hispanic, with median age of 36 yrs, HIV-1 RNA 4.58 $\log_{10}$ copies/mL, and CD4 count 338 cells/μL. Most AGEs increased following 96 weeks of ART initiation, but only MG-H1 levels were significantly higher at week 96 (mean fold change of 1.15, 95% CI [1.02, 1.30]), with no differences between arms At baseline, AGEs were positively associated with HOMA-IR, even after confounder adjustment. At week 96, additional associations emerged between various AGEs and cIMT, VAT, SAT, total fat, leptin and adiponectin, even after adjusting for confounders. A two-fold increase in MG-H1 over 96 weeks was independently associated with 0.1 $\log_{10}$ increase in HOMA-IR (95% CI: [0.05, 0.12]), 0.5% increase in cIMT (95% CI [0, 0.9]), and 0.7% increase in lean mass (95% CI [0.1, 1.2]).

Conclusion: Initiation of ART seems to increase levels of AGEs in ART-naïve participants with HIV, regardless of regimen used. Accumulation of AGEs is independently associated with subsequent cardiometabolic risk while on ART.

637 SINGLE-CELL TRANSCRIPTOMICS OF HIV HEART TISSUE IDENTIFIES UNIQUE NK CELL POPULATION

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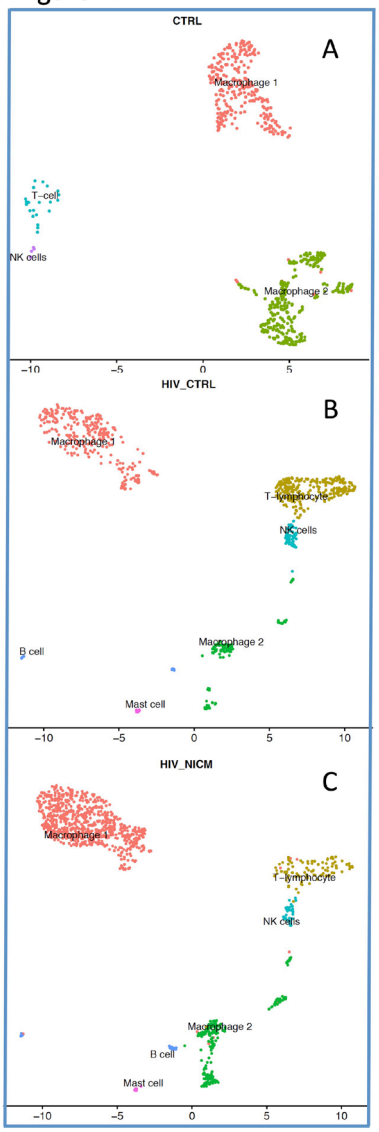
Background: Cardiovascular disease, in particular heart failure, is elevated among people living with HIV (PLWH) though the etiology of this disease process remains unclear. Using single cell RNA-seq approaches, we interrogated the spectrum of cell types and their gene expression in heart tissue from PLWH to further elucidate the underlying pathogenesis of HIV-associated heart disease.

Methods: Left ventricle tissue samples were obtained from 3 participants: 1) HIV uninfected without heart failure (CTRL); 2) HIV infected without heart failure (HIV_CTRL); 3) HIV infected with non-ischemic heart failure (HIV_NICM). Both PLWH donors were virally suppressed on therapy at the time of biopsy. Samples were immediately flash frozen in liquid nitrogen at collection. Nuclei were subsequently isolated from frozen tissue and processed for single-nuclear RNA-sequencing using the 10X Chromium platform. Clustering was performed using Seurat 3.0.

Results: Single nuclear transcriptomic data were obtained from 9008, 8746 and 8176 nuclei for CTRL, HIV_CTRL and HIV_NICM samples respectively. Cluster analysis was performed and clusters expressing high PTPRC (CD45+) were selected for further analysis. CD45+ cells were re-clustered and natural killer (NK) cells were identified using markers NCAM1 (CD56), Granulysin (GNLY), TBX21 and NKG7. NK cells expressed additional markers including Killer Cell Lectin Like Receptor C1 (KLRC1) and Killer Cell Lectin Like Receptor D2 (KLRD2) compared to T-lymphocytes (p-adj <10-17 and <10-7 respectively). Figure 1 shows cluster allocation for CD45+ cells from the 3 samples (panel A – CTRL, panel B – HIV_CTRL, panel C – HIV_NICM). As a proportion of all CD45+ cells, NK cells comprised 0.7%, 8.4% and 3.0% for samples CTRL, HIV_CTRL and NICM_CTRL respectively (p<0.001).

Conclusion: This study found a unique NK cell population in cardiac tissue from two PLWH compared to a person without HIV. Dysregulation of the immune system, including NK cells, has been associated with cardiac fibrosis, myocarditis and cardiac transplant rejection in the HIV uninfected population. This is the first study to our knowledge to apply single cell transcriptomics to evaluate the underlying mechanisms of HIV-associated cardiovascular disease. The direct impact of HIV, immune activation and NK cells on cardiomyocytes and heart failure merits additional investigation in larger studies.

Figure 1:



638 CAROTID PLAQUE BURDEN IN HIV IS ASSOCIATED WITH SOLUBLE MEDIATORS AND MONOCYTES

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Background: Maximal carotid plaque thickness (MCPT) is the measure of the largest plaque thickness in the carotid artery and reflects atherosclerotic plaque burden. MCPT may be a better predictor of cardiovascular disease (CVD) and cerebral vascular accidents (CVA) than cIMT because it identifies potential unstable arterial atherosclerotic plaques. We assessed relationships of monocyte (MO) and T-cell populations and soluble mediators in blood and MCPT.

Methods: Cross-sectional and longitudinal analysis of a cohort study of CVD risk in HIV-infected participants aged > 40 years on stable antiretroviral therapy (ART) > 6 months. High resolution B-mode ultrasound images of the

right carotid artery were obtained to assess maximal carotid plaque thickness at baseline and year 2. Peripheral blood mononuclear cells (PBMCs) were phenotyped by flow cytometry for MO subsets [classical MO (CD14++CD16-), intermediate (CD14++CD16+), non-classical (CD14low/+CD16++)] and T-cell (CD38+HLA-DR+) activation at baseline. Soluble biomarkers sE-selectin, sVCAM-1, sICAM-1, MMP-9, MPO, PAI-1, CRP, SAA, SAP, IL-1β, IL-6, IL-8, IL-10, TNF-α, MCP-1, VEGF, IFN-γ, NT ProBNP and Apolipoproteins were measured by Luminex technology. Variables were transformed using Log_{10}-transformation. Spearman correlation and multivariable regression were used for statistical analysis to identify factors associated with MCPT.

Results: We studied 125 HIV+: 85% male, 58% Caucasian, with a median age of 51, median CD4 count was 477 cells/μL (Q1: 325, Q3: 612), 86% undetectable HIV viral load. MCPT correlated with non-classical monocyte (r=.451, p=.046), MCP-1 (r=.487, p=.016), TNFα (r=.474 p=.019), sVCAM1 (r=.472, p=.020), ApoB6 (r=-.473, p=.019) and IL-6 (r=.455, p=.025). In a multivariable regression model, MCP-1, TNFα, and sVCAM1 remained significant even after adjustment for age. Longitudinal analysis of 15 HIV+ participants with two MCPT assessments revealed no correlation with types of ART; lipid lowering, hypertensive and antiplatelet medications; or illicit drug use.

Conclusion: Worsening carotid plaque burden is associated with increased non-classical monocytes and inflammatory markers. Changes in MCPT were not associated with anti-lipid therapy.

	MCPT Baseline*		MCPT Baseline, Adjusted with Age**	
Parameters	Correlation Coefficient (r)	P-value	Regression Coefficient (B)	P-value
MCP1	.487	.016	.455	.016
TNFα	.474	.019	.224	.030
sVCAM1	.472	.020	.719	.009
Nonclassical Monocyte	.451	.046	.239	.137
ApoB6	-.473	.019	-.129	.211
IL6	.455	.025	.051	.485

Further investigation into changes in monocyte and inflammatory cytokines on plaque burden is warranted.

* Spearman Correlation
** Multivariable linear regression

639 INCREASED LEUKOCYTE/PLATELET INTERPLAY WITH ENDOTHELIUM IN ABC-TREATED HIV PATIENTS

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Background: Abacavir (ABC) has been associated with a risk of myocardial infarction. We have demonstrated experimentally that clinical concentrations of ABC added in vitro, but not of tenofovir disopropil fumarate (TDF), have pro-inflammatory (it induces leukocyte-endothelium interactions) and pro-thrombotic (it causes the interplay of platelets with endothelial cells or leukocytes) actions. Furthermore, ABC promoted thrombus formation in a well-established in vivo model. The aim of the present study was to test the pro-inflammatory and pro-thrombotic status of HIV patients undergoing ABC versus TDF treatment by analysing leukocyte- and/or platelet-endothelium interactions in cells isolated from blood of these two groups of HIV patients.

Methods: This is a non-aleatorized prospective observational study in which we used blood cells from HIV-patients at Hospital Clínico Universitario de Valencia who had been receiving treatment, for at least 6 months, with a ART regime that included either ABC or TDF. Interactions of isolated leukocytes (peripheral blood mononuclear cells, PBMC) – rolling and adhesion - and isolated platelets – adhesion - with a non-infected endothelium monolayer were evaluated by means of a parallel-plate flow chamber system. Platelets were labelled with an anti-CD41 (specific platelet marker) antibody linked to Alexa-Fluor®488 in order to visualize them by Epi-fluorescence microscopy.

Results: 39 patients were included in the study, 18 of whom were receiving ABC and 21 of whom were receiving TDF. There were no significant differences in demographic and cardiovascular risk parameters between the two groups. PBMC rolling (Figure 1A) and adhesion (Figure 1B) along the endothelium were significantly higher in the ABC group than in the TDF group. Moreover, the number of platelets adhering to endothelial cells was higher in the ABC versus TDF group (Figure 1C).

Conclusion: Treatment with ABC enhances PBMC-endothelium interactions, thus promoting the initial phases of the inflammatory process. Furthermore, it induces platelet adhesion to endothelial cells, which is an important step in thrombus formation. Our results give support to the increased risk of myocardial infarction observed in ABC-treated HIV patients.

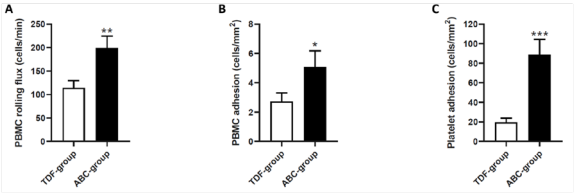


Figure 1: Effects of ABC on leukocyte-endothelium and platelet-endothelium interactions in HIV-infected patients. Peripheral blood mononuclear cells (PBMC) and platelet interactions with the endothelium were evaluated by employing a parallel-plate flow chamber system. Suspensions of leukocytes or platelets from TDF-treated (n=21) and ABC-treated (n=18) HIV patients, were drawn across a human endothelial monolayer. To visualize platelets, they were labelled with anti-CD41-Alexa®488 antibody. Images were recorded by an inverted microscope (Nikon Eclipse TE 2000-S, 40x) equipped with an Epi-fluorescence system and analysed by counting the number of cells (leukocytes or platelets) interacting with the endothelium. **(A)** PBMC rolling flux, **B)** PMBC adhesion and **(C)** Platelet-endothelium interactions. Results are mean ± SEM. *p<0.05 , **p<0.01 or ***p<0.001 vs. corresponding value in the TDF group (Unpaired t test with Welch's correction).

640 FIBROBLAST GROWTH FACTOR 21: EFFECT OF HIV THERAPY AND ASSOCIATION WITH CVD RISK

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Background: Fibroblast growth factor 21 (FGF21) is a pleiotropic signal molecule for several metabolically active organs. The liver releases FGF21 in response to a broad range of stress conditions resulting in beneficial effects on glucose, lipid and energy homeostasis. FGF21 may be part of a compensatory response to offset atherosclerosis in certain disease states. People with HIV (PWH) are at heightened risk for cardiovascular disease (CVD). Whether FGF21 is modified by antiretroviral therapy (ART) or could serve as a marker for subclinical atherosclerosis in PWH is not known.

Methods: Fasting plasma FGF21 concentrations were quantified by ELISA from ART-naïve HIV+ adults enrolled in a longitudinal study of carotid intima media thickness (IMT) progression and in ART-treated HIV+ adults matched by sex, race and body mass index (BMI) at entry (all participants), and weeks 48 and 96 (those who initiated ART at entry). Multivariable linear regression and mixed effects linear modeling were used to explore associations between ART status, FGF21 and common carotid artery (CCA) IMT at entry and over time.

Results: 162 participants (81 ART-naïve; 81 ART-treated) were included. Groups were similar except ART-treated were older (median 48 vs 41; p<0.01) had higher waist-to-hip ratio (0.96 vs 0.92; p=0.03) and HOMA-IR (2.4 vs 1.4) and lower nadir CD4+ count (191 vs 388 cells/mm_3). Overall, 80% were men; 63% were black; 52% were current smokers. Of those on ART, 60% were on an NNRTI, 36% on a PI, and all had HIV-1 RNA <20 copies/ml. FGF21 was higher in ART-treated (218 vs 166 pg/ml; p=0.01), but adjusting for age, waist-to-hip ratio, glucose or nadir CD4+ count attenuated the association. Older age, white race, current smoking, higher glucose, waist-to-hip ratio and interleukin-6 (IL6) were independently associated with higher entry FGF21. In those who initiated ART (n=51), regardless of ART class, FGF21 levels did not change significantly over 96 weeks (p=0.55). Unadjusted, entry FGF21 was positively associated with entry CCA IMT (p=0.02); however, adjusting for age, waist-to-hip ratio, or inflammation (IL-6 or soluble tumor necrosis factor alpha receptor-1) attenuated the association. Entry FGF21 tended to predict CCA IMT progression (p=0.08), but again the association was attenuated with adjustment for age or waist-to-hip ratio.

Conclusion: FGF21 concentrations are not decreased after successful ART, and although closely associated with traditional CVD risk factors, FGF21 did not independently predict IMT progression on ART.

641 MONOCYTE ACTIVATION AND CARDIAC-MRI–DERIVED VASCULAR DYSFUNCTION AMONG WOMEN WITH HIV

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Background: Women with HIV (WHIV) on ART face an increased risk of cardiovascular disease (CVD), including heart failure. Aortic vascular dysfunction, reflected by increased aortic pulse wave velocity (aPWV), presages, predicts, and promotes adverse CVD outcomes. Moreover, aortic vascular dysfunction – a proxy for vascular aging – is highly influenced by the local inflammatory milieu. Comparisons of aortic vascular function among predominantly male cohorts with vs. without HIV have yielded conflicting

results. Cognizant of sex-specific patterns of HIV-associated immune dysregulation, we compared aPWV among asymptomatic ART-treated women with vs. without HIV. We hypothesized that WHIV would evidence vascular dysfunction in association with monocyte activation.

Methods: 20 WHIV and 14 matched women without HIV underwent cardiac MRI, as well as metabolic and immune phenotyping. Women with a history of CVD, diabetes, or significant kidney disease were excluded.

Results: Women with vs. without HIV had comparable age (52 vs. 53 years) and BMI (32 vs. 32 kg/m$_2$). WHIV exhibited heightened systemic monocyte activation, reflected by increased levels of sCD163 (1260 vs 938 ng/mL, P=0.005). Among WHIV, duration of HIV was 19±8 years, CD4 count was 773 (526,1202) cells/mm$_3$ and viral load was 19 (19,19) copies/mL. aPWV was higher among women with vs. without HIV (8.6±1.3 vs 6.5±1.3 m/s), P<0.0001; Fig. 1A). Among the whole group and each sub-group, aPWV did not relate to age, BMI, cigarette smoking burden, or SBP. Among the whole group and among WHIV, aPWV related to sCD163 levels (whole group: R=0.65, P<0.0001; WHIV: R=0.73, P=0.0003; Fig. 1B). Among the whole group and among WHIV, aPWV also related to extracellular volume – a measure of myocardial fibrosis (whole group: R=0.54, P=0.001; WHIV: R=0.47, P=0.04). Both HIV status and sCD163 levels independently predicted aPWV, even after controlling for age, BMI, cigarette smoking status, and SBP (R2=0.63, P=0.0002; HIV status: P=0.02; sCD163: P=0.01). Among WHIV, sCD163 levels independently predicted aPWV after controlling for duration of HIV, CD4 count, and HIV viral load (R2=0.62, P=0.007; sCD163: P=0.0005).

Conclusion: Asymptomatic ART-treated WHIV demonstrated increased aPWV. Among WHIV, aPWV related to heightened monocyte activation as well as to downstream CVD pathology. Additional studies are needed to identify targeted immune-modulatory therapies which slow the progression from vascular dysfunction to incident CVD in this at-risk population.

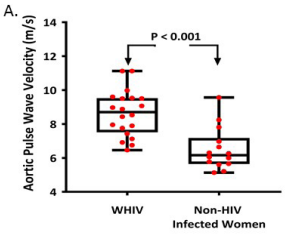


Figure 1a. Aortic pulse wave velocity among women with vs. without HIV
Aortic pulse wave velocity was significantly higher among women with HIV (WHIV) vs. women without HIV. [Data are graphically shown as median (interquartile range). Abbreviations: WHIV, women with HIV.]

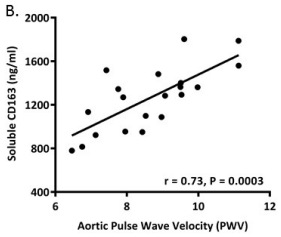


Figure 1b. Relationship between aortic pulse wave velocity and systemic monocyte activation among women with HIV (WHIV)
Among WHIV, aortic pulse wave velocity related directly to a marker of systemic monocyte activation, soluble CD163.

642 TESTOSTERONE THERAPY AND SUBCLINICAL ATHEROSCLEROSIS PROGRESSION AMONG MEN WITH HIV

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Background: Testosterone therapy (TTh) use is highly prevalent among middle-aged and older men with HIV (MWH) in the United States, but its cardiovascular safety is unclear. We assessed progression of subclinical coronary artery disease by TTh use status among MWH in the Multicenter AIDS Cohort Study (MACS).

Methods: MWH in the MACS CVD sub-study in 4 U.S. cities from 2010-17 were included, each of whom underwent two coronary CT angiography (CCTA) measurements 4.5±0.7 years apart. Inclusion criteria were age 40-70 without coronary intervention or kidney dysfunction. TTh use was self-reported semi-annually, and classified as never, prior to baseline CCTA (former), after baseline CCTA (new), or both (consistent). We evaluated associations between TTh and progression of subclinical atherosclerosis, specifically 1)coronary artery calcium (CAC), 2)total plaque volume, and 3)noncalcified plaque volume. CAC progression was defined by incident CAC if baseline CAC=0, ≥10 Agatston unit/yr increase if baseline CAC=1-100, and ≥10%/yr increase if baseline CAC>100, and analyzed by robust Poisson regression. Progression was defined by the upper tertile of annualized change in total and noncalcified plaque volume, using multinomial logistic regression. Regression models adjusted for demographic, cardiovascular risk, and HIV-related clinical factors, and baseline serum testosterone.

Results: Median age among the 300 MWH was 51 years, 48% were white, 41% were in the ASCVD high risk category, 91% were on antiretroviral therapy, and 81% had undetectable HIV viral load (<20 copies/mL). TTh trajectories were: 70% never, 8% former, 7% new, and 15% consistent use. Median total testosterone was 606 ng/dL (IQR=445,808). Adjusting for age, race, testosterone<300 ng/dL, and cardiovascular and HIV cofactors, the risk of significant CAC progression was 2.0 times greater among continuous users (p=0.03) and 2.4 times greater among new users (p=0.01) relative to former users. We observed a similar trend for total and noncalcified plaque volume progression, but these estimates were not statistically significant (Table).

Conclusion: MWH who continued or started TTh were twice as likely as former users to experience significant CAC progression over 4 years. To our knowledge, this is the first contemporary study of cardiovascular outcomes associated with TTh use among MWH; additional observational data should be leveraged to further elucidate the potential health implications of TTh use among MWH.

Estimated and observed measures of association for coronary artery calcium score, total plaque volume, and noncalcified plaque volume measured 4.5±0.7 years apart, by history of testosterone therapy among men with HIV

	Testosterone therapy use			
	New (n=21)	Consistent (n=44)	Former (ref) (n=24)	Never (n=211)
Coronary artery calcium score				
Baseline, median (IQR)	4 (0, 103)	11 (0, 113)	1 (0, 57)	0 (0, 51)
Crude annualized change, median (IQR)	6 (0, 31)	10 (0, 23)	1 (0, 7)	1 (0, 13)
Adjusted[1] relative risk of significant CAC progression[2] (p-value)	2.4 (0.01)	2.0 (0.03)	ref	1.7 (0.07)
Total plaque volume, mm^3				
Baseline, median (IQR)	45 (0, 122)	55 (16, 203)	32 (6, 167)	27 (0, 96)
Crude annualized change, median (IQR)	17 (3, 25)	13 (4, 24)	7 (1, 17)	7 (0, 23)
Adjusted[1] odds ratio for the 3rd tertile progression[3] [18-340mm^3/year] (p-value)	4.2 (0.15)	1.3 (0.74)	ref	2.0 (0.36)
Noncalcified plaque volume, mm^3				
Baseline, median (IQR)	30 (0, 73)	45 (13, 180)	26 (6, 108)	23 (0, 79)
Crude annualized change, median (IQR)	5 (2, 16)	8 (2, 17)	6 (0, 14)	5 (0, 18)
Adjusted[1] odds ratio for the 3rd tertile progression[3] [13-217 mm^3/year] (p-value)	3.9 (0.13)	2.1 (0.34)	ref	1.3 (0.69)

[1] Adjusted regression models included age, race, pack years of smoking between CT scans, average systolic blood pressure, total and HDL cholesterol, fasting glucose, and CD4 cell count in the interscan interval, use of medications for hypertension, cholesterol, or diabetes at ≥20% of interscan visits, undetectable HIV viral load over the interscan interval, and baseline serum testosterone levels. [2] Significant CAC progression was defined by the Berry criteria, where F=follow-up scan and b=baseline scan: 1) $CAC_F>0$ if $CAC_b=0$, 2) CAC_F $CAC_b \geq 10$/yr if $CAC_b=1$-100, or 3) (CAC_F CAC_b)/ $CAC_b \geq 10$/yr if $CAC_b>100$ [3] Plaque outcomes were annualized to adjust for interscan intervals prior to the generation of tertiles, and regression models included baseline levels of total or noncalcified plaque.

643 POSTDISCHARGE OUTCOMES FOLLOWING ACUTE CORONARY SYNDROME IN HIV

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Background: HIV-infected individuals are at increased risk of cardiovascular death. Most of this risk can be attributed to ischemic heart disease. Differences in the management of HIV-infected patients following hospitalization for acute coronary syndromes (ACS) may contribute to worsened outcomes in this population. We hypothesized that HIV-infected individuals have higher rates of mortality following discharge, and receive sub-optimal medical management compared with uninfected individuals.

Methods: This was a retrospective cohort study using data from Symphony Health, a nationwide data warehouse. All adults admitted between January 1st, 2014 and December 31st, 2016 with ACS were included, and their characteristics and outcomes were defined by ICD-9 and 10 diagnostic codes.

Results: A total of 1,125,126 patients were included, of whom 6,612 (0.59%) had HIV. The HIV-infected group was younger (57 vs 67 years old, p<0.0001), and had a higher burden of comorbidities such as diabetes, renal disease and substance use (p<0.0001). The type of ACS did not differ significantly between groups. The HIV-infected group had higher adjusted 30-day all-cause readmissions (14.3% vs 9.4%, OR 1.23, 95% CI 1.14-1.33, p<0.0001) and 1-year mortality (5.6% vs 5.1%, OR 1.34, 95% CI 1.2-1.5, p<0.0001). In the 12 month post-discharge period, the HIV+ group filled core cardiac medications such as statins (66.8% vs 73.7%, p<0.0001), beta blockers (67.9% vs 73.9%, p<0.0001), nitrates (31.8% vs 35.9%, p<0.0001) and antiplatelet agents (46.8% vs 51.8%, p<0.0001) at lower rates.

Conclusion: Following treatment for ACS, HIV-infected individuals are less likely to be taking guideline-recommended medical therapy and have worsened

clinical outcomes compared to uninfected individuals. Optimizing use of medical therapy and longitudinal care of this high risk group is greatly needed.

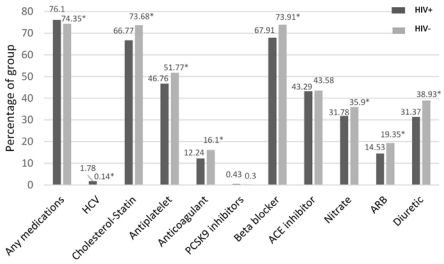


Figure 1: 12 month discharge medication prescription filling for HIV+ vs HIV- adults. HCV = hepatitis C, ACE = angiotensin-converting-enzyme, ARB = angiotensin II receptor blocker. * = p <0.05

644 INSOMNIA AND RISK OF INCIDENT MYOCARDIAL INFARCTION AMONG PEOPLE LIVING WITH HIV

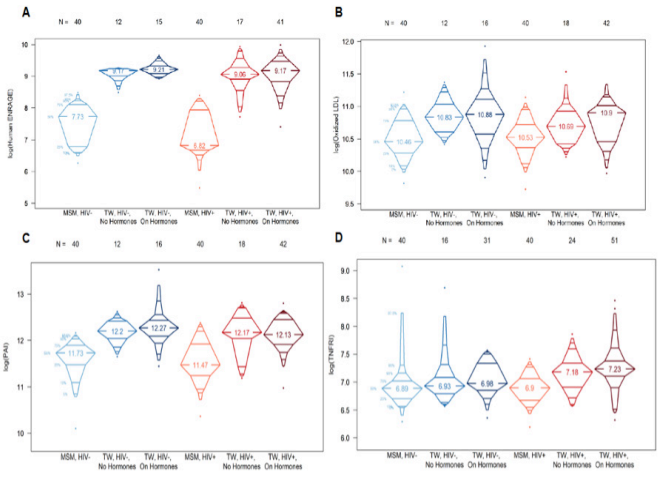
Bridget M. Whitney[1], Robin M. Nance[1], Joseph Delaney[2], Stephanie A. Ruderman[1], Matthew Budoff[3], W. C. Mathews[4], Richard D. Moore[5], Matthew J. Feinstein[6], Greer Burkholder[7], Michael J. Mugavero[7], Joseph J. Eron[8], Michael Saag[7], Mari M. Kitahata[1], Heidi M. Crane[1], for the CNICS Cohort
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Background: Current research suggests that people living with HIV (PLWH) suffer from a substantially higher burden of sleep disturbances, including insomnia, compared to the general population. Insomnia is associated with increased risk of cardiovascular disease (CVD) and may play a role in the increased incidence of myocardial infarctions (MIs) seen among PLWH. Type 1 MIs (T1MI) are due to atherothrombotic coronary plaque rupture, whereas type 2 MIs (T2MI) are from supply-demand mismatch, such as with sepsis or cocaine use; T2MIs are more common in PLWH than in the general population. The disaggregated risk of MI by type due to insomnia in PLWH is unknown.
Methods: The multisite Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort includes clinical data, patient-reported outcomes and measures (PROs), and centrally adjudicated MIs with distinction between T1MIs and T2MIs. Using data from PLWH in care at 5 CNICS sites between 2005-2019 we evaluated the relationship between insomnia and first incident MI. Insomnia, defined as having difficulty falling or staying asleep with symptoms that are bothersome, was measured at baseline via PRO as part of the HIV symptom index. The associations between insomnia and incident MI by type were evaluated using separate Cox models adjusted for age, sex, race/ethnicity, CD4 count, viral suppression (VL<400), and traditional CVD risk factors, including treated hypertension, treated dyslipidemia, kidney function (eGFR<30), and smoking.
Results: Among 11,189 PLWH there were 241 incident MIs (n=141 T1MIs and n=100 T2MIs) over an average of 4.3 years of follow-up. Sleep disturbance was common, with 6,405 (57%) PLWH reporting some difficulty falling or staying asleep and 5,415 (48%) PLWH reporting their insomnia symptoms were bothersome. In adjusted analyses, PLWH experiencing insomnia were 53% more likely to have an incident T2MI compared to PLWH without insomnia (Hazard Ratio (HR)=1.53, 95% confidence interval (CI): 1.02-2.29; p=0.04). T1MI was not associated with insomnia (HR=0.95, 95%CI: 0.67-1.32; p=0.75).
Conclusion: Approximately half of PLWH reported insomnia, an estimate consistent with the 50-70% prevalence reported in the literature. We found that PLWH with insomnia had a substantial increased risk of T2MI, but not T1MI, highlighting the importance of distinguishing MI types. Further investigation into the relationship between insomnia and T2MIs by T2MI cause may elucidate mechanisms underlying this association.

645 HORMONE USE AND HIV ALTER CARDIOVASCULAR BIOMARKER PROFILES IN TRANSGENDER WOMEN

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Background: Feminizing hormonal therapy (FHT) and HIV potentially alter cardiovascular disease (CVD) risk in transgender women (TW). We assessed serum biomarkers of CVD risk and inflammation among TW by HIV serostatus and FHT use, compared to cis-gender male (CM) controls.
Methods: TW were enrolled from community-based organizations and clinics in Los Angeles, CA and Houston, TX and frequency-matched to Multicenter AIDS Cohort Study CM on age, race, substance use and ART type. Serum biomarker concentrations were assessed via ELISA. Wilcoxon rank sum and Fisher's exact tests compared groups. Multivariable linear regression analyses assessed factors associated with $\log_{10}$-transformed biomarker concentrations.
Results: TW (HIV+ n=75, HIV- n=47) and CM (HIV+ n=40, HIV- n=40) had mean age of 43 and 45 years; 90%/91% were non-Hispanic black, Hispanic, or multi-racial, 26%/53% obese, and 34%/24% current smokers, respectively. Persons with HIV (PWH) had current median CD4+ T lymphocyte count 609 cells/uL; 67% of TW were on FHT (68% HIV+, 66% HIV-). ART use included 29% NNRTIs, 30% PIs, and 37% INSTIs. Among PWH, TW had higher median extracellular newly-identified receptor for advanced glycation end-products (EN-RAGE), lipoprotein-associated phospholipase A2 (LpPLA2), oxidized LDL (oxLDL), soluble TNF receptor type (sTNFR) I/II, interleukin (IL)-8 and plasminogen activator inhibitor (PAI)-1, but lower soluble CD14, von Willebrand factor (vWF) and endothelin (ET)-1 levels than CM, with similar findings for participants without HIV (all p<0.05). In PWH, ENRAGE, oxLDL, and sTNFRI concentrations were higher, and vWF and ET-1 were lower, moving from CM to TW not on FHT (n=24) to TW on FHT (n=51). For persons without HIV, ENRAGE, oxLDL and PAI-1 were higher moving from CM to TW not on FHT (n=16) to TW on FHT (n=31).
In multivariate analysis restricted to persons with undetectable HIV-1 RNA and adjusted for HIV serostatus, gender, age, race/ethnicity, BMI, and smoking, being a TW but not HIV status was associated with higher EN-RAGE, IL-6, IL-8, P selectin, PAI-1, oxLDL and sTNFRI/II concentrations, and lower vWF. Both being a TW and a PWH were associated with lower ET-1.
Conclusion: Compared to matched CM, TW have altered profiles of biomarkers associated with systemic inflammation and CVD that seem to be influenced by both FHT and HIV, even after adjusting for key risk factors. Clinical data are needed to understand the contributions of FHT and HIV to CVD risk among TW.



646 HIV SEVERITY AND INCIDENT HEART FAILURE AMONG PATIENTS IN A LARGE HEALTH CARE SYSTEM

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Background: Persons with HIV (PWH) are at increased risk for heart failure (HF) compared with uninfected persons but few studies have evaluated whether this risk varies by severity of HIV infection.
Methods: We conducted an observational cohort study of adults (age ≥21 years) with and without HIV, frequency-matched 1:10 by age, sex, race/ethnicity, primary medical facility and calendar year, who were members of Kaiser Permanente in Northern California, Southern California, Maryland, D.C. or Virginia between 2000 and 2016. Patients' electronic health records were reviewed to determine incident HF (either preserved or reduced left ventricular systolic function). Using Poisson regression, we estimated relative risk (RR) of incident HF by HIV status overall, and by HIV status with PWH stratified by recent CD4 count, nadir CD4 count, or HIV RNA level, with laboratory measures lagged by 6 months (i.e., at least 6 months prior to HF assessment). We adjusted for sociodemographic characteristics (sex, current age, race/ethnicity, socioeconomic status) and risk factors for HF, including BMI>25, antecedent acute myocardial infarction, hypertension, diabetes mellitus, dyslipidemia, ever documented history of smoking, alcohol use disorder and drug use disorder.
Results: The study included 38,868 PWH and 386,569 matched uninfected persons (average age 41 years at start of follow-up; 88% male; 38% White, 20% Hispanic, 21% Black). There were 414 HF cases among PWH and 3,298 HF cases among uninfected comparators (0.23 and 0.15 cases of HF per 100 person-years, respectively). Risk of HF was higher overall in PWH (vs. uninfected persons, adjusted RR 1.34, 95% CI: 1.21-1.49). However, when evaluating HF by HIV severity, heightened HF risk was observed only among PWH with lower recent CD4, lower nadir CD4 and higher HIV RNA level (Table). PWH with recent CD4≥500, nadir CD4≥200 and HIV RNA level ≤200 did not have significantly higher risk of HF compared with uninfected persons.
Conclusion: Higher HIV viremia and lower CD4 cell count (both recent and nadir) are associated with elevated HF risk. Our data suggest that, in addition to addressing cardiovascular risk factors, earlier HIV diagnosis and treatment, and adherence to antiretroviral therapy, are strategies to prevent HF in PWH.

Table. Relative risk of incident heart failure in HIV-infected (N=38,868) compared with HIV-uninfected (N=386,569) patients, overall and stratified by HIV severity as defined by recent CD4 count, nadir CD4 count or HIV RNA level

	Cases of HF n	Unadjusted RR (95% CI)	p	Adjusted[1] RR (95% CI)	p
By HIV status					
HIV uninfected	3,298	Ref		Ref	
HIV infected	414	1.46 (1.32-1.62)	<0.001	1.34 (1.21-1.49)	<0.001
By HIV severity[2]					
Recent CD4 count					
CD4≥500	160	1.11 (0.95-1.31)	0.18	0.98 (0.84-1.15)	0.82
CD4 200-499	189	1.68 (1.61-1.39)	<0.001	1.54 (1.33-1.78)	<0.001
CD4<200	65	2.92 (2.28-3.73)	<0.001	2.84 (2.22-3.65)	<0.001
Nadir CD4 count					
CD4≥500	26	0.84 (0.57-1.24)	0.39	0.99 (0.67-1.46)	0.95
CD4 200-499	150	1.14 (0.96-1.34)	0.13	1.17 (0.99-1.38)	0.07
CD4<200	238	1.98 (1.74-2.26)	<0.001	1.55 (1.35-1.77)	<0.001
HIV RNA level					
≤200	269	1.33 (1.17-1.50)	<0.001	1.09 (0.96-1.23)	0.19
201-9,999	52	1.56 (1.18-2.05)	0.002	1.76 (1.33-2.31)	<0.001
≥10,000	93	1.98 (1.61-2.43)	<0.001	2.92 (2.37-3.59)	<0.001

[1] Adjusted for sociodemographic characteristics sex, time-updated age, race/ethnicity, socioeconomic status, BMI>25, antecedent acute myocardial infarction, hypertension, diabetes mellitus, dyslipidemia, ever documented history of smoking, alcohol use disorder and drug use disorder
[2] Reference: HIV-uninfected patients

647 PLASMA INFLAMMATORY BIOMARKER SIGNATURE ASSOCIATED WITH CVD IN HIV INFECTION

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Background: We have recently shown that a specific isoform of the human proinflammatory cytokine IL-32 (IL-32D) is selectively upregulated in HIV+ individuals with cardiovascular disease (CVD). Here we extend our studies to screen for other inflammatory markers that could be combined with IL-32 to enhance the prediction of CVD in HIV infection.
Methods: Using the MesoScale Technology, we measured 84 inflammatory and anti-inflammatory factors in plasma from n=79 HIV+ aviremic males participating in the Canadian HIV and Aging Cohort Study (n=49 CVD+ with coronary artery atherosclerosis measured by cardiac computed tomography and n=30 CVD-) and HIVneg controls (n=25 CVD+ and n=24 CVD-). We used a generalized linear regression algorithm (glmnet) with Lasso regularization and Leave-One-Out cross validation to predict the presence of coronary artery atherosclerosis in the study participants.
Results: Alongside with the upregulation of IL-32D, we observed an HIV-specific signature characterized by higher plasma levels of IL-18, VEGF-A, FGF23, FLT3L and FSH in HIV+ individuals with CVD (univariate analysis, p=0.0016, 0.0053, 0.0386, 0.0075 and 0.049, respectively) combined with lower levels of TNF-related apoptosis inducing ligand (TRAIL), IFNb and IL-3 (p=0.0149, 0.0093 and 0.0288, respectively). By integrating IL-32D expression with these modulated factors in a multivariate analysis, CVD was predicted as a binary outcome (presence/absence) with a misclassification error of 34%. The prediction model was independent of age, statin treatment and smoking. Given the growing evidence for the atheroprotective role of TRAIL-expressing monocytes, we tested the functional link between IL-32 and TRAIL. We show here that primary human monocytes treated with IL-32 down-regulate TRAIL expression, acquire an M1 activated phenotype (CD206negCD163negCD80+TRAILneg) and produce inflammatory cytokines such as IL-6 and TNFα.
Conclusion: Here we report a specific plasma inflammatory signature that holds promise to predict CVD in HIV+ individuals independently of traditional risk factors. Moreover, the functional link between IL-32 and TRAIL and their opposite effects on monocyte functions further highlight the key role of IL-32 in CVD and its potential as a therapeutic target in HIV infection.

648 ASSOCIATION OF INFLAMMATORY MARKERS WITH CARDIAC INDICES IN THE MACS

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Background: People living with HIV (HIV+) are at increased risk of heart failure even after adjustment for demographics and cardiovascular risk factors. Among HIV+ without symptoms of heart failure, diastolic dysfunction has been reported to be highly prevalent. We hypothesized diastolic dysfunction to be an early marker of myocardial disease related to heightened inflammation in HIV infection.
Methods: The Multicenter AIDS Cohort Study (MACS) is a prospective observational cohort with both HIV+ and HIV-uninfected (HIV-) participants. We evaluated the association of echocardiographic parameters of left ventricular (LV) structure, systolic and diastolic function, and left atrial (LA) volumes to biomarkers of systemic inflammation and coagulation (CRP, IL-6, TNF-alpha and D-dimer). Associations between cardiac indices, biomarker quintiles and HIV serostatus were evaluated with multiple linear regression analyses after multivariable -adjustment for demographics and cardiovascular risk factors (body mass index, systolic blood pressure, hyperlipidemia and diabetes).
Results: We included HIV+ (n=384) and HIV- (n=254) men who had both echocardiograms and inflammatory markers in the analysis. HIV+ men were younger (age, 59.2 ±6.7 vs 62.5 ±7.5 years, p< 0.001), had similar systolic blood pressure (129 vs 131 mmHg, p<0.24) and body mass index (26.8 vs 27.3 kg/m_2, p<0.20). In multivariable-adjusted models (Table), there was a progressive association of LA volume index with increasing D-dimer quintiles and association with highest IL-6 quintile, independent of HIV serostatus. There were no significant associations between inflammatory markers and echo-derived parameters of diastolic function including transmitral flow velocity (E), mitral annular velocity (e') and E/e' ratio.
Conclusion: In this analysis of HIV+ and HIV- men, larger LA size was associated with markers of heightened systemic inflammation, regardless of HIV serostatus. As left atrial dilation predicts future risk of atrial fibrillation and stroke, further investigation is needed to evaluate whether systemic inflammation mediates increased atrial arrhythmic risk among both HIV+ and HIV- people.

Table 1: Correlates of serological inflammatory markers and parameters of cardiac structure and function

	Ejection fraction (%)	LV mass index (g/m^2)	LA volume index (mL/m^2)	Mitral valve E/e' ratio	Mitral valve E/A ratio	Mitral inflow velocity E (m/s)	Mitral annular e' velocity (cm/s)
HIV serostatus† [a]	0.85* (0.44)	3.25* (1.74)	0.92 (0.66)	0.17 (0.20)	**-0.07**** (0.03)	0.40 (1.61)	-0.17 (0.17)
IL-6‡ [b]	-0.76 (0.69)	0.10 (2.74)	**2.14**** (1.03)	-0.09 (0.31)	0.00 (0.05)	-4.07 (2.52)	-0.40 (0.27)
TNF-alpha‡ [b]	-0.80 (0.79)	0.46 (3.06)	0.10 (1.19)	0.45 (0.33)	0.03 (0.06)	1.65 (2.87)	-0.19 (0.30)
CRP‡ [b]	-0.18 (0.68)	-0.11 (2.71)	1.27 (1.03)	0.05 (0.30)	0.04 (0.05)	2.52 (2.49)	0.23 (0.26)
D-Dimer Quintiles‡ [b]:							
1st	-	-	-	-	-	-	-
2nd	-0.44 (0.68)	0.87 (2.63)	1.11 (1.01)	0.29 (0.30)	-0.01 (0.05)	-0.61 (2.47)	-0.42 (0.26)
3rd	-0.36 (0.70)	1.27 (2.72)	**2.14**** (1.04)	-0.05 (0.31)	-0.04 (0.05)	-1.92 (2.56)	-0.24 (0.27)
4th	0.32 (0.72)	-4.38 (2.78)	**2.16**** (1.07)	0.21 (0.32)	0.06 (0.05)	0.41 (2.63)	-0.19 (0.27)
5th	-1.23* (0.71)	2.94 (2.76)	**2.51**** (1.06)	0.61* (0.31)	0.05 (0.05)	0.79 (2.60)	-0.51* (0.27)

*** p<0.01, ** p<0.05, * p<0.1
Standard errors are in parenthesis
Multivariable adjusted regression coefficients for risk factors, describing the change in mean cardiac parameters (with their appropriate units):
† comparing to HIV-uninfected.
‡ independently comparing lowest quintile of inflammatory marker to highest quintile

LA, denotes left atrial; LV denotes left ventricular
a: Adjusted for age, race, body mass index (BMI), MACS site, and year of MACS enrollment (before/after 2001), hyperlipidemia, systolic and diastolic blood pressure, diabetes
b: Adjusted for HIV status, age, race, body mass index (BMI), MACS site, and year of MACS enrollment (before/after 2001), hyperlipidemia, systolic and diastolic blood pressure, diabetes

649 PHENOTYPIC CLUSTERING OF HIV-ASSOCIATED ATHEROSCLEROSIS AND AGE-RELATED OUTCOMES

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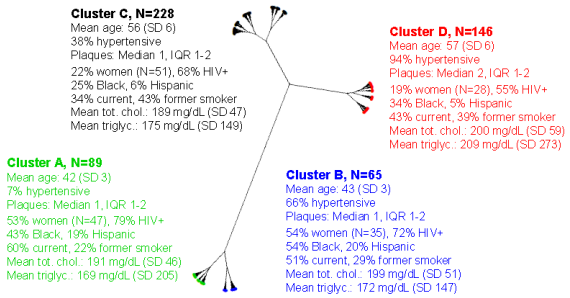
Background: People with HIV (PWH) have increased cardiovascular disease risk, but the underlying mechanisms are not fully elucidated. We used machine learning to develop phenotypic profiles of individuals with subclinical carotid atherosclerosis that incorporate multiple risk factor interactions, and determined whether these profiles differentially associate with age-related disease.

Methods: The MACS/WIHS CCS prospectively follows people with and without HIV at 14 sites. 2,796 participants had non-invasive B-mode ultrasound of the right carotid artery in 2004-2006, and 528 (30% women) were identified with plaque (focal IMT >1.5 mm). We used random forests and hierarchical clustering on 76 demographic, behavioral and clinical markers assessed near the time of the scan to classify individuals into phenotypically similar clusters among those with plaque. Over 13 years of follow-up, we assessed the association of each cluster with all-cause mortality, and in women, hospitalization rates and cognitive decline.

Results: Our approach identified 4 distinct clusters that differed by age and hypertension history (Figure). Clusters C and D (mean age 56-57) were on average 14 years older than A and B, and B and D were much more likely to be hypertensive than A and C (all p<0.001). Even though C and D were of similar age, C had less carotid disease (fewer plaques, less stiffness) than D (p<0.001), but similar levels as B. Compared with D, C also was significantly less likely to smoke (34% vs 43%) or be diabetic (12% vs 21%), more likely to be treated for hypertension (among hypertensives, 92% vs 52%), and had lower BMI (mean 25 vs 27 kg/m$_2$) and higher bilirubin (mean 0.85 vs 0.69 mg/dL). Among PWH, C was more likely to be on ART (73% vs 65%) than D and more likely to have history of AIDS (36% vs 25%) and lower CD4+ count (mean 478 vs 523 cells/uL). Over time, C had better survival (HR 0.56, 95% CI 0.36-0.88), fewer hospitalizations (RR 0.79, 95% CI 0.48-1.29), and less decline in processing speed (difference in Z-score for Trail Making Test A 0.03, 95% CI 0.001-0.05) than D. Outcomes for C were similar to A and B despite older age.

Conclusion: Our current analysis identified a profile of individuals with subclinical atherosclerosis who, as they entered their 6th decade, seemed to represent more of a "healthy aging" phenotype than others of the same age. Future work should further characterize this group and identify mechanisms underlying their apparent resiliency.

Figure. Unrooted dendogram showing clustering of MACS/WIHS CCS participants with carotid artery plaque (N=528).
Each "leaf" represents a single participant. Distance between leaves denotes random forest-based proximity (average participant-to-participant distance), using no. of plaques, common carotid artery intima-media thickness (IMT), distensibility/stiffness, echogenicity as labels.



650 MYOCARDIAL INFARCTION BY ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) RISK SCORE

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Background: Physicians who care for people with HIV (PWH) need to know the person's risk for myocardial infarction (MI) to initiate discussions about preventive interventions. We aimed to estimate the absolute rate and cumulative incidence of MI by AHA/ACC 10-year atherosclerotic cardiovascular disease (ASCVD) risk score (which includes sex, age, race, cholesterol, blood pressure, and history of diabetes, smoking, and hypertension treatment) among PWH in North America.

Methods: PWH from NA-ACCORD cohorts that validated type 1 MIs (induced by plaque rupture with thrombus) were included. Study entry began as the later date of NA-ACCORD enrollment, age 40, ART initiation date, 1 Jan 2000, or the cohort start date of MI observation. Study exit was defined as the earliest of MI date, death date, loss to follow up (2 years with no HIV RNA or CD4 measurements), age 80, 31 Dec 2015, or the cohort start date of MI observation. 10-year AHA/ACC ASCVD risk score was calculated at study entry and categorized <5%, 5-<10%, 10-<15%, 15-<25%, ≥25% risk. Cumulative incidence of MI from the time of study entry up to 10 years were estimated using Kaplan-Meier methods and compared using log-rank tests. MI incidence rates (per 1000 person years) with 95% confidence intervals [,] were estimated using Poisson regression models.

Results: 20,675 adults (17,247 men and 3,428 women) contributed 282 MIs and 140,543 person years. Median age at study entry was 44.4 (interquartile range [IQR] 40.0, 50.5) years, median CD4 was 381 (IQR 203, 597) cells/mm$_3$, and median follow-up was 6.0 (IQR 3.0, 10.1) years. Log-rank tests indicated significant heterogeneity by ASCVD score (p<0.001). Individuals with an ASCVD risk score ≥25% (n=7,698) attained a cumulative incidence of 25% at 4 years after study entry, and 50% at 7 years (Figure 1a). Those with an ASCVD risk score 15-<25% (n=6,674) and 10-<15% (n=3,216) attained a cumulative incidence of 25% by year 6 and 8 after study entry, respectively. The incidence rates increased with increasing ASCVD risk score in men, with women having lower risk and a plateau after an ASCVD risk score of 15% (Figure 1b).

Conclusion: The 10-year ASCVD risk score underestimated the cumulative incidence of MI among those with risk >10%. For PWH who have an ASCVD risk score >10%, aggressive cardiovascular prevention efforts should be initiated immediately, including smoking cessation, lipid control, and blood sugar control.

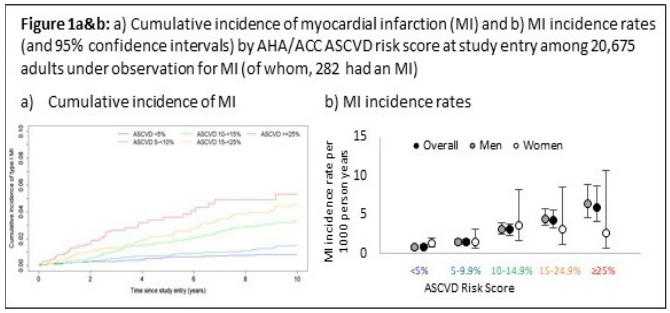


Figure 1a&b: a) Cumulative incidence of myocardial infarction (MI) and b) MI incidence rates (and 95% confidence intervals) by AHA/ACC ASCVD risk score at study entry among 20,675 adults under observation for MI (of whom, 282 had an MI)

651 CONTRIBUTION OF TELOMERE LENGTH AND CLINICAL RISK FACTORS TO CORONARY ARTERY DISEASE

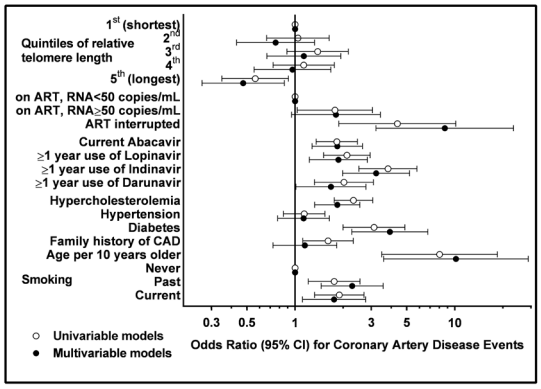
Isabella C. Schoepf[1], Tanja Engel[1], Marieke Raffenberg[1], Neeltje A. Kootstra[2], Peter Reiss[2], Christian Thorball[3], Jacques Fellay[3], Roger Kouyos[4], Huldrych F. Günthard[4], Bruno Ledergerber[4], Philip E. Tarr[1], for the Swiss HIV Cohort Study
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Background: In the general population, leukocyte telomere length (TL) shortening, as occurs with advancing age, is associated with coronary artery disease (CAD) events. The relative contribution of TL, HIV-related and traditional risk factors to CAD has not been quantified in HIV-positive persons.

Methods: We measured TL in stored peripheral blood mononuclear cells (PBMC) as previously described (Cobos Jimenez J Infect Dis 2016) by quantitative PCR, using the single copy albumin gene as control. Relative TL was estimated using a standard curve prepared from healthy blood donors. Study participants were white Swiss HIV Cohort Study participants. Cases had a 1st CAD event during the study period (1.1.00-31.12.17). We used incidence density sampling and matched 1-3 controls (CAD event-free) on gender, age, and date of registration. We obtained univariable and multivariable odds ratios (OR) for a first CAD event from conditional logistic regression analyses, including as variables TL, age, gender, smoking, family history, hypertension, diabetes, hypercholesterolemia, and HIV-related factors (recent exposure to abacavir, exposure >1 year to indinavir, lopinavir/ritonavir, darunavir; ART discontinuation; on ART but HIV RNA>50 copies/mL).

Results: We included 333 cases (median age at CAD event, 54 years; 14% women; 83% with HIV RNA<50) and 745 controls. Median (IQR) time of TL measurement was 9.4 (5.9-13.8) years prior to CAD event. Participants in the 5th (longest) TL quintile, compared to the 1st (shortest) TL quintile had univariable CAD odds ratio of 0.56 (95% confidence interval, 0.35-0.91; p=0.02), and a multivariable OR of 0.47 (0.26-0.86; p=0.01; Figure). In comparison, the OR for current smoking was 2.28 (1.46-3.56), hypercholesterolemia 1.84 (1.33-2.55), diabetes 3.92 (2.26-6.78), on ART/HIV RNA>50 1.80 (0.95-3.42); recent abacavir, cumulative lopinavir, indinavir, darunavir exposure 1.84 (1.28-2.64), 1.87 (1.23–2.84), 3.22 (1.99-5.21), and 1.68 (1.01-2.78), respectively.

Conclusion: HIV-positive persons with the longest telomeres (measured >9 years prior to CAD event) had approx. half the odds of developing CAD of those with the shortest telomeres. TL measurement may, in addition to traditional and HIV-related risk factors, provide prognostic information with respect to CAD risk.



652 PREVALENCE OF SUBCLINICAL MYOCARDIAL ABNORMALITIES IN HIV: SMASH STUDY RESULTS

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Background: It is unknown whether HIV infection remains an independent risk factor for subclinical myocardial disease in the era of combination antiretroviral therapy (cART). We assessed differences in cardiac structure and function by cardiac magnetic resonance (CMR) imaging among people with (HIV+) and without HIV (HIV-) after controlling for potential confounders.

Methods: 432 participants (71% men, 63% HIV+) in the Multicenter AIDS Cohort Study, AIDS Linked to the Intravenous Experience study, and Women's Interagency HIV Study, aged 40-70 years, underwent CMR for biventricular volumes and mass, left atrial (LA) volumes, and left ventricular (LV) and LA strain. CMR with contrast and T1 mapping comprehensively assessed scar patterns and burden.

Results: Median participant age was 55 years, 47% smokers, 53% hypertensive, 13% diabetic, and 59% dyslipidemic. Prevalence of stimulant, opioid and marijuana use was 39%, 32%, and 44%. Among HIV+ persons, 89% were on cART, 74% had viral suppression (HIV RNA<50 copies/ml), and most recent median CD4 count was 610/ul (IQR 398-826). For most characteristics, HIV- and HIV+ participants were similar. Median LV ejection fraction (EF) was normal and similar by HIV serostatus (73% for HIV- vs. 72% for HIV+, p=0.53; n=2 with LVEF<40%) as were right ventricular EF, biventricular volumes and masses. Focal myocardial scar prevalence was also similar (32% vs. 37%, p=0.38) with similarly low median scar extents (4.1 vs. 5.0 grams, p=0.46). The pattern of myocardial scar was predominantly non-ischemic. An ischemic scar pattern was found among only 3% of HIV- vs. 5% of HIV+ (p=0.56). Indices of nonischemic diffuse fibrosis did not differ by HIV serostatus. After adjusting for demographics, parent cohort, education, cardiac risk factors, and drug use, LA volumes (maximal, minimal and pre-atrial) were the only CMR parameters that differed significantly by HIV serostatus and were ~10% larger for HIV+(Table). Among HIV+ people, LA volumes did not differ by viral suppression status.

Conclusion: Among a comparable group of HIV- and HIV+ people with similar characteristics and patterns of recreational substance use, prevalent ventricular disease was rare and ventricular indices did not differ by HIV serostatus. However, HIV+ serostatus was independently associated with larger LA phasic volumes, possibly reflecting diastolic dysfunction and predisposal to atrial arrhythmias.

Table: Risk factors for larger indexed LA volumes in multivariable linear regression

	Mean difference in indexed maximal LA volume*	p-value	Mean difference in indexed minimal LA volume*	p-value	Mean difference in indexed pre-atrial LA volume*	p-value
HIV+	2.32	(0.02)	1.34	(0.02)	1.93	(0.02)
Age(/5 yrs)	0.22	(0.59)	0.25	(0.29)	0.69	(0.05)
White/Caucasian	0.87	(0.55)	-0.14	(0.87)	0.60	(0.62)
Female	2.05	(0.25)	0.15	(0.88)	0.63	(0.66)
MACS	reference		reference		reference	
WIHS	-0.97	(0.68)	-0.06	(0.96)	0.17	(0.93)
ALIVE	2.30	(0.15)	0.84	(0.35)	2.45	(0.06)
Education	0.83	(0.14)	0.34	(0.29)	0.80	(0.09)
Cardiac history	1.62	(0.42)	2.04	(0.07)	2.03	(0.22)
Hypertension	0.16	(0.88)	-0.24	(0.68)	0.23	(0.79)
Diabetes	-2.68	(0.07)	-0.86	(0.31)	-2.17	(0.07)
Dyslipidemia	-2.52	(0.01)	-1.70	(0.00)	-1.98	(0.02)
Pack years of smoking (5 years prior)	0.05	(0.86)	0.02	(0.68)	0.02	(0.93)
Alcohol use>13 drinks/week (5 years prior)	0.74	(0.64)	-0.33	(0.72)	0.51	(0.69)
Marijuana use (5 years prior)	-0.25	(0.81)	0.49	(0.40)	0.45	(0.60)
Opioid use (5 years prior)	1.99	(0.13)	1.59†	(0.03)	1.54	(0.15)
Stimulant use (5 years prior)	-2.16	(0.06)	-0.77	(0.25)	-1.64	(0.09)
Erectile dysfunction drug use† (5 years prior)	-0.52	(0.73)	0.19	(0.82)	-0.29	(0.82)
Nitrite use (5 years prior)	-0.30	(0.86)	-0.29	(0.77)	-0.16	(0.91)
Constant (mean)	26.87	.	12.97	.	20.26	.

*Volumes are indexed for body surface area with units of ml/m^2.
†among men

653 AORTIC DILATATION IS PRESENT AMONG MEN WITH HIV

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Background: In the antiretroviral era, cardiovascular disorders have become more prevalent in people living with HIV. However, it is unclear whether HIV

affects the extracardiac vascular system. Ascending aortic aneurysms are associated with increased risk for dissection and rupture. It is possible that increased inflammation resulting from HIV may increase the risk for dilatation. To date, no large studies have been conducted evaluating dilatation of the aortic root and ascending aorta in people with HIV. The aim of this study is to compare the prevalence and features of ascending aortic dilatation in men with HIV (HIV+) and without HIV (HIV-) in the Multicenter AIDS Cohort Study (MACS).

Methods: 1179 MACS participants underwent complete echocardiograms. Linear regression was performed to assess the association between HIV serostatus and aortic diameters indexed for body surface area (BSA) at the aortic root and supravalvular levels, after adjusting for potential confounders. The multivariable model adjusted for age, race/ethnicity, MACS site, enrollment period (pre/post 2001), atherosclerotic risk factors (systolic blood pressure, medications to treat hypertension, smoking history, diabetes, total cholesterol level, high density lipoprotein level) and statin use.

Results: We included 653 HIV+ men (mean age 54.6 years, 47.8% white, 32.6% black, 16.8% diabetic, 13.0 pack-year smoking history) and 526 HIV- men (mean age 60.4 years, 69.0% white, 21.7% black, 11.8% diabetic, 12.5 pack-year smoking history). After adjusting for the aforementioned covariates and indexing for BSA, aortic root ($p<0.01$), sinotubular junction ($p<0.01$), and ascending aorta ($p<0.001$) were all significantly larger in HIV+ compared to HIV- men. There was no significant difference in aortic root annulus size (Table 1). Among HIV+ men, indexed aortic root, sinotubular junction and ascending aorta were all significant smaller in men with nadir CD4 count >500 cells/mm_3 compared to men with CD4 counts <200 cells/mm_3 prior to initiating antiretroviral therapy ($p<0.05$).

Conclusion: To our knowledge this is the first study to demonstrate an independent association between HIV serostatus and ascending aortic dilatation, even after controlling for traditional cardiovascular risk factors, which may have implications for ongoing surveillance and management.

Table 1. Mean adjusted differences* in indexed aortic diameters in men with compared to those without HIV

	Mean difference in aortic annulus (cm/m2)	Mean difference in aortic root (cm/m²)	Mean difference in sinotubular junction (cm/m²)	Mean difference in ascending aorta (cm/m²)
HIV+	0.02 [-0.01-0.05] p=0.26	0.04 [0.01-0.06] p<0.01	0.04 [0.01-0.07] p<0.01	0.05 [0.02-0.07] p<0.001
Constant (mean)	1.48	1.62	1.38	1.41

* Adjusted for age, race/ethnicity, MACS site, enrollment period (pre/post 2001), atherosclerotic risk factors (systolic blood pressure, medications to treat hypertension, smoking history, diabetes, total cholesterol level, and high density lipoprotein level) and statin use.

654 PREVALENCE OF PULMONARY HYPERTENSION IN HIV-INFECTED PATIENTS AND REDUCED OUTCOME

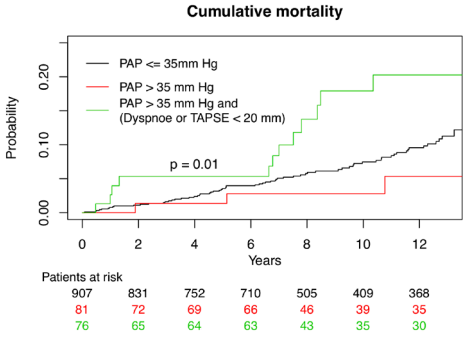
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Background: The epidemiology and prognostic impact of increased pulmonary pressure among HIV-infected individuals in the antiretroviral therapy era is not well described. We therefore examined the prevalence and outcomes of increased echocardiographic pulmonary pressure in HIV-infected individuals.

Methods: This study evaluated subjects from the HIV-HEART study. The HIV HEART study (HIVH) is an ongoing prospective observational cohort study in the German Ruhr Area starting in 2004 to assess the rate of cardiovascular disease (CVD). This longitudinal analysis included HIV+ patients with up to 12 years of follow-up. Echocardiography with reported pulmonary artery systolic pressure (PASP) and tricuspid annular plane systolic excursion (TAPSE) as sign of right heart dysfunction was obtained in almost all patients.

Results: PASP was documented in 1064 subjects. The mean follow-up was 8.9 ±4.1 years. Pulmonary hypertension (PH) > 35mmHg was detected in 157/ 1064 patients (14.8%). Of these, 81 (51%) were asymptomatic and 76 (49%) patients presented with dyspnoe/ TAPSE < 20mm as a sign of right heart dysfunction. PASP was lower in patients without PH compared to patients with PASP > 35mmHg but without symptoms and patients with and PASP > 35mmHg and signs of right heart dysfunction (23 ±6.6 mmHg vs. 33.2 ±10.3 mmHg vs. 37 ±8.2 mmHg). Overall, 82 (8%) of patients with follow-up data had died. Mortality was associated with an increased functional impairment (Figure 1).

Conclusion: Echocardiographic screening detected PH in a relevant proportion of HIV-positive patients. PH and symptoms of right heart dysfunction were associated with higher mortality.



655 CARDIAC EVENTS IN HIV-INFECTED PATIENTS WHO USE TENOFOVIR ALAFENAMIDE (TAF)

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Background: Although cardiac events (CEs) were not reported as side effects of TAF in registration trials, we observed some new CEs in HIV positive patients who started TAF. We retrospectively studied all CEs in our HIV cohort, with special focus on the use of TAF compared to tenofovir disoproxil fumarate (TDF).

Methods: All OLVG patients receiving cART between January 1st, 2016 and May 31st, 2018 were selected and allocated to 3 mutually exclusive groups according to cART component prior May 31st, 2018. Patients that used TAF (TAF), patients that used TDF but never used TAF (TDF) and patients without ever using a tenofovir cART (NT). The start date was registered as the first day of treatment with the group defining component of tenofovir; for the NT group this was the date of initial cART start. CEs were defined as myocardial infarction, cardiomyopathy, arrythmia or angina pectoris. CEs-free survival was estimated using Kaplan-Meier analysis. Hazard ratios (HR) for CEs were adjusted for previous cardiac history, BMI, gender, age per quartile and smoking using Cox regression analysis.

Results: We included 2985 patients: 1170 in TDF, 1537 in TAF and 278 in NT. Median follow-up was 2.2 years (IQR: 1.4-2.6) for TAF, 7.0 years (IQR: 4.0-9.9) for TDF and 9.0 years (IQR: 3.5-17.0) for NT. In TDF 58(5.0%) CEs were reported, in TAF 43(2.8%) and in NT 11(4.0%). Cardiac history was more frequent in TAF vs. TDF, odds ratio: 1.9 (95% CI: 1.3-2.9; P=0.001). Kaplan-Meier analysis showed a significant difference between groups (figure 1; log-rank test: P<0.001). Unadjusted Cox regression showed an increased hazard for CEs in TAF vs. NT, HR: 7.0 (95% CI: 2.9-17.2; P<0.001) and in TAF vs. TDF, HR: 2.8 (95% CI: 1.6-5.0; P<0.001). After adjusting for covariates, the HR of CEs in TAF vs. NT decreased to 3.9 (95% CI: 1.5-9.8; P=0.005) and in TAF vs. TDF to 1.9 (95% CI: 1.0-3.6; P=0.034).

Conclusion: The occurrence of CEs in TDF and in NT were significantly different compared to TAF. In contrast to registration trials, an older population with more cardiac history might explain our unexpected observation in this real-life cohort. Since follow-up of TAF was short and the rate of CEs low, confirmation of our observation in larger cohorts is necessary, to better advise about TAF use in elder patients with a history of CEs.

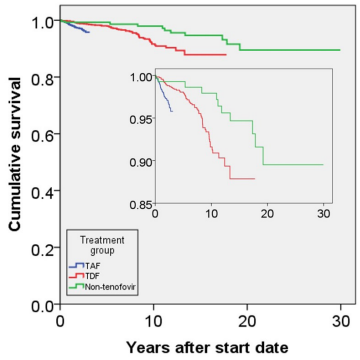


Figure 1. Kaplan-Meier CEs-free survival by treatment group. Treatment group was an independent predictor of CEs (P<0.001).

656 INPATIENT OUTCOMES FOR HIV-INFECTED PATIENTS HOSPITALIZED FOR ACUTE CORONARY SYNDROME

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Background: HIV-infected adults have excess morbidity and mortality from cardiovascular disease. Differences in the presentation and management of acute coronary syndromes (ACS) in this population may drive these findings. We hypothesized that HIV-infected adults admitted with ACS are less likely to receive percutaneous coronary intervention and have greater adverse outcomes compared with uninfected patients.
Methods: This was a retrospective cohort study using inpatient claims data from Symphony Health, a nationwide data warehouse. All adults admitted between January 1st, 2014 and December 31st, 2016 with ACS were included. Patient characteristics and outcomes were defined by ICD-9 or ICD-10 billing codes. Logistic regression adjusted for clinical characteristics was used to evaluate outcomes.
Results: A total of 1,125,126 patients were included, of whom 6,612 (0.59%) had HIV. The HIV-infected group was younger (57 vs 67 years old, p<0.0001) and had a higher burden of medical comorbidities such as diabetes and substance abuse (p<0.0001). Rates of ST-elevation myocardial infarction were similar between groups. In adjusted analysis, HIV-infected individuals were less likely to receive coronary angiogram (31.6% vs 33.4%, OR 0.85, 95% CI 0.80-0.89, p <0.0001) or drug eluting stents (16.5% vs 18.2%, OR 0.88, 95% CI 0.82-0.94, p =0.0001). They also had significantly higher inpatient mortality (5.5% vs 5.3%, OR 1.28, 95% CI 1.15-1.43, p <0.0001) despite having fewer complications such as acute heart failure (19.9% s 23.2%, OR 0.82, 95% CI 0.76-0.88, p <0.0001) or major bleeding (2.8% vs 3.5%, OR 0.82, 95% CI 0.70-0.95, p =0.0074).
Conclusion: Among contemporary HIV-infected patients hospitalized with acute coronary syndrome, disparities in treatment persist, with less use of percutaneous coronary interventions. Further attention is needed in order to improve the use of guideline-based therapies with the goal of optimizing the care and outcomes among persons living with HIV.

Table 1: Inpatient Procedures and Outcomes

	HIV+ (n = 6,612)	HIV- (n=1,118,514)	Adjusted*	
			OR (95% CI)	p-value
Procedures				
Balloon angioplasty	117 (1.77%)	17,710 (1.58%)	1.05 (0.87-1.26)	0.6333
Bare metal stent	227 (3.43%)	32,589 (2.91%)	1.15 (1.0-1.31)	0.0504
Drug eluting stent	1,088 (16.45%)	203,624 (18.20%)	0.88 (0.82-0.94)	0.0001
Left heart catheterization	2,091 (31.62%)	373,917 (33.43%)	0.85 (0.80-0.89)	<.0001
Transthoracic echocardiography	358 (5.41%)	41,977 (3.75%)	1.44 (1.29-1.60)	<.0001
Outcomes				
Inpatient mortality	366 (5.54%)	59,316(5.30%)	1.28 (1.15-1.43)	<.0001
Acute heart failure	1,317 (19.92%)	259,240 (23.18%)	0.82 (0.76-0.88)	<.0001
Acute kidney injury	1,075 (16.26%)	175,361 (15.68%)	1.03 (0.97-1.11)	0.3398
Major bleed	184 (2.78%)	39,240 (3.51%)	0.82 (0.70-0.95)	0.0074
Stroke	155 (2.34%)	33,638 (3.01%)	0.98 (0.83-1.15)	0.7757

*Adjusted for age, sex, substance use, medical comorbidities.

657 PREVALENCE AND CORRELATES OF CAROTID PLAQUE IN A MIXED HIV-SEROSTATUS UGANDAN COHORT

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Background: The risk of atherosclerotic cardiovascular disease (CVD) is increased amongst people living with HIV in the global north. However, there is scant data on the contributions of HIV infection and its treatment on atherosclerosis in sub-Saharan Africa.
Methods: We conducted an analysis of baseline data from the Ugandan Noncommunicable Diseases and Aging Cohort Study, which is a longitudinal cohort consisting of PLWH older than 40 years of age on antiretroviral therapy (ART) for at least 3 years,and a population-based control group of HIV-uninfected persons matched by age and sex. We conducted carotid ultrasonography and collected CVD risk factor data. Our outcome of interest was carotid plaque at enrollment, defined as a thickness of >1.5 mm measured from the intima-lumen interface to the media-adventitia interface. We fit multivariable logistic regression models to estimate adjusted correlates of plaque, including HIV infection and traditional cardiovascular risk factors.
Results: Carotid ultrasounds were completed among 150 (49%) PLWH and 155 (51%) HIV-uninfected individuals. Among PLWH, median CD4 count was 433 (IQR, 336-559)at enrollment and the median duration of ART was 10 years. The crude prevalence of carotid plaque was 8.4% (13/155) in PLWH and 3.3% (5/150) in HIV-uninfected controls. HIV infection (aOR 1.99; 95% CI, 1.19-3.30), active smoking (aOR 2.11; 95% CI, 1.01-4.38) and untreated hypertension (aOR 4.16; 95% CI, 1.65-10.48) were associated with an increased odds of carotid plaque. Physical activities of moderate intensity (aOR 0.10; 95% CI, 0.01-0.87) and vigorous intensity (aOR 0.21; 95% CI, 0.08-0.52) were associated with lower odds of carotid plaque.
Conclusion: The prevalence of carotid plaque was greater among PLWH compared with age- and sex-matched HIV-uninfected comparators in southwestern Uganda. Other correlates of plaque included smoking and untreated hypertension. These data suggest that treated HIV infection might predispose PLWH in rural Africa to increased risk of atherosclerosis. Future work should explore the mechanisms underlying this observation, and whether improved treatment of hypertension and lifestyle modifications might reduce atherosclerotic burden among PLWH in the region.

Correlates of Carotid plaque

Characteristic	Multivariable Model Adjusted Odds Ratio (95%CI)	*P*-value
Age	1.03 (0.99, 1.06)	0.057
HIV Serostatus		
Uninfected	REF	REF
Infected*	1.99 (1.19, 3.30)	0.008
Sex		
Male	REF	REF
Female	1.08 (0.65, 1.81)	0.773
Hypertension		
Normotension	REF	REF
Undiagnosed	0.78 (0.30, 2.09)	0.627
Untreated*	4.16 (1.65, 10.48)	0.002
Uncontrolled	1.32 (0.47, 3.66)	0.596
Controlled	0.43 (0.05, 3.34)	0.417
Diabetes		
Absent	REF	REF
Present	0.42 (0.97, 1.82)	0.246
Physical Activity		
Low	REF	REF
Moderate*	0.10 (0.01, 0.87)	0.037
Vigorous*	0.21 (0.08, 0.52)	0.001
Smoking status		
Non-smoker	REF	REF
Current*	2.11 (1.01, 4.38)	0.046
Former	1.09 (0.64, 1.85)	0.751
BMI		
Low	REF	REF
Normal	0.87 (0.44, 1.71)	0.690
Overweight/obesity	0.66 (0.28, 1.55)	0.343

658 MEASURES OF ADIPOSE-TISSUE REDISTRIBUTION AND ATHEROSCLEROTIC CORONARY PLAQUE IN HIV

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Background: People with HIV (PWH) well-treated on antiretroviral therapy (ART) remain at increased risk of cardiovascular disease. Prior studies have not evaluated parallel imaging features using cardiac CT and coronary CTA in relation to specific adipose compartments [visceral and subcutaneous adipose tissue(VAT, SAT)]. We hypothesized abnormal fat redistribution, particularly related to increased VAT and reduced SAT, would be associated with features of atherosclerotic coronary plaque.
Methods: 148 PWH and 68 uninfected individuals were previously enrolled. Abdominal VAT and SAT area were measured using CT scan. Coronary artery calcium (CAC) score was derived by non-contrast cardiac CT and coronary plaque composition by coronary CT angiography. We assessed presence of plaque and CAC>0 in relation to body composition parameters using logistic regression.
Results: PWH and uninfected individuals were of similar age (47±7 vs. 46±7 yrs), race (55% vs. 53% Caucasian) and sex (65% vs. 60% male). The HIV group (duration HIV 14±6yrs, duration ART 8±5yrs) had good immunological parameters (CD4+ count 549±293cells/μ l, log_{10} viral load 1.82±0.47copies/mL). VAT (108[61, 209] vs. 103[55, 177]cm_2) was similar, whereas SAT (198[125, 287] vs. 241[150, 380]cm_2, P=.02) was significantly lower among PWH vs. uninfected individuals, resulting in a higher VAT:SAT ratio in the HIV group. Increased VAT was significantly related to increased presence of plaque (OR 1.55 per 100cm_2, 95% CI[1.10, 2.17],P=.008) and CAC>0 (OR 1.56 per 100cm_2, 95% CI[1.13, 2.16],P=.006) in the HIV group. In contrast, increased SAT was related to reduced presence of plaque (OR 0.79 per 100cm_2, 95% CI[0.61, 1.01],P=.057) and reduced CAC>0 (OR 0.69 per 100cm_2, 95% CI[0.52, 0.92],P=.007) among PWH. VAT, but not SAT, were predictors of plaque and CAC in the uninfected group. BMI did not relate to plaque or CAC score in either group. By plaque composition,

VAT:SAT ratio showed a strong relationship to presence of calcified plaque (OR 3.30, 95% CI[1.12, 9.74],P=.03) in the HIV group and did not relate to non-calcified plaque. Controlling for traditional CVD risk (Framingham Risk Score) and HIV parameters, VAT(P=0.04) and VAT:SAT(P=.02) remained independently related to increased CAC score.

Conclusion: Fat redistribution phenotyping by simultaneous quantification of VAT and SAT as independent measures, could help identify those PWH at higher risk of CVD, potentially at an earlier subclinical stage, and inform therapeutic targets for CVD risk reduction.

659 MAJOR VASCULAR EVENTS IN ADULTS ON ART IN A SOUTH AFRICAN HIV MANAGEMENT PROGRAMME

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Background: Studies from high-income settings found increased risk of major vascular events (MVEs) in people living with HIV (PLWH). Data on MVE incidence in PLWH in Africa are limited. We aimed to describe incidence of MVEs and factors associated with MVEs in PLWH on antiretroviral therapy (ART) in the Aid for AIDS (AfA) private sector cohort.

Methods: This was a cohort analysis of adults (≥18 years) starting ART through AfA from 1 January 2011 to 30 September 2018. We defined MVE as hospitalisation claims for stroke, acute coronary syndrome, or coronary revascularization procedure. We excluded hospitalisations with evidence for concomitant infectious or neoplastic diseases that may mimic stroke presentations. We calculated MVE incidence. We explored associations with MVE using Cox regression. We identified hypertension, diabetes, and dyslipidaemia from hospitalisation claims, drug claims, and laboratory results, and included these as time-updated variables.

Results: We included 125,978 patients, of whom 75,485 (60%) were women, with total follow-up 320,176 person-years. At entry, median [IQR] age was 38 [33-45] years, CD4 count 276 [140-446] cells/μL, and viral load 4.4 [2.6-5.1] $\log_{10}$ copies/mL. 5,344 patients (4.2%) died. Hypertension was present in 18%, diabetes in 8%, and dyslipidaemia in 9%. Efavirenz/nevirapine with two nucleoside reverse transcriptase inhibitors (NRTIs) was in use for 89% of person-time.

There were 788 first MVEs: 457 (58%) strokes, and 331 (42%) acute coronary syndromes and revascularization procedures. Incidence of MVE was 2.5 per 1,000 person-years follow-up.

In the Cox regression model, adjusted for other variables, MVE was associated with older age, male sex, longstanding HIV infection, lower CD4 count at first AfA ART claim, unsuppressed viral load at first AfA ART claim, hypertension, diabetes, and dyslipidaemia. In addition, ART regimens consisting of two NRTIs with a protease inhibitor, or two NRTIs with rilpivirine/etravirine were associated with increased risk of MVE, versus a regimen of two NRTIs with efavirenz/nevirapine.

Conclusion: In this young, mostly female, African cohort, MVE incidence was 2.5 per 1,000 person-years. Background incidence data from this setting is lacking. Stroke predominated, in contrast to high-income settings, where coronary disease is more common. The MVE associations with specific ART regimens we identified deserve further study.

	Unadjusted analysis		Adjusted analysis	
Variable	**Hazard ratio (95% CI)**	**p**	**Adjusted HR (95% CI)**	**p**
Age				
Per 10-year increase	1.8 (1.7 to 2.0)	<0.001	1.2 (1.1 to 1.4)	<0.001
Gender				
Male (versus female)	1.7 (1.5 to 2.0)	<0.001	1.3 (1.1 to 1.5)	0.001
Year of HIV diagnosis				
Up to 2001 (versus 2002 and later)	1.7 (1.1 to 2.6)	0.017	1.8 (1.1 to 2.7)	0.013
Not known (versus 2002 and later)	0.89 (0.77 to 1.0)	0.12	1.0 (0.90 to 1.2)	0.60
CD4 cell count at first AfA ART claim				
<50 (versus ≥350) cells / mm³	1.5 (1.2 to 1.9)	0.001	1.3 (1.0 to 1.7)	0.031
50 to 199 (versus ≥350) cells / mm³	1.2 (0.99 to 1.4)	0.070	1.1 (0.92 to 1.3)	0.27
200 to 349 (versus ≥350) cells / mm³	1.0 (0.83 to 1.2)	0.99	1.0 (0.83 to 1.2)	0.93
HIV viral load at first AfA ART claim				
Unsuppressed (≥ 400 versus suppressed < 400 copies/mL)	1.5 (1.2 to 1.8)	<0.001	1.4 (1.1 to 1.6)	0.01
Hypertension				
Present (versus not present)	6.5 (5.6 to 7.5)	<0.001	4.4 (3.7 to 5.1)	<0.001
Diabetes mellitus				
Present (versus not present)	4.9 (4.2 to 5.8)	<0.001	1.9 (1.6 to 2.3)	<0.001
Dyslipidaemia				
Present (versus not present)	3.9 (3.3 to 4.6)	<0.001	1.6 (1.3 to 1.9)	<0.001
Current ART regimen (all versus 2NRTIs with efavirenz or nevirapine)				
2 NRTIs with rilpivirine or etravirine	1.9 (1.2 to 3.0)	0.011	1.6 (1.0 to 2.6)	0.050
2 NRTIs with a protease inhibitor	1.4 (1.1 to 1.7)	0.009	1.4 (1.1 to 1.7)	0.009
2 NRTIs with an integrase inhibitor	2.3 (0.58 to 9.3)	0.23	1.7 (0.43 to 7.0)	0.44
Other regimen	0.79 (0.42 to 1.5)	0.46	0.73 (0.39 to 1.4)	0.33

660 ASSOCIATION OF HYPERTENSION AND ART USE IN A POPULATION-BASED COHORT, RAKAI, UGANDA

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Background: Antiretroviral therapy (ART) has prolonged survival of people living with HIV (PLHIV). Some studies have reported that HIV and prolonged ART use may result in inflammation, metabolic syndrome and lipodystrophy and that some specific antiretrovirals are associated with development of hypertension. We assessed the association between ART duration and hypertension in a well characterized community cohort.

Methods: We conducted a cross-sectional study among HIV infected adults (35-49) years old on ART in the Rakai Community Cohort Study (RCCS) using 18th survey data conducted from August 2016 to May 2018. Systolic and diastolic blood pressure was measured twice, averaged, and classified as: hypertension (stage 1): Systolic blood pressure (BP) ≥ 140mmHg and/or diastolic BP ≥ 90mmHg, and/or taking anti-hypertensive medication; Severe hypertension (stage 2): Systolic BP> 160mmHg and/or diastolic BP > 100mmHg; hypertensive crisis (stage 3): Systolic BP > 180mmHg and/or diastolic BP > 110mmHg. ART duration was categorized as short (< 2 years), moderate (2-5 years), or prolonged (>5 years). Confounding variables included: age, gender and body mass index (BMI). We used logistic regression to estimate adjusted odds ratios (aOR) of hypertension associated with ART duration.

Results: A total of 1775 HIV infected adults on ART with documented BP information were identified in the RCCS of whom 265 (14.9%) had hypertension stage 1, 119 (6.7%) had hypertension stage 2 and 64 (3.6%) had hypertension stage 3. The rest of the patients (1351) did not have any hypertension and were included in the study. As shown in Table 1, risk of developing all stages of hypertension significantly increased beyond 5 years of ART treatment (Stage 1 aORs=1.55 (95%CI=1.07-2.26); stage 2 aOR=1.70 (95% CI 0.97- 3.01) and stage 3 at aOR=2.32 (95% CI 1.05-5.16).

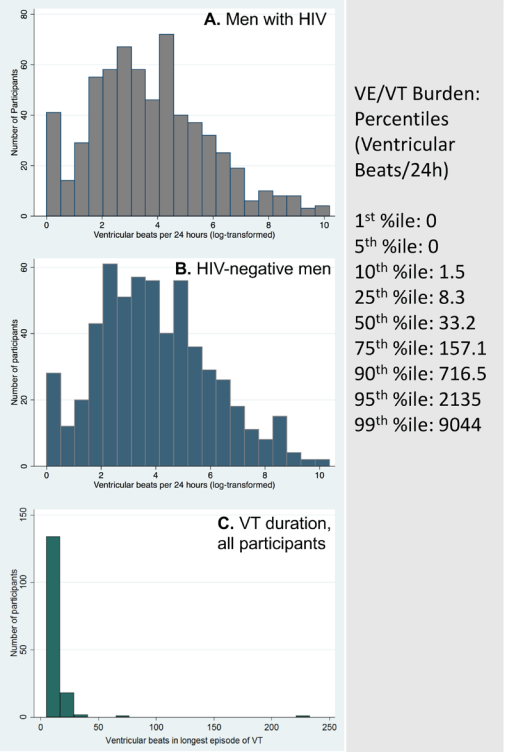
Conclusion: The risk of developing hypertension significantly increases after 5 consecutive years of ART treatment. Routine screening for hypertension should be incorporated into clinical care of PLHIV. Further studies to elucidate the mechanism for prolonged ART use and hypertension are needed.

Table 1: Association of ART duration and risk of Hypertension in HIV infected adults						
Exposure Characteristics		cases /n (%)	unadjusted odds ratios (95% CI)	P Value	Adjusted odds ratios (95% CI) *	P Value
Hypertension ≥ 140-90 mmHg 265/1775 (14.93%)						
ART duration						
	< 2 years	51/455(11.21%)	Ref		Ref	
	2-5 years	55/361(15.24%)	1.36 (0.95-1.94)	0.09	1.3(0.92-1.85)	0.14
	> 5 year	59/333(17.72%)	1.58 (1.12-2.24)	0.01	1.55(1.07-2.26)	0.022
Severe hypertension ≥ 160-100 mmHg 119/1775 (6.70%)						
ART duration						
	< 2 years	22/455 (4.84%)	Ref		Ref	
	2-5 years	25/361 (6.93%)	1.43(0.82-2.50)	0.206	1.34(0.77- 2.35)	0.296
	> 5 years	31/333 (9.31%)	1.93(1.14-3.26)	0.015	1.7(0.97- 3.01)	0.066
Hypertensive crisis >180-110 mmHg 64/1775 (3.61%)						
ART duration						
	< 2 years	11/455 (2.42%)	Ref		Ref	
	2-5 years	10/361 (2.77%)	1.15(0.49- 2.67)	0.752	1.04(0.44- 2.44)	0.926
	> 5 years	23/333 (6.91%)	2.86(1.41- 5.78)	0.004	2.32(1.05-5.16)	0.038

661 VENTRICULAR ARRHYTHMIA PREVALENCE AND FREQUENCY: THE MULTICENTER AIDS COHORT STUDY

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Background: People with HIV (PWH) have higher risks for myocardial scar, heart failure, and sudden cardiac death compared with HIV-uninfected (HIV-) persons. However, little is known regarding the relative burden and characteristics of ventricular ectopy and ventricular tachycardia (VE/VT) among PWH.
Methods: We evaluated ventricular arrhythmias among men with HIV (MWH) and HIV- men in the Multicenter AIDS Cohort Study (MACS). We included 666 MWH (mean age 54.4 ± 11.1 years, 51.3% white, 31.1% black, 46.2% current smokers, 15.6% diabetic, last CD4 count mean 720 ± 308, and 80.7% with last HIV RNA (viral load) undetectable) and 586 HIV- men (mean age 60.5 ± 11.7 years, 72.3% white, 19.2% black, 54.4% current smokers, 14.3% diabetic) who underwent continuous ambulatory electrocardiographic monitoring (Ziopatch® by iRhythm) for a median of 12.7 days (interquartile range 5.7-13.8 days). The primary endpoint was the occurrence of any VE/VT, comparing PWH vs. HIV-. The secondary endpoint was the total number of ventricular ectopic beats per 24 hours. Additional analyses of primary and secondary endpoints were performed among PWH by CD4 count and viral load.
Results: One participant had sustained VT and 43 participants had VT lasting ≥10 (19/666 MWH and 24/586 HIV- men, p=0.22). Any VT/VE was present among 336 PWH (50.4%) and 325 HIV- men (55.9%). Figure 1 displays the distribution of ventricular ectopic beats per 24 hours (log-transformed), by HIV serostatus, and the duration of VT episodes among all participants with any episodes lasting ≥4 beats. After adjustment for age, sex, race, MACS center, smoking, illicit drug use, body-mass index, hypertension, and diabetes, the odds for any VE/VT was similar among PWH vs. HIV- (aOR=1.17 95%CI=0.82-1.68; p=0.39). HIV serostatus with similarly not associated with number of ventricular beats per 24 hours (aOR=123 more beats/24 hours for MWH, 95%CI=-107-354, p=0.29). Among PWH, there was a borderline significant association of lower CD4 count with ventricular beats (per 100 cells/mm$_3$ lower CD4 count: 86 beats more per 24 hours; 95% CI=-181-8; p=0.07); HIV RNA level was not associated with ventricular beats (p=0.69).
Conclusion: We observed no significant difference in the presence or frequency of VT/VE by HIV serostatus among men in the MACS. Among this group of well-controlled PWH, higher CD4 count was associated with marginally less ventricular ectopy at a level not reaching statistical significance.



662 ASSOCIATION BETWEEN HIV AND THE PREVALENCE OF ATRIAL FIBRILLATION AND ATRIAL FLUTTER

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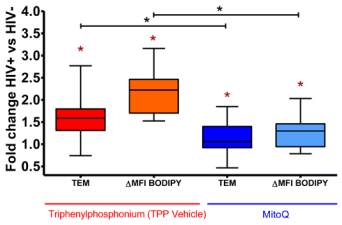
Background: People living with HIV are at increased risk for cardiovascular disease (CVD). The association between HIV serostatus and atrial arrhythmias is incompletely understood. This study was conducted to study the relationship between HIV and atrial fibrillation/flutter (AF/AFL).
Methods: HIV infected (HIV+) and uninfected (HIV-) participants in the 4-city Multicenter AIDS Cohort (MACS) were assessed for AF/AFL by standard resting 12 lead electrocardiograms (EKG) and/or ambulatory EKG monitoring using Zio patch (iRhythm) in 2016-17. Multivariable logistic regression was used to evaluate the association between the composite outcome of AF/AFL and the primary exposure of HIV infection. Associations were adjusted sequentially, first for demographic variables (age, race and study center), and second for both demographic and CVD risk factors (body mass index, cumulative pack year of smoking, cocaine use since last visit, use of medications to treat hypertension or diabetes, heavy alcohol use (>13 drinks/week), fasting glucose level and systolic BP).
Results: The sample included 1669 men; HIV+ men were younger than HIV- men (median 55.5 vs 61.7 years, p<0.001) and were more likely to be African-American (30.6% vs 17.9%, p<0.001). Most HIV+ men (80.0%) had undetectable viral load (<20 copies/mL). Zio patch was worn for a median of 13.0 days (IQR 5.9,14.0). AF/AFL was present in 12 (1.3%) HIV+ men and 25 (3.2%) HIV- men. There was only 1 case of AF/AFL in African-Americans, and 36 cases in Caucasians (2.7% vs 97.3% p<0.001). Although there was a lower odds of AF/AFL among HIV+ compared to HIV- men in unadjusted analyses (odds ratio, 0.41; 95% confidence interval [CI], 0.03-0.82; p= 0.012), there was no association between the odds of AF/AFL and HIV serostatus after adjusting for age, race, and study center (odds ratio, 0.79; 95% CI, 0.38 -1.63; p= 0.53) and after further adjustment for CVD risk factors (odds ratio, 0.88; 95% CI, 0.34 -2.24; p=0.79). There was a 6% increase in the odds of AF/AFL for each yearly increase in age after adjusting for demographics and CVD risk factors (odds ratio, 1.06; 95% CI 1.00-1.03, p<0.001), regardless of HIV serostatus.

Conclusion: HIV serostatus was not associated with prevalent AF/AFL in this cohort of HIV+ men with suppressed viral replication. The prevalence of AF/AFL was low, strongly associated with aging, and rare in African-American men

663 MitoQ ATTENUATES EX VIVO PROATHEROGENIC EFFECTS OF HIV PLASMA IN CHRONIC TREATED HIV

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Background: The mechanisms that drive atherosclerotic cardiovascular disease (CVD) in treated HIV remain unclear. (Pre)clinical studies have shown that the antioxidant MitoQ improves vascular endothelial function by reducing reactive oxygen species production by mitochondria, but its effects in HIV-CVD are unknown. We used an established model of arterial wall to assess ex vivo the impact of MitoQ on early mechanisms of atherogenesis in the presence of plasma from HIV+ individuals on potent antiretroviral therapy (ART).
Methods: Human umbilical vein endothelial cells (HUVECs) were pretreated with MitoQ or vehicle control at 200 nM for 24 hours. Peripheral blood mononuclear cells from healthy donors (n=10) were added to HUVEC for 24 hours on type I collagen gels to undergo transendothelial migration (TEM) and form foam cells [monocyte-derived foam cell formation (MDFCF)] in the presence of pooled plasma (PMID: 28926407). Pooled plasma was isolated from healthy (18-40 years old) and HIV+ (40-60 years old) males with no known inflammatory comorbidities other than HIV or risk factors for CVD and on stable potent ART. Flow cytometry assessed MDFCF (BODIPY signal) and TEM. (Un)paired t-tests were used for statistical comparison between and within compared groups.
Results: When media containing HIV+ compared to HIV- plasma was added to HUVECs pretreated with vehicle, a significantly increased proportion of monocytes underwent TEM (mean 1.6 fold increase) and CD33+ macrophages inside the collagen gel had increased lipid content per cell (mean 2.4 fold increase in ΔMFI BODIPY)($P<0.05$). When media containing HIV+ compared to HIV- plasma was added to HUVECs pretreated with MitoQ, a significantly increased proportion of monocytes underwent TEM (mean 1.2 fold increase) and CD33+ macrophages inside the collagen gel had a mean 1.3 fold increase in ΔMFI BODIPY($P<0.05$). In collagen gels treated with HIV+ plasma, pretreatment of HUVEC with MitoQ attenuated both TEM and MDFCF compared to vehicle control ($p<0.05$ for all comparisons).
Conclusion: MitoQ attenuated proatherogenic effects of HIV-plasma from patients on potent ART with no clinical CVD in ex vivo model of arterial wall. The role of MitoQ in CVD in chronic treated HIV needs to be further studied in vivo.



Red asterisks indicate paired comparisons in measured parameters between HIV+ vs HIV- plasma

Black asterisks indicate unpaired comparisons in measured parameters between MitoQ vs vehicle control groups.

664 HIV AND AGEING: PRIMARY AND SECONDARY PREVENTION OF CAD AMONG PLHIV

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Background: With the introduction of combined antiretroviral therapy for HIV patients, the clinical focus has shifted from AIDS-related opportunistic infections to age-related co-morbidities, specifically cardiovascular disease (CVD). As of 2019, there are approximately 7,760 People living with HIV (PLHIV) in Sweden. This study aims to assess the incidence of MI and stroke among PLHIV in Sweden, as well as their the socio-demographic and biological risk factors. Furthermore, this study aims to compare patients with any CVD with and without HIV with regard to baseline and presentation characteristics and mortality.
For this retrospective cohort study, a total of 6,987 PLHIV were included from the Swedish National HIV Registry database and linked to the National patient register and the cause of death register to gather information on the incidence of MI or stroke. To determine whether HIV was a risk factor for mortality following a CVD event, data from an existing national quality registry for coronary care was merged with the Swedish National HIV Registry. As many as 751,889 patients were included for analysis.
Results: The incidence of MI and stroke among PLHIV in Sweden was 5.2%. The multivariable Cox regression model revealed that the hazard of MI or stroke among PLHIV increased, compared to patients aged ≤30 years old, by 90% (95% CI: 1.3-2.8, p=0.001) among patients 31-40 years old, 2.9 times (95% CI: 2.0-4.3, p<0.001) among patients 41-50 years old, and almost 9-fold (95% CI: 6.1-12.5, p<0.001) among patients >50 years old. Patients who injected drugs had a double hazard (95% CI: 1.4-2.8, p<0.001) compared to patients infected through heterosexual intercourse, while patients infected in Sweden had a 40% higher hazard (95% CI: 1.0-1.8, p=0.020). A multivariable Cox regression model assessing risk factors for mortality following a CVD event showed that HIV positive patients had a 67% (95% CI: 0.93-3.02, p=0.008) higher risk of mortality than HIV negative patients.
Conclusion: The increased incidence of MI in PLHIV compared to the general population of Sweden calls for an increased focus on prevention of CVD in PLHIV. Given that older age is a risk factor for MI among PLHIV, CVD prevention efforts targeting older PLHIV should be scaled up. Moreover, the increased risk of mortality among HIV patients following a CVD event highlights the need for secondary prevention following a CVD event.

Table 4 Effect of HIV status on mortality among 732,830 patients admitted January 1991 and December 2017: a multivariable Cox regression model

Characteristics	Adjusted Hazard Ratio (95 % CI)	P-value
HIV status		
Negative	Ref.	
Positive	1.67 (0.93-3.02)	0.088
Gender		
Male	Ref.	
Female	0.91 (0.89-0.93)	<0.001
Age (years)	1.11 (1.11-1.11)	<0.001
Smoking status		
Never smoker	Ref.	
Ex-smoker (>1 month)	1.20 (1.17-1.23)	<0.001
Smoker	1.98 (1.91-2.05)	<0.001
Snus status		
Never used snus	Ref.	
Ex snus user	0.93 (0.87-0.99)	0.037
Snus user	1.10 (1.04-1.16)	0.001

665 COST-EFFECTIVENESS OF STATIN USE IN HIV-POSITIVE PERSONS IN THE USA: THE D:A:D STUDY

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Background: People living with HIV (PLHIV) have an elevated risk of atherosclerotic cardiovascular disease (CVD) compared to people without HIV. Expanding statin use for the primary prevention of CVD may help alleviate this burden. However, the choice of statin in the context of antiretroviral therapy is challenging. Pravastatin and pitavastatin are preferred agents because they improve cholesterol levels in PLHIV without interacting substantially with antiretroviral therapy. They are also more expensive than most statins. We evaluated the cost-effectiveness of using pravastatin and pitavastatin regardless of cholesterol level for the primary prevention of CVD among PLHIV aged 40-75 years and not currently using lipid-lowering therapy.
Methods: We developed a model that randomly selected (with replacement) individuals from the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. The model simulated each individual's probability of experiencing CVD over 20 years. We evaluated: 1) treating no one with statins; 2) treating everyone with pravastatin 40mg/day (drug cost $236/year); and 3) treating everyone with pitavastatin 4mg/day (drug cost $2,828/year). Direct medical costs (in 2019 US dollars) and quality-adjusted life-years (QALYs) were assigned in annual cycles

and discounted at 3% per year. We assumed the US healthcare sector perspective. Comprehensive sensitivity and scenario analyses were undertaken.

Results: PLHIV receiving pravastatin accrued 0.028 additional QALYs compared with PLHIV not receiving a statin, at an incremental cost of $2,195, giving an incremental cost-effectiveness ratio (ICER) of $79,000/QALY gained. PLHIV receiving pitavastatin accumulated 0.008 additional QALYs compared with PLHIV using pravastatin, at an additional cost of $26,864, giving an ICER of $3,160,000/QALY gained. These findings were most sensitive to the quality-of-life decrement associated with taking an additional daily pill, statin costs and statin efficacy. In scenario analyses, whereby the treatment strategies were only administered to PLHIV at higher risk of CVD, our ICERs improved but did not alter the main conclusions (Table).

Conclusion: At a cost-effectiveness threshold of $100,000/QALY gained, pravastatin was projected to be cost-effective compared with no statin. However, pitavastatin was not cost-effective compared with pravastatin as the incremental benefit was modest.

Table – Incremental cost-effectiveness of statins for primary prevention of CVD among PLHIV over a 20-year time horizon

Strategy	MI, per 1,000 person-years	Ischemic stroke, per 1,000 person-years	Fatal CVD, per 1,000 person-years	Total cost, $	Incremental cost, $	QALYs	Incremental QALYs gained	ICER, $/QALY gained^
Base-case analysis								
No statin	6.5	3.5	2.7	370,721	-	10.739	-	-
Pravastatin 40mg	5.5	3.0	2.3	372,916	2,195	10.767	0.028	79,000
Pitavastatin 4mg	5.2	2.8	2.2	399,780	26,864	10.776	0.008	3,160,000
Scenario 1) Treat only PLHIV with >1% risk of CVD in the next 5 years								
No statin	7.2	3.8	2.9	366,502	-	10.541	-	-
Pravastatin 40mg	6.1	3.2	2.4	368,654	2,152	10.572	0.031	70,000
Pitavastatin 4mg	5.6	3.0	2.3	394,970	26,316	10.583	0.010	2,526,000
Scenario 2) Treat only PLHIV with >5% risk of CVD in the next 5 years								
No statin	12.5	6.5	5.0	336,374	-	9.278	-	-
Pravastatin 40mg	10.6	5.7	4.4	337,990	1,616	9.322	0.044	37,000
Pitavastatin 4mg	10.0	5.3	4.1	360,570	22,580	9.339	0.017	1,363,000

Incremental cost-effectiveness for each strategy was measured relative to the next best strategy in terms of QALYs gained (i.e. pravastatin versus no statin, and pitavastatin versus pravastatin); Costs, QALYs, and life-years were discounted at 3%/year; MI, myocardial infarction; CVD, cardiovascular disease; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; ^Rounded to nearest thousand

666 DEPRESSION COGNITIVE BEHAVIORAL THERAPY TO IMPROVE HIV-CVD RISK: A PILOT RCT

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Background: Depression is associated with an increased risk of cardiovascular disease in the HIV+ population. We hypothesized that reducing depressive symptoms would improve cardiovascular risk in HIV.

Methods: We conducted a single-center, randomized (1:1), controlled, parallel-group, assessor-blinded trial comparing Beating the Blues (BtB) - an evidence-based, 8-session, internet cognitive behavioral therapy for depression - with usual care (UC) in HIV+ patients receiving virologically-suppressive ART (VL <75c/mL) and with Patient Health Questionnaire (PHQ)-9 scores ≥10. The primary endpoint was change in brachial artery flow-mediated dilation (FMD) at 12 weeks. Secondary endpoints were FMD change at 24 weeks and inflammation, coagulation and metabolic biomarker changes at 12 and 24 weeks. Changes in endpoint comparisons were performed using Student t-tests with a p-value <0.05 considered statistically significant. Pre-specified comparisons were also performed for those completing at least 6 sessions in the BtB arm (BtB6-8). FMD comparisons were further adjusted for baseline characteristics using ANOVA.

Results: 54 patients were randomized [17% women, 67% Black, Entry mean age 45.1 yrs, PHQ-9 15.6, Symptom Checklist Depression Scale (SCL)-20 2.2, FMD 3.1%, 69% on antidepressants); 15 in the BtB arm completed at least 6 sessions. Table 1 shows the study results. Mean reductions in PHQ-9 were significantly greater at 12 and 24 weeks with BtB vs. UC; reductions in SCL-20 were significantly greater with BtB vs. UC at 24 weeks. Changes in FMD between arms were no different at 12 or 24 weeks. ANOVA models adjusting for Entry FMD, ART regimen, SCL-20, or antidepressant use or for changes in VL over the study period did not affect FMD comparisons, though significantly worse FMD at 12 weeks (but not 24 weeks) was now found in the BtB6-8 arm compared to UC. Significant reductions in sCD14 and sCD163 were found with BTB at 12 and 24 weeks, respectively.

Conclusion: BtB resulted in greater and clinically relevant improvements in depressive symptoms but did not improve FMD compared to usual care. There was an unexpected greater transient worsening in FMD in the BtB group in those who completed a majority of treatment sessions. Monocyte activation may also be reduced by depression treatment. These data support performing larger studies to determine the short and long term effects of depression treatment on HIV-CVD risk.

Table 1. Changes [mean (SD)] in Endpoints at 12 and 24 weeks

Changes in Endpoint from Entry	UC (n=27)	BtB (n=27)	BtB_{6-8} (n=15)	P-value UC v. BtB	P-value UC v. BtB_{6-8}
DEPRESSION SYMPTOM SCORES					
12 week PHQ-9	***-1.52 (4.55)***	***-5.60 (5.59)***	***-5.80 (6.27)***	***0.007***	***0.017***
24 week PHQ-9	***-1.38 (5.00)***	***-6.00 (6.60)***	***-6.87 (7.07)***	***0.008***	***0.007***
12 week SCL-20	-0.51 (0.49)	-0.63 (0.78)	-0.71 (0.76)	0.51	0.37
24 week SCL-20	***-0.35 (0.44)***	***-0.72 (0.73)***	***-0.83 (0.87)***	***0.029***	***0.06***
FMD					
12 week FMD%	0.29 (2.93)	-0.47 (2.65)	-1.60 (2.89)	0.32*	0.051
24 week FMD%	-0.84 (2.31)	-1.02 (1.37)	-1.11 (1.57)	0.72	0.68
INFLAMMATION, COAGULATION, METABOLIC BIOMARKERS					
12 week hsCRP (mg/L)	1.06 (4.71)	1.22 (3.89)	1.71 (4.44)	0.90	0.68
24 week hsCRP (mg/L)	0.92 (4.79)	-0.26 (2.55)	-0.52 (2.59)	0.33	0.27
12 week IL-6 (pg/mL)	1.24 (4.16)	2.38 (8.71)	3.54 (11.11)	0.57	0.47
24 week IL-6 (pg/mL)	0.56 (2.36)	-0.24 (2.31)	-0.96 (2.53)	0.27	0.08
12 week D-dimer (ng/mL)	-10.26 (651)	3.69 (466)	-28.05 (396)	0.93	0.93
24 week D-dimer (ng/mL)	30.50 (108)	-53.52 (452)	-97.38 (353)	0.75	0.63
12 week sCD14 (ng/mL)	***330 (596)***	***-89 (530)***	***-170 (453)***	***0.014***	***0.010***
24 week sCD14 (ng/mL)	118 (406)	-134 (571)	-125 (523)	0.11	0.14
12 week sVCAM-1 (ng/mL)	-5.48 (47.25)	-4.30 (52.04)	3.95 (48.48)	0.94	0.56
24 week sVCAM-1 (ng/mL)	-0.67 (69)	-3.52 (51)	0.33 (53)	0.88	0.96
12 week sCD163 (ng/mL)	0.99 (6.18)	-0.06 (8.23)	1.97 (8.71)	0.62	0.69
24 week sCD163 (ng/mL)	***4.71 (9.96)***	***-1.36 (5.88)***	***-1.03 (5.28)***	***0.024***	***0.037***
12 week HOMA-IR	1.30 (4.43)	-0.63 (4.47)	-1.31 (4.75)	0.14	0.10
24 week HOMA-IR	2.92 (4.80)	0.33 (5.61)	-0.46 (4.97)	0.11	0.053

*Primary objective comparison

667 FAT GAINS OCCUR AFTER ART WITHOUT CHANGES IN METABOLIC RATE OR CALORIC INTAKE

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Background: Increases in weight and fat gains with antiretroviral treatment (ART) are serious problems in people with HIV (PWH), but the pathogenesis is poorly understood. Some have suggested changes in resting metabolic rate (RMR) and/or caloric intake are responsible, but no data exists. We examined changes in RMR, oxygen consumption (V02), and dietary intake and associations with changes in weight and body composition after ART initiation.

Methods: ART-naïve PWH were prospectively enrolled and underwent a comprehensive clinical and laboratory assessment at baseline and at 6 and 12 months after ART initiation. Fasting RMR/V02 and body composition were measured by indirect calorimetry and whole-body DXA, resp. Nutrient intake was assessed by a registered dietician via 24-hour dietary recalls x3 at each time point and analyzed using dietary analysis software. Changes in variables and associations were assessed using linear mixed effects models.

Results: 30 PWH were enrolled (mean age: 31 yrs, 77% male, 74% black; mean baseline CD4 444 cells/mm_3; HIV RNA 267,148 copies/mL, BMI 28.6 kg/m_2, RMR 1420 kcal/day, V02 205 mL/min, 1690 total kcal average daily intake). All but 1 initiated an integrase inhibitor-based regimen (53% DTG; 37% TAF). By 6 and 12 months, all but 3 and 1 participant, respectively, had an HIV RNA <200 copies/mL. At both time points, there was a significant increase in mean weight, total fat and trunk fat (6 mo/12 mo: +3.8/+10.2 kg, +2.4/+4.6 kg, +1.6/+3.4 kg, resp; all P<0.05), but a nonsignificant increase in total lean body mass (+1.7/+2.7 kg; P=0.09/P=0.71). Over the study period, there were no significant changes in RMR, V02 or dietary intake (kcal, total fat, saturated fat, fiber, protein, total sugars, fructose, branched-chain amino acids, or arginine) (all P>0.70). All body composition changes were significant after adjusting for sex, baseline HIV RNA and RMR (or V02) at both time points except for lean body mass at 12 months.

Conclusion: Significant increases in weight and fat gains were seen after ART initiation, despite a lack of significant changes in RMR, V02 or diet. All body composition changes except for lean body mass at 12 months were significant after adjusting for RMR or V02. These data do not support the hypothesis that changes in RMR or caloric intake are responsible for increases in weight and fat gains after ART initiation in PWH.

668 GREATER WEIGHT GAIN AFTER SWITCH TO InSTI-BASED REGIMEN FROM NNRTI VS PI REGIMENS

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Background: Recent reports describe greater weight gain among antiretroviral therapy (ART)-naïve persons with HIV (PWH) starting integrase strand transfer inhibitor (INSTI)-based antiretroviral therapy (ART) vs. protease inhibitor (PI) or non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based ART. Since many PWH have switched from non-INSTI to INSTI-based regimens, we assessed weight over time among PWH switched to an INSTI regimen (before the introduction of tenofovir alafenamide) in the multisite North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).
Methods: Adult PWH with >2 years of no HIV-1 RNA measurements >1000 copies/mL prior to and following the switch from an NNRTI- or PI- to INSTI-based ART were included. Piecewise linear mixed models with random intercepts and slopes estimated pre- and post-switch weight over time, adjusting for age, sex, race, cohort site, HIV acquisition mode, calendar year, pre-switch ART class (NNRTI vs. PI), and CD4+ T cell count and BMI at the time of switch. We included interaction terms for sex, race, and age (<50 vs. >=50) with regimen and time.
Results: A total of 2255 participants switched to an INSTI and had the required follow-up time; of these, 877 met viral suppression criteria and were included. At switch, median age was 50 years, BMI 26 kg/m$_2$, and CD4+ count 619 cells/mm$_3$; 83% were men, and 59% were white. Overall, the annualized weight slope among PI users was +0.80 (95% CI: 0.57 to 1.04) kg/year before switch, which decreased by -0.46 (-0.67 to -0.26) after switch to an INSTI (absolute slope +0.34 kg/year after switch). For NNRTI users, the slope before switch was +0.63 (0.34 to 0.91) kg/year, increasing by +0.50 (0.23 to 0.77) after switch to an INSTI (absolute slope +1.13 kg/year after switch). This difference was primarily driven by an increase in the weight slope among women, non-whites, and older PWH in the NNRTI group (table). Among individual INSTI drugs, the slope change after switch from NNRTI was highest for dolutegravir (DTG) at +0.93 (0.39 to 1.46) kg/year vs +0.44 (-0.04 to 0.92) kg/year for elvitegravir and +0.23 (-0.13 to 0.58) kg/year for raltegravir.
Conclusion: Women, non-whites and older PWH with viral suppression had greater annualized weight gain after switch from NNRTI- to INSTI-based ART, which was greatest for dolutegravir, whereas those switched from a PI had slowing of weight gain. These findings may reflect a heterogenous effect of ART class and agent on body weight regulation.

Table: Estimated change in weight-over-time following a switch from NNRTI- vs. PI-based to INSTI-based ART regimens by sex, race, and age

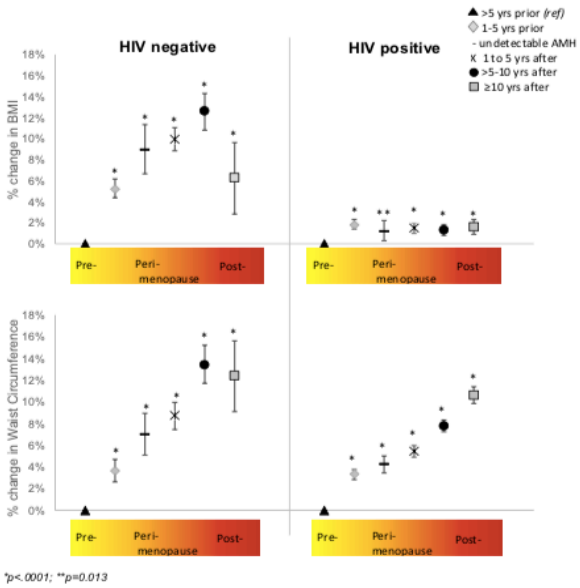
Group	Females		Males		Non-white		White		Age <50		Age ≥50	
Pre-switch regimen	**NNRTI**	**PI**	**NNRTI**	**PI**	**NNRTI**	**PI**	**NNRTI**	**PI**	**NNRTI**	**PI**	**NNRTI**	**PI**
Weight over time slope before switch (95% CI)*	0.14 (-0.68 to 0.95)	0.94 (0.42 to 1.46)	0.72 (0.40 to 1.03)	0.77 (0.51 to 1.03)	0.76 (0.30 to 1.22)	1.04 (0.69 to 1.39)	0.60 (0.23 to 0.98)	0.61 (0.31 to 0.92)	0.97 (0.57 to 1.37)	0.87 (0.54 to 1.19)	0.21 (-0.22 to 0.65)	0.70 (0.37 to 1.04)
Change in slope after switch to INSTI (95% CI)	+1.44 (0.78 to 2.11)	-0.45 (-0.92 to 0.03)	+0.32 (0.02 to 0.61)	-0.47 (-0.69 to -0.24)	+1.27 (0.87 to 1.68)	-0.60 (-0.91 to -0.29)	-0.11 (-0.47 to 0.25)	-0.36 (-0.63 to -0.08)	-0.08 (-0.44 to 0.29)	-0.24 (-0.54 to 0.07)	+1.17 (0.78 to 1.57)	-0.66 (-0.94 to -0.38)
p-value for slope change	**<0.001**	0.07	**0.04**	**<0.001**	**<0.001**	**<0.001**	0.54	**0.01**	0.69	0.13	**<0.001**	**<0.001**

*Slope values refer to kilograms per year over the 2 years after switch to INSTI

669 BODY COMPOSITION CHANGES OVER THE MENOPAUSAL TRANSITION IN HIV+ AND HIV– WOMEN

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Background: Both overall and central adiposity are reported to increase during the menopausal transition. Whether HIV infection affects adiposity changes during this transition is unknown. We hypothesized that body mass index (BMI) and waist circumference (WC), a marker of visceral adiposity would increase over the menopausal transition and that HIV infection would blunt increases in BMI, and to a lesser extent WC due to the known effects of HIV on subcutaneous fat.
Methods: Between 2000 and 2013, 632 HIV+ and 218 HIV– Women's Interagency HIV Study participants underwent serial measures of BMI, WC, and Anti-Müllerian Hormone (AMH), a biomarker of ovarian reserve. The menopausal transition was categorized as: premenopause(>5years[yrs] before AMH became undetectable), early perimenopause(1-5yrs before), late perimenopause(first visit with undetectable AMH and up to 5yrs after), menopause(>5-10yrs after), and late menopause(>10yrs after). We used multivariable linear mixed regression models which adjusted for demographic, behavioral, viral hepatitis, and CD4 count to estimate percentage(%) changes in BMI and WC relative to premenopause.
Results: Women were mostly African-American (58%); mean age at onset of late perimenopause was ~45yrs in both HIV+ and HIV- women. HIV+ had lower BMI and WC than HIV– (mean:29 vs. 32kg/m$_2$;p<0.0001 and 94 vs 98cm;p=0.004, respectively). Figure shows the % BMI and WC change after adjustment. In HIV– women, we found the expected increase in BMI across the menopausal transition (from 5.2 to 12% higher than in premenopause) whereas in HIV+, the increase was much lower (1.2-1.8% higher) and blunted across the entire menopausal transition (difference in BMI change by HIV status at every stage,p<0.01). By contrast, WC progressively increased over the menopausal transition in HIV+ but the increase was blunted (difference in WC change by HIV status,p<0.01 except early perimenopause,p=0.41 and late menopause,p=0.14).
Conclusion: Our findings suggest that HIV infection blunts the expected trajectory of increase in BMI over the menopausal transition, whereas the expected trajectory of increase in WC is preserved but also blunted. Studies are needed to examine whether women with HIV in the menopausal transition are at greater risk for perturbations associated with visceral obesity (e.g. insulin resistance, fatty liver disease) and to determine optimal timing of interventions to reduce visceral obesity.



*p<.0001; **p=0.013

670 RESISTIN GENE POLYMORPHISM RELATED TO WEIGHT GAIN AND PSYCHIATRIC SYMPTOMS ON InSTI

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Background: Weight gain and psychiatric symptoms (PSs) have been reported in persons living with HIV (PLWH) receiving ART, especially integrase strand transfer inhibitors (INSTI). Obesity and PSs are correlated with chronic inflammatory states characterized by insulin resistance. Resistin is a pro-inflammatory adipokine and plays a key role in the insulin responsiveness of peripheral tissues and the central nervous system. A single-nucleotide polymorphism (SNP) at −420C>G in the resistin gene is correlated with serum resistin level in Japanese people. We clarified the influence of SNP −420C>G on weight gain and PSs in PLWH receiving INSTI.
Methods: Participants were PLWH who started ART with INSTI (n=220) or protease inhibitors (PI; n=62). Body mass index (BMI) was measured before and 6 months after starting ART. PSs was evaluated with the Profile of Mood States or Self-rating Depression Scale. SNP −420C/G was investigated using PCR. Linear regression analysis was used to assess factors associated with BMI change and PSs. We examined several variables in addition to SNP −420C/G that may affect BMI and PSs. Variables that were significant in univariate analyses were incorporated in multivariate models.
Results: BMI increased by 0.86 kg/m$_2$ (p<0.001, paired t-test) in the INSTI group and 0.33 kg/m$_2$ (p=0.04, paired t-test) in the PI group. In total, 24% of the INSTI group and 14% of the PI group showed PSs. The simple regression

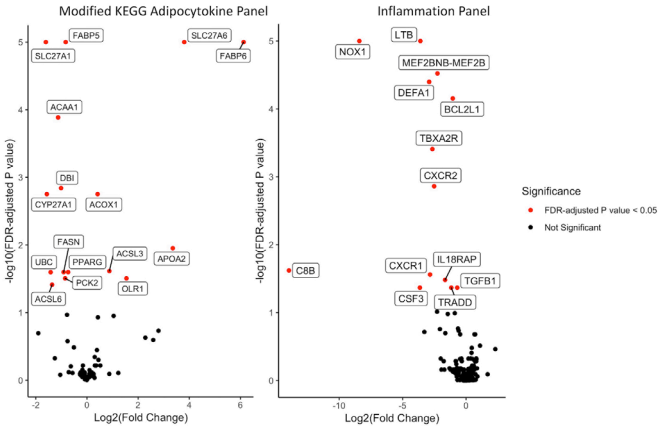
analysis showed BMI increase was significantly associated with low body weight and low CD4 counts before ART, use of tenofovir alafenamide (TAF) as the treatment backbone, smoking, and the SNP −420G allele in the INSTI group. In this group, the fully adjusted multiple linear regression analysis showed low body weight (p=0.016) before ART, use of TAF(p=0.028), smoking (p=0.027), and the SNP −420G allele (p=0.005) were associated with BMI increase. PSs was significantly associated with smoking and the SNP −420G allele in simple (p=0.027, p=0.004) and fully adjusted (p=0.026, p=0.001) linear regression analyses. In the PI group, BMI increase was associated with low BMI before ART (p=0.0014), but no factors were associated with PSs.
Conclusion: We showed that the −420C>G resistin gene is independently associated with weight gain and PSs in PLWH on INSTI. This highlights the pivotal role of resistin in linking INSTI-related symptoms characterized by insulin resistance.

671 ADIPOCYTE DYSFUNCTION DESPITE REDUCED ADIPOSE INFLAMMATION IN DIABETICS WITH HIV

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Background: Adipose tissue has a central role in the regulation of metabolism. Exposure to early antiretroviral therapy (ART) regimens, including thymidine analogues, was associated with increased adipose tissue inflammation and risk of diabetes in persons with HIV (PWH). Few studies have assessed the relationship of adipose tissue inflammation and insulin resistance in PWH on newer ART regimens.
Methods: 73 PWH with > 12 months sustained viral suppression, principally on integrase inhibitor-based ART and < 10% with historic thymidine analogue exposure, were classified as insulin sensitive (n = 46; hemoglobin A1c < 5.7% and fasting blood sugar < 100 mg/dL) vs. diabetic (n = 27; on anti-diabetic medications) and underwent subcutaneous abdominal adipose tissue liposuction. Tissue was immediately flash frozen for subsequent total RNA extraction, and mRNA was quantified using the Nanostring nCounter® human inflammation panel containing 250 genes, and a separate panel containing 77 genes modified from the KEGG adipocytokine pathway. mRNA expression was compared by diabetes status adjusting for age, sex, and body mass index (BMI).
Results: 78% of study participants were male. The median age was 45 years and 55 years, and median BMI 31 kg/m_2 and 34 kg/m_2, for non-diabetic and diabetic participants, respectively. Analysis of adipocyte-related genes revealed that diabetic individuals had lower expression of genes involved in the AMPK signaling (FASN, PPARG, PCK2) and fatty acid biosynthesis (FASN, ACSL6) pathways, and increased expression of genes involved in fatty acid degradation (ACOX1, ACSL3) (FDR-adjusted p value < 0.05; Figure 1). Inflammatory gene analysis showed that diabetics had lower expression of genes related to inflammation than non-diabetics, including NF-kappa B signaling and cytokine-cytokine interaction pathways (FDR-adjusted p value < 0.05; Figure 1).
Conclusion: In one of the largest and broadest assessments of adipose tissue gene expression in non-diabetic vs. diabetic PWH on modern ART, we found pronounced differences in adipocyte-related genes, consistent with dysregulation of metabolic pathways in diabetes, but less evidence of increased adipose tissue inflammation in contrast to studies of PWH on older ART. Single-cell studies are planned to investigate whether adaptive immune cells or other mechanisms that may not be captured in whole tissue contribute to adipocyte dysfunction and diabetes.

Figure 1. Volcano plot showing $\log_2$ fold change (diabetic compared to insulin sensitive) gene expression vs. -$\log_{10}$ FDR-adjusted p value for genes associated with the KEGG pathway (77) and inflammation panel genes (249). Genes with FDR-adjusted p values < 0.05 are labeled.



672 INCREASED INFLAMMATORY CX3CR1+GPR56+CD57+ CD4+ T CELLS IN FAT FROM HIV+ DIABETICS

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Background: Persons with HIV are at higher risk of diabetes mellitus compared to the general population, which may be due, in part, to altered lipid metabolism and storage. Compared to HIV+ non-diabetics, adipose tissue from HIV+ diabetics is enriched for CX3CR1+ GPR56+ CD57+ (i.e., 'C-G-C') CD4+ T cells and a separate population of CD69+ CD4+ T cells. CX3CR1 and GPR56 are associated with anti-viral responses, including against cytomegalovirus (CMV). To assess if these cells are also common in HIV-negative diabetics, we compared C-G-C and CD69+ T cells in the adipose tissue of HIV+ vs. HIV-negative diabetics of similar age and body mass index.
Methods: We performed subcutaneous abdominal liposuction and T cell isolation on 11 diabetic persons (6 HIV+ and 5 HIV-negative, all subjects CMV+), followed by flow cytometry phenotyping and single-cell sorting of memory T cells. Single-cell cDNA libraries were created using well-specific barcodes followed by 3' and 5' amplification and sequencing. Pooled data were demultiplexed and the transcriptome was linked to the indexed flow cytometry phenotype. We compared the proportion of C-G-C and CD69+ CD4+ T cells by HIV status using Mann-Whitney tests. Differential expression and pathway analyses were performed for immune genes in C-G-C and CD69+ CD4+ T cells in the HIV+ and HIV-negative participants.
Results: A larger fraction of the adipose tissue memory CD4+ T cells from HIV+ diabetics expressed the C-G-C combination (23% versus 3% in HIV-negative, p<0.05; Fig. A), CD69+ cells trended higher in the HIV-negative (54% versus 28% in HIV-positive, p= 0.18). The proportion of adipose tissue C-G-C cells was positively correlated with the percent of T effector memory RA+ cells (p < 0.01), a subset expanded in CMV infection. Compared to adipose tissue C-G-Clo cells, pathway analysis of the top 100 immune genes expressed by C-G-C cells in the HIV+ diabetics indicated TH1, interferon-gamma response (Fig. B) and IL-27 signaling pathways (a promoter of TH1 polarization).
Conclusion: Adipose tissue of diabetic HIV+ is enriched for an inflammatory population of potentially anti-viral CD4+ T cells expressing CX3CR1, GPR56 and CD57, which are present at far lower levels in HIV-negative diabetics. Adipose tissue serves as a reservoir for HIV, CMV, and other viruses, and further studies will determine if C-G-C cell responses target viral antigens and may impair adipocyte function.

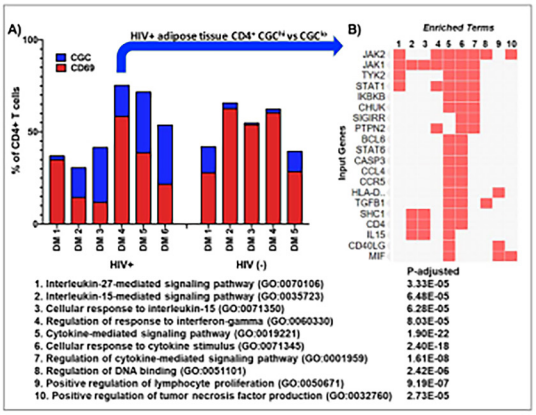


Figure Legend: (A) Higher relative levels of CX_3CR1^+ $GPR56^+$ $CD57^+$ (i.e., 'C-G-C') $CD4^+$ T cells as a percentage of all memory $CD4^+$ T cells in adipose tissue of HIV+ diabetics, while $CD69^+$ $CD4^+$ T cells are more common in HIV-negative diabetics. **(B)** Within the diabetic HIV+ participants, single cell RNA transcriptome of C-G-C $CD4^+$ T cells as compared to C-G-C^{lo} $CD4^+$ T cells shows enrichment for pro-inflammatory T_H1 cell polarization and response pathways.

673 TELMISARTAN DECREASES MONOCYTE CX3CR1 EXPRESSION IN TREATED HIV INFECTION

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Background: Telmisartan is an angiotensin receptor blocker and PPAR-g agonist that is active in adipose tissue (AT) and has anti-inflammatory properties. Secretion of fractalkine by adipocytes and expression of its receptor, CX3CR1, on monocytes/macrophages have been implicated in AT inflammation, obesity and cardiovascular disease (CVD). Fractalkine/CX3CR1 expression are mediated by PPAR-g suppression and endotoxemia, both sequelae of HIV. We hypothesized that telmisartan would improve the profile of AT immune cells and AT function in persons with HIV (PWH) on suppressive antiretroviral therapy (ART).

Methods: AIDS Clinical Trials Group study A5317 randomized (2:1) PWH >/=18 years old on ART and with HIV-1 RNA <50 copies/mL for >/=48 weeks to receive telmisartan or no drug (controls) for 48 weeks. In a secondary analysis of persons remaining on study drug (if applicable) and ART, maintaining HIV-1 RNA < 200 copies/mL and having subcutaneous AT biopsy samples at weeks 0 and 48, AT immune cell profiling was performed via flow cytometry and IL-6, adiponectin and insulin gene expression determined by PCR array. 48-week changes were compared used two-sided rank-sum, signed-rank tests, and Spearman correlations (a=0.05).

Results: Thirty-five participants (22 telmisartan, 13 control) met inclusion criteria; 94% were male and 49% white non-Hispanic. Median age was 49 years and CD4+ T cell count 572 cells/mm_3. Over 48 weeks, median CD14+16-CX3CR1+monocyte numbers decreased -10.4% in telmisartan-treated PWH, and increased 13.1% in controls (between-group p=0.029). Similar trends were observed for CD14+16+CX3CR1+, CD14lo16+CX3CR1+and CD163+CX3CR1+monocytes (Table). CD14+16-TLR4+monocytes decreased -4.2% in telmisartan-treated PWH vs 0.0% change in controls (between-group p=0.036). Trends were seen for correlations between decreases in CD14+16-CX3CR1+monocytes/increases in insulin gene expression (r=-0.50, p=0.07, n=14), and decreases in CD14+16-TLR4+ monocytes/increases in adiponectin gene expression (r=-0.50, p=0.08, n=13).

Conclusion: In PWH on suppressive ART, telmisartan reduced CX3CR1 and TLR4 expression on monocytes, changes that correlated with improved markers of AT function. Given the role of CX3CR1 in AT inflammation, obesity and CVD, telmisartan has the potential to modulate CVD risk in PWH.

	Telmisartan		Control		Between-group P value[2]
	Median (IQR)	P value[1]	Median (IQR)	P value[1]	
$CD14^+16^-CX3CR1^+$	-10.4% (-33.3, 13.6)	0.33	13.1% (-0.8, 19.1)	0.06	0.029
$CD14^+16^+CX3CR1^+$	-18.7% (-44.8, 22.9)	0.31	10.7% (-13.3, 26.8)	0.38	0.15
$CD14^{lo}16^+CX3CR1^+$	-15.7% (-42.7, 31.3)	0.55	11.6% (-13.0, 35.5)	0.31	0.25
$CD163^+CX3CR1^+$	-15.4% (-33.9, 13.8)	0.18	12.1 (-17.6, 17.7)	0.68	0.29
$CD14^+16^-TLR4^+$	-4.2% (-12.0, -0.6)	0.002	-0.0% (-5.5, 3.1)	0.68	0.036

[1] Signed-rank test; [2] two-sided rank-sum test.

674 GUT INTEGRITY MARKERS AND ASSOCIATIONS WITH ADIPOSITY IN PEOPLE WITH AND WITHOUT HIV

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Background: Fat accumulation after ART initiation remains a serious problem in people with HIV (PWH), but little is known about its pathogenesis. Gut barrier dysfunction may play a role, but data are inconsistent and lack adequate control groups. We compared gut integrity markers in PWH before and after ART to an uninfected control group and assessed associations between gut integrity markers and body composition.

Methods: Data from uninfected controls (matched by age, sex, and race) were prospectively collected and compared to data from participants prospectively enrolled in a treatment initiation study, ACTG A5260s, at 2 timepoints: pre-ART and 96 weeks after suppressive ART. Plasma levels of gut integrity markers, zonulin, intestinal fatty-acid binding protein (I-FABP), lipopolysaccharide binding protein (LBP) and beta-D-glucan (BDG), were measured by ELISA. Body composition was assessed by whole-body DXA. Groups were compared using logistic or linear regression with adjustment for matching factors, and associations were assessed using linear regression models.

Results: 234 PWH and 116 controls were included. Groups were similar in age and race (PWH: mean 38 yrs, 65% white, non-Hispanic), but PWH included more men (90% vs 80%; P=0.01). PWH pre- and post-ART had significantly higher levels of I-FABP and zonulin (mean difference: 0.37 to 0.59 log_{10} pg/mL and 0.54 to 0.56 log_{10} ng/mL, resp), but lower levels of LBP (mean difference: 2.65 to 2.66 log_{10} ng/mL) vs controls (all P<0.001). PWH had similar levels of BDG pre-ART, but higher levels post-ART vs controls (mean difference: 0.14 log_{10} pg/ml, P=0.004). In all models for controls, LBP, I-FABP and BDG showed associations with body composition measures (Table); however, associations with SAT were slightly attenuated when adjusted for sex. In PWH post-ART, I-FABP was significantly associated with outcomes in both unadjusted and adjusted models with effect sizes larger in magnitude than in controls (Table); limited associations were observed with I-FABP at the pre-ART time point.

Conclusion: Levels of gut integrity markers, I-FABP and zonulin, were higher in PWH both pre- and post-ART, and BDG was higher in PWH post-ART. Gut integrity markers showed significant associations with several body composition measures in uninfected controls, but the strongest associations were seen with I-FABP among PWH on suppressive ART. I-FABP levels may help predict deleterious fat changes after ART initiation.

Regression Estimates for Associations between Gut Integrity Markers and Outcome Measures

Outcome	Uninfected Controls								PWH Post-ART	
	LBP		BDG		Zonulin		I-FABP		I-FABP*	
	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
VAT Area (cm^2)	26.07 (4.46, 47.68)	**0.019**	-4.71 (-9.48, 0.07)	0.053	0.55 (-10.6, 11.73)	0.923	-7.34 (-17.5, 2.84)	0.156	-4.57 (-16.6, 7.44)	0.454
SAT Area (cm^2)	56.48 (10.12, 102.8)	**0.017**	-8.84 (-19.1, 1.45)	0.092	8.27 (-15.7, 32.22)	0.495	-23.2 (-44.8, -1.58)	**0.036**	-51.2 (-82.2, -20.2)	**0.001**
Trunk Fat (kg)	3.72 (1.04, 6.40)	0.077	-0.45 (-1.05, 0.15)	0.129	0.82 (-0.57, 2.21)	0.244	-0.95 (-2.22, 0.33)	0.143	-2.12 (-3.38, -0.86)	**0.001**
Total Fat (kg)	5.80 (1.29, 10.31)	**0.012**	-0.81 (-1.82, 0.19)	0.133	1.14 (-1.19, 3.47)	0.333	-1.99 (-4.11, 0.12)	0.065	-3.94 (-6.21, -1.68)	**<0.001**
BMI (kg/m^2)	2.74 (0.44, 5.05)	**0.020**	-0.54 (-1.05, -0.03)	**0.037**	0.79 (-0.39, 1.97)	0.187	-0.72 (-1.81, 0.37)	0.193	-2.02 (-3.11, -0.92)	**<0.001**
WC (cm)	6.77 (0.60, 12.94)	**0.032**	-1.27 (-2.63, 0.09)	0.066	2.31 (-0.84, 5.46)	0.150	-2.28 (-5.17, 0.61)	0.121	-4.57 (-7.32, -1.82)	**0.001**
HOMA-IR (log_{10})	0.10 (-0.02, 0.23)	0.096	-0.01 (-0.04, 0.02)	0.392	0.04 (-0.03, 0.10)	0.265	0.01 (-0.05, 0.07)	0.744	0.01 (-0.06, 0.07)	0.780

Non-normal data were log-transformed on the log-10 scale. Gut marker estimates are presented as per 0.3 log_{10} units, which is equivalent to a 2-fold difference. P values <0.05 are bold-faced. *Significant associations all remained P≤0.002 after adjustments for age, sex, race, smoking, drug use and excessive alcohol use. VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index; WC, waist circumference; HOMA-IR, homeostasis model of insulin resistance

675 CONTRIBUTION OF InSTI, BMI, PHYSICAL ACTIVITY, CALORIC INTAKE TO WEIGHT GAIN IN PWH

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Background: Weight gain in people living with HIV (PWH) is a multifactorial phenomenon in which the relative contribution of traditional and HIV specific modifiable risk factors is not known. The aim was to assess the population

attributable fractions (PAFs) of lifestyles and INSTI regimens in PWH who experienced a 5% weight gain over 4 years.

Methods: In an observational cohort study from 2007 to 2019 at Modena HIV Metabolic Clinic, virally suppressed ART-experienced but INSTI-naive PWH were grouped in INSTI-switchers vs non-INSTI on stable ART. Groups were matched for sex, age, 1st visit BMI and follow-up duration. Significant weight gain was defined as an increase of ≥5% from 1st visit weight over follow-up. Physical activity was assessed with International Physical Activity Questionnaire (IPAQ) as metabolic equivalent of task (MET). Daily caloric intake (DCI) was evaluated with a 3 day food diary. PAFs and 95% CIs were estimated to quantify the proportion of outcomes that could be avoided if the risk factor was prevented, using the following dichotomic variables: BMI >25 kg/m_2 vs <25 kg/m_2, DCI >2500 kcal vs <2500 kcal, IPAQ MET <600 vs MET>600, quitting vs continuing smoking, INSTI vs no-INSTI regimens, and CD4/CD8 ratio <1 vs >1.

Results: Of 304 PWH (74% males), mean follow-up was 4.2 years (±1.8 SD), age 54.3 (±7.8 SD) years, median duration since HIV diagnosis 22.3 years (IQR 15.5-27.5), CD4 cell count 716 cells/mL (IQR 564-893);98.7% had undetectable HIV-1 RNA (Table). PAF for weight gain was the greatest for BMI (41%, 24-56, p<0.001), followed by CD4/CD8 ratio (38%, 19-55, p<0.001) and physical activity (33%, 95% CI 8-53, p<0.02). PAF was not significant for DCI (-1%, 9-13, p=0.99), smoking cessation (5%, 0-13, p=0.1) and INSTI switch (9%, -20-33; p<0.51).

Conclusion: Our findings suggest that weight gain is mostly influenced by pre-existing weight and low physical activity. High CD4/CD8 ratio suggest additional immunologic mechanisms linked to weight gain.

Study population at follow-up	<5% Weight gain n=225	≥5% Weight gain n=79	p
Age, years, mean (± SD)	54.9 ± 7.8	53 ± 7.7	**0.003**
Male sex, %	79%	59.5%	**0.001**
BMI	23.5 ± 3.2	25.6 ± 4	**<0.001**
Obesity, %	4.9	15.2	**0.007**
Multimorbidity, n (%)	105 (46.7%)	34 (43%)	0.67
Smoke pack year, median (IQR)	16 (1.88-30)	14.5 (1.15-30.95)	0.88
IPAQ score, MET (± SD)	977.7 ± 976.6	642.4 ± 652.9	**0.002**
Daily calories intake, mean	1951 ± 533	1953 ± 499	0.8
HIV duration, years, median (IQR)	22.3 (16,4 - 27.6)	22.2 (14.1 – 27.3)	0.51
Current CD4 cell count, cells/µL median (IQR)	711 (538 – 844)	794 (602 – 1042)	**0.01**
Nadir CD4, cells/µL, median (IQR)	200 (99-200)	162 (89 – 264)	0.12
CD4/CD8 ratio, mean (± SD)	0.92 ± 0.5	1.1 ± 0.5	**0.005**
Exposure to INSTI, n (%)	93 (41.3%)	36 (45.6%)	0.6

676 UNDERSTANDING WHO DOES AND DOES NOT GAIN WEIGHT WITH INTEGRASE INHIBITORS (InSTI)

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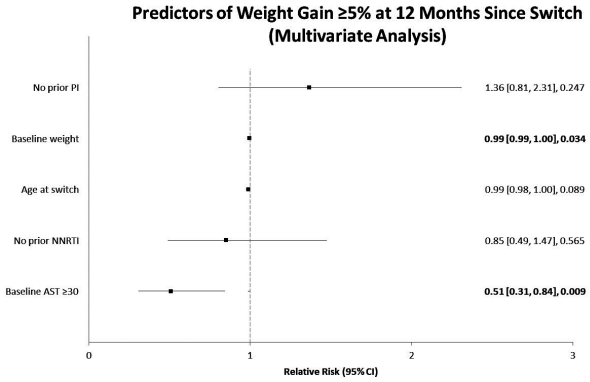
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Background: Randomized clinical trials have shown greater weight gain with INSTI regimens vs other classes of antiretrovirals. Why do some patients gain weight on INSTI and others do not? Are there synergies with other ARV agents and INSTI? We examine HIV patients (pts) in US clinical care switching to INSTIs and compare those with gain ≥5% body weight vs loss or gain <5% after 12 months (mo) on INSTIs.

Methods: A retrospective evaluation of 38000 HIV pts with EMR records selected 2384 virally suppressed pts per protocol. Subgroup analysis was conducted in 387 subjects: pts ≥18 years, switched to INSTI regimens in Jan 2015-Jun 2018 for ≥12 mo, with ≥6 mo history, viral suppression and weights at baseline [BSL] and 12 mo (±2 mo). Univariate analyses [UV] were conducted via chi-square and t-test. Multivariate analysis [MV] with a binary outcome of gain ≥5% at 12 mo was conducted using log binomial model; variables significant in UV and demographics were considered; final model included continuous variables age, BSL weight and categorical BSL AST <30 vs ≥30, use of prior protease inhibitors [PI] and prior non-nucleoside reverse transcriptase Inhibitors [NNRTI].

Results: Of 387 pts switched to INSTIs, 103 (27%) gained ≥5% weight, 140 (36%) lost weight or had 0% change, 144 (37%) gained <5%. In comparison to other study pts, those who gained ≥5% had significantly lower BSL weight, BMI, AST (but not ALT; alcohol abuse by ICD-10 observed in <4%), lower use of prior PI, and higher use of prior NNRTI. There were no statistically significant differences by NRTI backbone and specific INSTIs between those who gained ≥5% vs those who did not. In MV, pts were less likely to gain ≥5% if they had BSL AST≥30 (relative risk [RR]=0.51 [CI 0.31-0.84], p=0.009) or higher BSL weight (RR=0.99 [CI 0.98-1.00], p=0.034).

Conclusion: Of 387 pts switching to INSTIs, over 1/3 lost or maintained weight, over 1/3 experienced weight gain <5%, while remaining 27% experienced gain ≥5% after 12 mo on therapy. UV indicated ≥5% gain was associated with prior regimen components and BSL factors of which only BSL weight and AST remained significant in MV. Future research questions include clinical significance of weight gain thresholds that have implications for morbidity, as well as heterogeneity of responses to ARV agents.



677 DRUG CONCENTRATIONS AND BODY WEIGHT GAIN IN PLWH SWITCHED TO 3TC & DOLUTEGRAVIR (DTG)

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Background: Weight gain after initiation of DTG-containing ART has recently been reported in clinical trials and cohorts, but pathophysiology remains unclear. In most switch studies, DTG was associated with a 2-NRTIs backbone. We evaluated changes in body weight in virologically suppressed PLWH switched to 3TC plus DTG dual therapy (ANRS 167 Lamidol trial).

Methods: Virologically suppressed patients included in the ANRS 167 Lamidol [Joly et al. Antimicrob. Agents Chemother. , 2019], a single arm study, received 8 weeks DTG (50 mg qd) combined with 2 NRTIs backbone (phase 1, from W-8 to D0) before switching to DTG/3TC for 48 weeks (phase 2, from D0 to W48, 104 patients). All patients entering phase 2 were evaluated, except for 8 subjects exposed to DTG prior to study entry. Body weight was recorded at each visit i.e. W-8, W-4, D0, W8, W16, W24, W36 and W48. The evolution of weight over time was analyzed using a linear mixed effects model. Total DTG and 3TC plasma concentrations (C_{min}) were measured at D0, W24 and W48 using UPLC-MS/MS. The relationships between weight variation between W-8 and W48 and the geometric means of DTG and 3TC concentrations were studied using the Spearman correlation coefficient.

Results: 96 patients were evaluated (median age 45.2 years, range 23.9-70.6). 82 (85.4%) were male. Before inclusion in the trial, ART regimen included a PI in 24 patients, a NNRTI in 58 patients and an INSTI other than DTG in 14 patients. Median baseline weight was 73.5 kg (IQR 65-80). Weight gain was 1.15 kg (IC 95% 0.45-1.85, p=0.002) during phase 1 and 1.22 kg (IC 95 1.04-1.40, p<0.0001) during phase 2. Weight gain was significantly more rapid during phase 1 (p<0.0001). There was no relationship between weight variation and geometric means of DTG and 3TC C_{min}.

Conclusion: In this population of virologically controlled patients, administration of DTG was associated with significant weight increase. This effect was more important at initial phase of DTG administration when DTG was associated to a 2 NRTIs backbone, but persisted when DTG was combined with 3TC only, and was not related to trough plasma DTG concentrations. These

results suggest that other factors than intensity of drug exposure are involved in weight increase under DTG.

678 RACE IMPACT ON DOLUTEGRAVIR-ASSOCIATED WEIGHT GAIN AMONG PREVIOUSLY ART-NAIVE PLWH

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Background: Initiation of dolutegravir (DTG)-based antiretroviral therapy (ART) has been associated with weight gain in some people living with HIV (PLWH), and race has been proposed as a risk factor. Prior studies have mixed naïve and treated PLWH or used historic regimen comparisons complicating interpretation. Therefore, we examined the role of race in substantial weight gain among previously ART-naïve PLWH initiating DTG vs other currently used non-integrase inhibitor-based regimens in a US cohort.

Methods: We included ART-naïve PLWH who initiated ART between 2012-2018 across 8 Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) sites. ART regimens included efavirenz, rilpivirine, atazanavir, darunavir, and DTG-based ≥3 drug regimens. We compared DTG to regimens without integrase inhibitors to assess the association between DTG and substantial weight gain, defined as ≥15kg, an empirically-based cut-off, 1 year following ART initiation. We restricted race to white vs black and baseline BMI to ≥18.5 kg/m_2. Data were modeled using logistic regression with the rare disease assumption and adjusted for age, sex, hepatitis B and/or C virus coinfection, smoking, diabetes, and baseline BMI, with an interaction between race and DTG use. We conducted sensitivity analyses including baseline HIV disease severity as measured by lowest CD4 count ($cells/mm_3$) and limiting regimens to tenofovir (TDF) with emtricitabine/lamivudine backbones.

Results: Among 822 PLWH (n=302 with DTG; n=520 without DTG), DTG users were more likely to gain ≥15kg compared to non-DTG users (RR:1.7 95%CI:0.9-3.0). Overall, 52 (6%) PLWH gained ≥15kg, with 26 (50%) taking DTG, and of those, 19 (73%) were black. Within DTG users, black PLWH gained an average of 5.1kg while their white counterparts gained an average of 3.3kg. Black DTG users had a 3.2 times greater risk of gaining ≥15kg compared to white DTG users in their first year after ART initiation (95%CI:1.3-8.0). The risk was attenuated after accounting for HIV disease severity (RR:2.4 95%CI:0.9-6.3) and limiting regimens to those with TDF (RR:2.3 95%CI:0.7-7.3), and no longer significant due to smaller size but remained suggestive. Differences in risk of weight gain between black and white participants was not observed for non-DTG based regimens.

Conclusion: Black PLWH had an increased risk of substantial weight gain compared to white PLWH in their first year after DTG initiation. Additional studies are needed to clarify reasons for racial disparities.

Table. Logistic regression for the risk of gaining at least 15kg, including an interaction term for race and DTG use (n=822)

Group	RR	95%CI		p-value
White not on DTG [a] (*ref*)	1.00	--	--	--
White on DTG	1.01	0.39	2.61	0.99
Black not on DTG [a]	1.39	0.62	3.14	0.43
Black on DTG [b]	3.20	1.50	6.83	0.00
Race x DTG interaction	2.29	0.68	7.69	0.18
Black on DTG compared to white on DTG [b, c]	3.18	1.27	7.97	0.01

RR: relative risk (from logistic regression using the rare disease assumption); CI: confidence interval; DTG: Dolutegravir. Adjusted for age, sex, hepatitis B and/or C virus coinfection, smoking, diabetes, and baseline BMI category.
[a] Regimens not including DTG or other integrase inhibitors.
[b] Estimated using linear combinations of RRs.
[c] Note different reference group.

679 DTG PRESCRIBING PATTERNS IN PLWH ≥65 YEARS: THE IMPACT OF 2DR AND WEIGHT GAIN

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Background: No randomised clinical studies assessed antiretroviral (ART) prescription in geriatric HIV patients. Data can be obtained from observational studies or geriatric HIV cohorts. The aim of this study was to characterize ART prescription patterns of INSTI naïve virally suppressed ART-experienced people living with HIV (PLWH) ≥65 years who switch to a DTG based regimen (DTG-s) vs remaining INSTI-naive (INSTI-n) on stable ART.

Methods: People were prospectively recruited in the Geriatric Patients Living with HIV/AIDS (GEPPO) cohort, a prospective observational multicentre study in PLWH ≥65 years with a special focus on ART prescription and anthropometric changes. Body weight was assessed at 1st study visit and at last evaluation. In the DTG-s group, the 1st visit was prior to switch.

Results: Out of 591 PLWH (16.2% females),164 were in the DTG and 427 in the INSTI-n group. At study entry, median age was 70.8 (±4.6) years, CD4 cell count was 661 (±243) c/mL and HIV RNA was undetectable in 96% of PLWH. Mean weight at 1st visit was 74.4 (±13.9) kg in INSTI-n and 70.9 (±12.4) kg in DTG-s (p=0.053). A significantly higher proportion of patients in DTG-s received dual therapy (2DR) compared to INSTI-n (60.7% DTG vs. 44.6% INSTI-n, p<0.001). Table describes top five 2DR and 3DR regimens. No difference in demographic, immunovirological, multimorbidity and polypharmacy prevalence were observed between the two groups (all p>0.05). After an average follow up of 2.8 (±0.76) years we still observed no significant difference in CD4 (669 vs 663, p=0.57) or virologic suppression (96.3% vs. 96.2%, p=0.99). At follow-up, no change in body weight was present in the two groups: mean absolute weight change was -0.1 (±7.4) in INSTI-n and -0.3 (± 4.8) in DTG-s (p=0.7). Weight gain (≥5%) was not significant in study arms.

Conclusion: This report analyzed real-life data of geriatric PLWH switching to DTG as first INSTI regimen. DTG initiation was not associated with important immune-virological changes, but led to double proportion of PLWH undergoing a 2DR. This option may be considered as a deprescribing recommendation in elderly. Over a follow-up, no change in absolute body weight nor significant weight gain was observed, indicating that this phenomenon is not present in geriatric PLWH.

2DR

INSTI-n (67)	DTG-s (75)
Darunavir/c- lamivudine (N=11, 16.4%)	DTG – lamivudine (N=29, 38.7%)
Atazanavir/c – lamivudine (N=9, 13.4%)	DTG - rilpivirine (N=18, 24.0%)
Darunavir/r – lamivudine (N=8, 11.9%)	DTG - Atazanavir (N=7, 9.3%)
Darunavir - etravirine (N=7, 10.4%)	DTG – darunavir/c (N=6, 8.0%)
Darunavir- abacavir (N=5, 7.5%)	DTG -atazanavir/c (N=4, 5.3%)

3DR

INSTI-n (295)	DTG-s (85)
Rilpivirine – TAF/FTC (N=91, 30.8%)	DTG - abacavir/lamivudine (N=53, 62.4%)
Nevirapine - abacavir/lamivudine (N=29, 9.8%)	DTG - TAF/FTC (N=25, 29.4%)
Atazanavir/c -Abacavir/lamivudine (N=16, 5.4%)	DTG -darunavir - lamivudine (N=1, 1.2%)
Efavirenz/emtricitabine/TDF (N=15, 5.1%)	DTG - darunavir - etravirine (N=1, 1.2%)
Efavirenz – abacavir/lamivudine (N=13, 4.4%)	DTG- Darunavir/c – lamivudine (N=1, 1.2%)

680 DIABETES, WEIGHT GAIN, AND INTEGRASE INHIBITOR USE IN NORTH AMERICAN HIV+ PERSONS

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Background: Integrase strand transfer inhibitor (INSTI)-based regimens have been implicated in greater weight gain in antiretroviral therapy (ART)-naïve HIV+ persons starting ART, though metabolic consequences are unclear. We examined the impact of initial ART regimen class on incident diabetes mellitus (DM) and potential mediation of this effect by weight change in a large North American HIV cohort.

Methods: We included treatment-naïve adults (≥18 years) initiating INSTI-, protease inhibitor (PI)-, or non-nucleoside reverse transcriptase inhibitor

(NNRTI)-based ART from 01/2007-12/2016 with 12-month (±6 months) weights in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). We followed individuals until incident DM (HgA1c >6.5%, initiation of diabetes-specific medication, or DM diagnosis along with diabetes-related medication, precluding prevalent DM or pre-diabetes), virologic failure (≥400 copies/mL), regimen core switch, administrative close, death, or loss to follow-up (≥12 months with no visit or lab before cohort close). We excluded those with incident DM before 12-month weight measure, and we multiply imputed missing baseline data. Cox regression stratified by clinic site and adjusting for age, sex, race, HIV transmission risk, year of ART initiation, and baseline weight, CD4+ cell count, and HIV-1 RNA yielded adjusted hazard ratios (HR) and 95% confidence intervals (CI) for incident DM by ART class. We conducted mediation analysis including 12-month weights along with all covariates from the primary analysis.
Results: Among 16,305 eligible ART initiators, 8,082 (50%) started NNRTIs, 5,152 (32%) PIs, and 3,071 (19%) INSTIs, with median follow-up of 3.3, 2.8, and 2.1 years, respectively. Among INSTI initiators, 18% started dolutegravir (DTG), 30% raltegravir (RAL), and 52% elvitegravir (EVG). Overall, 333 (2%) developed DM. Tenofovir alafenamide (TAF) was part of <1% of regimens. Those starting INSTIs vs. NNRTIs had elevated incident DM risk (HR=1.30; CI: 0.89-1.90), greater than PI- vs. NNRTI-initiators (HR=1.07; CI: 0.83-1.38). Mediation analysis revealed an INSTI-DM association attenuated 5% (HR=1.24; CI: 0.85-1.81) by including 12-month weight in the full model (Figure).
Conclusion: Initiating ART with INSTI- vs. NNRTI-based regimens may confer greater risk of incident DM, and this risk is likely only partially due to 12-month weight gain. Research to elucidate metabolic changes after INSTI initiation and identify interventions to mitigate them continues.

Figure. Adjusted hazard ratios (aHR) and 95% confidence intervals for the association between antiretroviral therapy (ART) regimen classes and incident diabetes mellitus (DM) in fully-adjusted regression models excluding ("Total Effect") and including ("Mediated Effect") 12-month weight gain as a potential mediator.

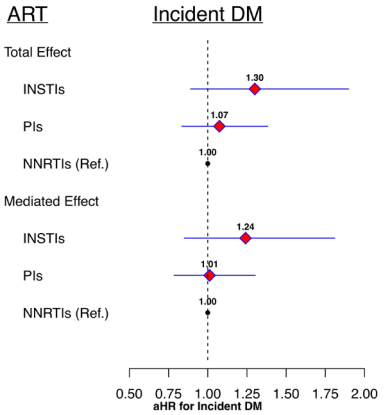


Figure footnotes:
•INSTI: integrase strand transfer inhibitor; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor
•Continuous covariates were modeled using restricted cubic splines with 5 knots to relax linearity assumptions, missing data were multiply imputed, and all models were stratified by site

681 WEIGHT GAIN AT 18 MONTHS FOR ART-EXPERIENCED PATIENTS WHO SWITCHED TO DTG IN NIGERIA

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Background: Weight gain has been associated with dolutegravir (DTG). A pilot study in Nigeria, found an increase in appetite was a prominent self-reported side effect; and an increase in weight at 12 months follow up (12m), in the predominantly antiretroviral therapy (ART) treatment experienced cohort. This analysis looked at weight and body-mass index (BMI) changes for the same cohort at 18 months follow up (18m).
Methods: ART experienced adult patients with an intolerance to NNRTIs switched to TDF/3TC/DTG (TLD) over a 6-month period starting July 2017 at 3 pilot sites in Nigeria. Study patients completed 18 months on TLD by end of July 2019 were included in the analysis. We analyzed weight and BMI changes at 18m from 12m and from baseline, using generalized estimated equations adjusted for facility clustering.
Results: 271 patients were enrolled in the original study, of these, 151 patients were ART experienced and had weight and BMI data at baseline and 18m; 35% were female, mean age 46, 61% had a normal baseline BMI and mean weight of 60kgs, 81% switched from TLE and 95% were virally suppressed time of switch (n=130). For patients with a normal baseline BMI there was a statistically significant weight increase of 5kg (p<.01) at 18m, an average 9% increase (p<.01). There was a 1.8kgs increase (p<.01) from 12m weight. Patients of all BMI categories gained 7% (p<.01) from their baseline weight. At 18m, 36% of normal baseline BMI patients had a weight gain of 10% or greater, and 29% had increased BMI category to overweight. There was no interaction of gender and weight gain at 18m. Patients with overweight or obese baseline BMI were not found to gain weight at 18m (p=.95).
Conclusion: Supplementing previous findings of a weight increase in the DTG cohort at 6 and 12 months, there was continued weight increase at 18m. Patients with above normal baseline BMI did not show a weight increase at 18m nor a gender association. While the original study was not designed to measure weight changes and has not been compared to a control group, the real world findings show that weight gain may be expected in ART experienced patients that were predominantly virally suppressed at time of switch in African patients.

682 RISK FOR INCIDENT DIABETES IS GREATER IN PREDIABETIC MEN WITH HIV THAN WITHOUT HIV

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Background: Abnormalities in glucose metabolism contribute to the pathogenesis of aging-related comorbidities in people with HIV (PWH). Hyperglycemia below the diabetic range has been termed pre-diabetes mellitus (pre-DM) and may be more common in PWH compared to those without HIV. It is unclear whether the progression from pre-DM to DM differs by HIV serostatus.
Methods: Fasting glucose (FG) was measured at each semi-annual visit among men in the Multicenter AIDS Cohort Study (MACS) since April 1999. Men who had confirmed pre-DM, defined as a FG 100-125 mg/dL (baseline visit), were included. Men with prevalent DM at the baseline visit were excluded. Incident DM was defined as a FG ≥126 mg/dL, confirmed at a subsequent visit with anti-DM medication use or a second FG ≥126 mg/dL; self-reported DM, confirmed at a subsequent visit with anti-DM medication use or two FG ≥126 mg/dL; or report of anti-DM medication use at a visit. We used binomial transition models to determine whether the progression from pre-DM to DM from one visit to the next differed by HIV serostatus, after adjustment for age, race/ethnicity, body mass index (BMI), and hepatitis C virus (HCV) infection.
Results: Between 1999 and 2018, 1548 men (772 with HIV [MWH], 776 men without HIV) men with pre-DM were included. At baseline, MWH were younger (median 48 vs 51 years, p<0.01), had lower BMI (median 25 vs 27 kg/m$_2$, p<0.01), were more likely to be non-white (44% vs 28%, p<0.01), and were more likely to be HCV-infected (9% vs 5%, p<0.01) than men without HIV. Over a median of 12 years of follow-up (Q1, Q3 8, 14), 22% (166/772) of pre-DM MWH and 22% (169/776) of pre-DM men without HIV developed DM. In adjusted analyses, the probability of developing DM among men with pre-DM was 40% [95% CI: 10% to 80%] higher among MWH than men without HIV (p=0.02).
Conclusion: Among men with pre-diabetes, HIV serostatus was associated with increased risk of incident diabetes after adjustment for competing DM risk factors. Given the increased risk, diabetes prevention strategies in PWH may be particularly effective and should be investigated.

683 GLYCEMIC STATUS AND PHYSICAL FUNCTION AMONG MEN WITH AND WITHOUT HIV

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Background: Gait speed and grip strength decline faster in persons with HIV (PWH) compared to those without HIV. Abnormal glucose metabolism has been associated with impaired physical function in cross-sectional studies. We

evaluated longitudinal relationships between hyperglycemia and objective measures of physical function in men with and without HIV.
Methods: The Multicenter AIDS Cohort Study (MACS) is a prospective study of men with or at risk for HIV. MACS participants undergo semi-annual assessments, including measures of glycemic status (fasting blood glucose and hemoglobin A1C (HbA1C)), grip strength and gait speed. Glycemic status was categorized as normal, impaired fasting glucose (IFG), controlled diabetes mellitus ((DM) (HbA1C <7.5%)) or uncontrolled DM (HbA1C >7.5%). Linear mixed models with random intercept were used to assess associations between glycemic status, gait speed and grip strength between 2006-2018.
Results: Of 2,575 men, 54% were PWH. Mean age at baseline was 45.0 years among PWH and 49.2 years among men without HIV. At baseline, DM was more common among men with vs without HIV (p <0.05) and PWH had slower gait speed (p=0.001) but not reduced grip strength compared to seronegative controls. In multivariate models including all participants, HIV serostatus was not significantly associated with change in gait speed or grip strength (all p>0.05). Compared to men with normal glucose, those with controlled DM had greater gait speed decline (-0.015 m/s [-0.028, -0.001], p=0.03) and those with uncontrolled diabetes had greater grip strength decline (-0.877 kg [-1.623, -0.130], p=0.021) regardless of serostatus. In multivariate models restricted to PWH, neither IFG nor DM had significant effects on gait speed, but uncontrolled DM was associated with significantly greater decline in grip strength (-1.818 kg [-2.868, -0.767]; p=0.001), with a larger effect among men with HIV vs all participants (-1.818 vs -0.877 kg).
Conclusion: Abnormal glucose metabolism was associated with declines in gait speed and grip strength regardless of HIV serostatus, with uncontrolled DM exerting a greater effect on grip strength decline among PWH. These data suggest that improved glucose control, independent of virologic suppression, is an intervenable target to prevent progression of physical function limitations among PWH.

684 GREATER INCIDENCE OF DIABETES OVER 10 YEARS AMONG DEPRESSED US VETERANS WITH HIV

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Background: Persons living with HIV (PLWH) have an increased prevalence of depression and incidence of cardiovascular disease (CVD) and diabetes mellitus (DM). We previously found that depressed US veterans with HIV have a greater incidence of CVD, possibly due to biological (increased systemic inflammation/coagulation) and/or behavioral (smoking, sedentary lifestyle, insomnia, poor medication adherence) mechanisms. As these mechanisms may also predispose to DM, we evaluated whether baseline depressive symptom severity predicts incident DM in US veterans living with HIV.
Methods: We used the Veterans Aging Cohort Study (VACS)-Survey Cohort and included patients without DM at baseline. Baseline DM was identified by a validated measure consisting of ICD-9 codes, laboratory tests, and DM medications. Baseline depressive symptom severity was assessed using the Patient Health Questionnaire-9 (PHQ-9), with prevalent depression defined by a score ≥10. Participants were followed until incident DM, death, or last follow-up date (12/31/14). Incident DM cases were identified by ICD-9 codes. Multivariate Cox regression models were run to examine the associations between baseline PHQ-9 variables (continuous and categorical) and incident DM.
Results: 2,936 PLWH were included, 628 (21%) of whom had prevalent depression. The median follow-up time was 9.6 years, and a total of 466 (15.8%) incident diabetes cases were identified. The unadjusted incidence rate of DM per 100 person-year was 21.4 (95% CI: 17.5-25.8) in depressed veterans vs 18.9 (95% CI: 17.0-20.9) in nondepressed veterans. Cox models revealed that each 1-SD increase in PHQ-9 score (5.6 points of a 0-27 scale) was associated with a 12% (HR=1.12, 95% CI: 1.02-1.22, p=0.015) and 10% (HR=1.10, 95% CI: 1.00-1.20, p=0.048) increase in the risk of incident diabetes after adjustment for demographics alone and demographics plus traditional DM risk factors, respectively. Similarly, compared to nondepressed veterans, depressed veterans (PHQ-9 score≥10) had a 24% (HR=1.24, 95% CI: 1.00-1.55, p=0.050) and 18% (HR=1.18, 95% CI: 0.94-1.47, p=0.148) greater risk of incident diabetes after adjustment for demographics alone and demographics plus traditional DM risk factors, respectively.
Conclusion: Among US veterans with HIV, depression is associated with a significant increase in the incidence of DM. Future research should examine whether depression treatment lowers diabetes risk in PLWH.

	Depressed	Not Depressed
Total	628	2308
Age, median (IQR)	48.5 (10.7)	49.1 (11.6)
Male	609 (97%)	2239 (97%)
White Race	149 (24%)	453 (20%)
BMI ≥ 30 kg/m²	79 (13%)	291 (13%)
LDL ≥ 160 mg/dL	35 (6%)	164 (8%)
Current Smoker	405 (65%)	1182 (51%)
Essential Hypertension	359 (57%)	1734 (75%)
Protease Inhibitor Use	291 (46%)	1093 (47%)

TABLE. Baseline characteristics of participants enrolled in study

685 TRICARBOXYLIC ACID METABOLITES PREDICT METABOLIC COMORBIDITIES AND DEATH IN AGING PWH

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Background: Monocyte activation is implicated in the pathogenesis of age-associated comorbidities in people with HIV (PWH). Upon activation, macrophages switch or remodel their metabolism from predominantly oxidative phosphorylation to glycolysis resulting in accumulation of the tricarboxylic acid (TCA) metabolites, succinate, and citrate. These metabolites engage diverse cellular pro-inflammatory pathways that may contribute to comorbidity.
Methods: Associations between entry fasting plasma succinate and citrate concentrations, quantified by liquid chromatography mass spectrometry, and incident comorbidities were analyzed by proportional hazard models from a random sample of participants in the prospective, multicenter AIDS Clinical Trials Group HIV Infection, Aging, and Immune Function Long-Term Observational (HAILO) study. Clinically relevant variables, age, sex, race/ethnicity, and smoking, were evaluated as confounders by adding them one at a time to univariate models.
Results: 376 participants were included. Median age was 51 (range 40-77) years, 81% were male and 53% were black or Hispanic. Median BMI was 27 (interquartile range or IQR 24-30) kg/m$_2$ and 60% were current or former smokers. Median entry and nadir CD4+ cell counts were 613 (IQR 449-825) and 203 (IQR 68-317) cells/mm$_3$, respectively, and 93% had HIV-1 RNA levels <50 copies/ml with 7.7 (IQR 4.3-11.8) median years of prior antiretroviral therapy. The median follow-up duration was 240 weeks. Higher succinate concentrations were associated with an increased hazard of hypertension; higher citrate concentrations were associated with each of the following: the composite endpoint of cardiovascular disease (CVD) or death, diabetes, and death due to all causes (see Table for estimates). Age attenuated the associations with hypertension and CVD or death; including other covariates did not change the results.
Conclusion: These associations implicate metabolic remodeling in the pathogenesis of age-associated comorbidities among PWH.

Metabolite	Outcome	N At Risk	N Events	Unadjusted HR per 1SD metabolite increase	P	Age-adjusted HR per 1SD metabolite increase	P
Succinate	HTN	213	20	1.37 (1.04, 1.81)	0.03	1.29 (0.99, 1.70)	0.06
Citrate	CVD/Death	329	22	1.35 (1.03, 1.79)	0.03	1.24 (0.92, 1.67)	0.15
	Diabetes	305	56	1.26 (1.02, 1.56)	0.03	1.25 (1.01, 1.54)	0.04
	Death	376	10	1.68 (1.23, 2.30)	0.001	1.63 (1.18, 2.26)	0.003

[1] SD, standard deviation; HTN, hypertension; CVD, cardiovascular disease

686 ISLATRAVIR METABOLIC OUTCOMES IN PHASE IIB TRIAL OF TREATMENT-NAIVE ADULTS WITH HIV-1

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Background: Islatravir (ISL, MK-8591) is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI) in development for the treatment of HIV-1 infection. Decreases in bone mineral density (BMD) and changes in body fat have been reported in people taking antiretroviral therapy for HIV-1. We evaluated changes in BMD and body fat distribution, as well as related metabolic endpoints (weight, body mass index [BMI], fasting glucose and lipid levels), in a Phase 2B trial of treatment-naïve adults with HIV-1 who received ISL as part of a combination antiretroviral regimen for up to 48 weeks.
Methods: In this randomized, double-blind, dose-ranging trial, participants were initially assigned to receive once-daily ISL (0.25 mg, 0.75 mg, or 2.25 mg) with doravirine (DOR, 100 mg) and lamivudine (3TC, 300 mg) or a fixed-dose combination of DOR, 3TC, and tenofovir disoproxil fumarate (DOR/3TC/TDF). Participants receiving ISL who achieved HIV-1 RNA <50 copies/mL at Week 20 or later stopped taking 3TC at their next study visit and continued DOR+ISL at the initial dosage (most participants stopped 3TC at Week 24). Hip BMD, spine BMD, peripheral fat, and trunk fat were assessed by dual-energy x-ray absorptiometry (DEXA) performed in all randomized participants at Weeks 0 and 48 and evaluated by a central imaging reader. Change (with 95% confidence interval) from baseline to Week 48 was calculated for each of the DEXA endpoints, weight, BMI, and fasting plasma levels of glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides.
Results: A total of 121 participants (92.6% male, 76.0% white, mean age 31 years) received study therapy and were included in the analyses. At baseline, the mean CD4+ T-cell count was 492 cells/mm$_3$ and 22% of participants had HIV-1 RNA >100,000 copies/mL. Changes in metabolic endpoints from baseline to Week 48 are shown below (see table).
Conclusion: The ISL regimens, regardless of dose, demonstrated minimal impact on BMD and similar changes in fat distribution, weight, and BMI compared to the DOR/3TC/TDF group, through 48 weeks of treatment.

Change in metabolic endpoints from baseline to week 48*

	ISL 0.25 mg† (N=29)	ISL 0.75 mg† (N=30)	ISL 2.25 mg† (N=31)	ISL All Doses† (N=90)	DOR/3TC/TDF (N=31)
	Change (95% CI)	Change (95% CI)	Change (95% CI)	Change (95% CI)	Change (95% CI)
Hip BMD (%)	-0.23 (-1.00, 0.54)	-1.06 (-1.72, -0.40)	-2.00 (-2.81, -1.19)	-1.07 (-1.52, -0.63)	-3.45 (-4.47, -2.43)
Spine BMD (%)	-0.81 (-2.07, 0.45)	-1.96 (-3.21, -0.71)	-1.28 (-2.26, -0.29)	-1.34 (-2.00, -0.68)	-2.16 (-3.54, -0.78)
Peripheral fat (%)	13.34 (6.92, 19.76)	10.36 (1.71, 19.02)	6.41 (-2.60, 15.42)	10.17 (5.71, 14.64)	9.60 (2.57, 16.63)
Trunk fat (%)	18.38 (10.57, 26.18)	18.30 (5.29, 31.32)	7.77 (-3.63, 19.16)	15.04 (8.96, 21.13)	12.85 (4.55, 21.16)
Weight (kg)	4.25 (2.20, 6.29)	3.65 (1.38, 5.92)	0.74 (-1.49, 2.98)	2.94 (1.69, 4.20)	2.09 (0.43, 3.74)
BMI (kg/m²)	1.35 (0.70, 2.01)	1.19 (0.44, 1.94)	0.24 (-0.48, 0.97)	0.95 (0.54, 1.36)	0.72 (0.19, 1.24)
Glucose§	2.96 (-2.56, 8.49)	3.38 (-0.90, 7.66)	0.42 (-4.68, 5.53)	2.32 (-0.43, 5.07)	-1.99 (-13.77, 9.80)
Total Cholesterol§	4.47 (-5.90, 14.84)	7.54 (-1.31, 16.39)	4.00 (-5.87, 13.88)	5.41 (0.06, 10.76)	-6.45 (-17.89, 4.99)
HDL-cholesterol§	3.82 (-0.39, 8.03)	5.12 (-2.73, 12.98)	3.89 (1.28, 6.50)	4.30 (1.22, 7.39)	0.77 (-2.81, 4.36)
LDL-cholesterol§	-4.99 (-11.93, 1.95)	3.20 (-5.51, 11.92)	-0.86 (-9.02, 7.30)	-0.83 (-5.29, 3.64)	-4.67 (-14.98, 5.64)
Triglycerides§	19.46 (-25.77, 64.68)	-4.83 (-44.11, 34.44)	4.62 (-17.08, 26.31)	6.15 (-14.53, 26.83)	-10.86 (-38.84, 17.13)

* Mean percent change for DEXA endpoints; mean change for others.
† All doses of ISL were given with DOR 100mg and 3TC 300mg for at least 24 weeks, and with DOR 100mg thereafter.
§ All laboratory values reflect fasting levels and are shown in mg/dL.
N=number randomized; for each test, the number of participants with evaluable data may be slightly lower.

687 NONCOMMUNICABLE DISEASES AND RISK FACTORS AMONG PEOPLE LIVING WITH HIV IN CAMBODIA

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Background: HIV and antiretroviral therapy (ART) had been linked with increased risk of non-communicable diseases (NCDs) such as diabetes and hypertension alongside other well-established traditional risk factors. Empirical evidence from low- and middle-income countries (LMICs) on this relationship are scarce. Therefore, we examined the prevalence of NCDs in people living with HIV (PLWH) and the general population in Cambodia to assess the contribution of HIV and ART on NCDs and identify if locally adapted policies and/or interventions are needed.
Methods: We merged data from two surveys conducted among PLWH (n=510) and the general population (n=2747) by KHANA Center for Population Health Research (nongovernmental organization) in 2015 and by the University of Health Sciences in 2016, respectively. Both employed a standardized questionnaire and physical/biochemical measurement protocols developed by the World Health Organization (STEPwise Approach to Surveillance or STEP survey or STEPS) and were conducted across selected provinces in Cambodia. We computed NCD prevalence and performed logistic regression to examine the relationship between NCDs and HIV while adjusting for age, sex, residence types, behavioral risk factors (such as smoking, heavy alcohol consumption, less than 5 servings of fruits and vegetables and low physical activity) and body mass index (BMI).
Results: The prevalence was 9% (n=46) for diabetes, 13% (n=67) for hypertension and 3% (n=16) for high cholesterolemia among PLWH, all of which (except diabetes) were lower than that of the general population. Half of PLWH had prediabetes compared with only 16% of the general population. In logistic regression, PLWH were more likely to present prediabetes, aOR=6.94 (95% CI: 5.41, 8.90) and diabetes, aOR=1.41 (95% CI: 0.95, 2.09), and less likely to present hypertension and high cholesterolemia, aOR=0.59 (95% CI: 0.42, 0.81) and aOR=0.13 (95% CI: 0.08, 0.23), respectively.
Conclusion: In Cambodia, compared to the general population, PLWH had an alarmingly high prevalence of prediabetes and, to a lesser extent, diabetes, while hypertension, prehypertension, high and borderline-high cholesterolemia appeared to be significantly lower. Differences in the host factors, the ART regimen and the traditional risk factor distribution could explain these contrasting findings in certain conditions in most Western studies. Our findings underscore the need to put in place proper measures to address prediabetes and diabetes among this vulnerable population.

Table 1. Non-communicable diseases and their risk factors among study participants. Data from the 2015 KHANA (n=510) and 2016 UHS (n=2747) STEP surveys, Cambodia.

Characteristics	PLWH (n=510)		General Population (n=2747)	
	n	%	n	%
Fasting blood glucose†				
Prediabetes	255	55.2	374	16.1
Diabetes	46	9.1	185	7.4
Blood pressure ‡				
Prehypertension	148	33.5	810	38.0
Hypertension	67	13.2	600	22.0
Fasting blood total cholesterol ¶				
Borderline-high	93	18.9	671	32.3
High	16	3.2	517	19.9

† Prediabetes: fasting blood glucose between 101-125 mg/dL.
Diabetes: fasting blood glucose ≥ 126 mg/dL and/or on anti-diabetic drugs.
‡ Prehypertension: systolic blood pressure between 120-139 mmHg and/or diastolic blood pressure between 80-89 mmHg.
Hypertension: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or on anti-hypertensive drugs.
¶ Borderline-high cholesterolemia: fasting blood cholesterol between 201-239 mg/dL.
High cholesterolemia: fasting blood cholesterol ≥ 240 mg/dL and/or on cholesterol lowering drugs.

688 VALIDATION OF THE D:A:D CHRONIC KIDNEY DISEASE RISK SCORE IN A LARGE AFRICAN COHORT

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Background: A prognostic risk score for chronic kidney disease (CKD) in persons living with HIV (PLHIV) has been developed using data from the D:A:D cohort (PLoS Med. 2015;12(3):e1001809) but this score has not been validated in sub-Saharan Africa. We assessed performance of the D:A:D risk score in a large cohort of PLHIV in West Africa.
Methods: We used longitudinal data from 15,528 PLHIV initiating antiretroviral treatment between 1996 and 2018 in 4 clinics in Burkina Faso (n=1), Côte d'Ivoire (n=2), Togo (n=1) participating in the International epidemiology Databases to Evaluate AIDS (IeDEA) West Africa collaboration. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. Participants included had ≥3 creatinine measurements, a follow-up in the cohort ≥3 months and a baseline eGFR >60 ml/min/1.73m^2. CKD was defined as a confirmed (>3 months apart) eGFR ≤ 60 ml/min/1.73m^2. The risk score (short version) was calculated based on age, gender, nadir CD4 and baseline eGFR and categorized as low (<0), medium (0-4) and high (≥5) risk groups. Discrimination

was assessed by the C-statistics and calibration parameters were expressed as ratio of observed / expected events.

Results: In 15,528 participants (71% % female, median age : 38 years; median nadir CD4 : 186 cells/mm$_3$) followed for a median duration of 6 years (interquartile range : 3 to 9), 692 (4.5%) progressed to CKD, with an incidence (95% CI) of 7.6 (7.9;10.7) per 1,000 person-years (PY). The D:A:D score ranged from -7 to 17 with a median of -2. Incidence increased markedly across the risk score groups : 2.4 (2.0;2.8); 8.3 (7.0;9.8) and, 30.1 (27.3;33.2) per 1,000 PY in the low, medium and high risk groups, respectively (Table). In the high risk group, 14.6 % (95% CI: 13.1;16.2) had progressed to CKD at 5 years. Discrimination was acceptable with a C-statistics of 0.81 (95% CI: 0.79-0.82). In predicting CKD, score ≥ 0 and ≥ 5 performed at sensitivities of 78% and 59% and specificities of 67% and 85%, respectively.

Conclusion: The performance of the D:A:D score in predicting CKD was acceptable. PLHIV with a score ≥0 could benefit from a closer monitoring of renal function to prevent progression to end-stage renal disease. Introduction of additional predictors such as hepatitis C, hypertension or diabetes should improve the performance of the D:A:D score

Table. Performance of the D:A:D risk score to predict CKD in the IeDEA West Africa collaboration cohort

Risk group	Low score (<0)		Medium score (0-4)		High score (≥5)		Total	
N	10,156		2,807		2,565		15,528	
no. events	149		135		408		692	
CKD Incidence, %% person-years	2.41	[2.05-2.83]	8.29	[7.01-9.82]	30.12	[27.33-33.19]	7.6	[7.9;10.7]
KM progression at 5 years to CKD, %	0.87	[0.69-1.10]	3.43	[2.76-4.27]	14.57	[13.11-16.17]	3.5	[3.2 ;3.9]
Calibration (O/E)	2.46	[2.09-2.88]	0.76	[0.60-0.95]	0.42	[0.35-0.50]	1.30	[1.21-1.40]

Estimates are given with 95% confidence intervals
CKD, chronic kidney disease; KM, Kaplan-Meier; O/E, Observed/Expected events

689 eGFR RECOVERY 96 WKS AFTER A TDF TO TAF OR ABC SWITCH FOR TDF-ASSOCIATED eGFR DECLINE

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Background: Use of tenofovir-disoproxil fumarate (TDF) containing ART can result in an accelerated decline of the estimated glomerular filtration rate (eGFR). Limited data are available on the reversibility of this decline and if a switch to T-alafenamide (TAF) is non-inferior to abacavir (ABC) regarding eGFR recovery.

Methods: The BACTAF-studies are 2 multicenter studies; a prospective randomized (NCT02957864) and a retrospective study with similar goals; Evaluate the reversibility of the TDF-associated eGFR decline and compare eGFR recovery between pts switching to TAF or ABC. Pts switched from TDF to TAF or ABC for a significant eGFR-decline, defined as >3mL/min/yr during ≥5yrs of TDF or decline of >25% or eGFR<70mL/min with eGFR>90mL/min at TDF initiation. We excluded pts with ABC resistance, HBV/HCV coinfection and detectable HIV-RNA at switch. To increase the likelihood of TDF-relatedness of the eGFR decline, pts with diabetes, cardiovascular disease, uncontrolled hypertension, use of >1 antihypertensive drug, use of nephrotoxic medication, or with another kidney disease that may explain the eGFR-decline were excluded as well. The prim. endpoint was an eGFR recovery of >50% 48 wks after the switch with the 96 wks results as a sec. endpoint.

Results: Of 250 pts included, 130 switched to TAF and 120 to ABC. During 7.5 and 5.5yrs of TDF use, eGFR had declined by 4.4mL/min/yr and 5.9 mL/min/yr, respectively. eGFR was 73mL/min at TAF and 68mL/min at ABC initiation, and 20% and 28% had an eGFR<60mL/min. W48 results were available for 213 while data were not available for 37 (discontinuation of TAF or ABC before w48 in 17, LTFU in 4, other reasons in 16). Significant eGFR increases were observed by 5.0mL/min with TAF and 6.0mL/min with ABC (p<0.001 compared to baseline for both, p>0.1 for TAF versus ABC). A >50% recovery was observed in 23/121(19%) and 18/99(18%) respectively (p>0.1). Of the 52 pts with an eGFR<60 at TDF discontinuation, 33 (57%) showed an eGFR recovery to >60ml/min at w48. At w96 a >50% recovery was observed in 18/101(18%) and 24/88(27%), respectively(p>0.1). Of the 44 pts with an eGFR<60ml/min at TDF discontinuation, 30(68%) recovered to >60ml/min at w96. More pts discontinued ABC than TAF(15% vs 2%, p<0.001), mainly for drug-related AE (13% vs 2%, p<0.01). HIV-RNA remained suppressed in all but 3 pts.

Conclusion: Although improvements in eGFR were observed after TDF discontinuation, a minority recovered >50% of the eGFR lost during TDF. Recovery on TAF and ABC was comparable.

690 CHRONIC KIDNEY DISEASE IN PEOPLE WITH HIV OF AFRICAN ANCESTRY IN THE UK

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Background: Black ethnicity is a risk factor for chronic kidney disease (CKD) due to HIV-associated nephropathy (HIVAN) and hypertensive kidney disease through carriage of apolipoprotein L1 risk alleles. Among Africans, substantial regional variability in CKD prevalence has been reported. We prospectively evaluated kidney function and CKD risk factors in black-African and black-Caribbean people with HIV (PWH) in the UK.

Methods: Participants were recruited from HIV and dialysis/transplantation clinics. Renal risk factors including hypertension, diabetes mellitus and smoking status, current kidney function (estimated glomerular filtration rate, eGFR mL/min/1.73m$_2$; CKD-EPI) and urine protein/creatinine ratio (uPCR) were obtained. Multivariable logistic regression was used to analyze factors associated with CKD (eGFR <60), end-stage kidney disease (ESKD; eGFR <15 or renal replacement therapy) and proteinuria (uPCR >15 mg/mmol in those without ESKD). These cross-sectional analyses were restricted to those with both parents born in the same region (East/Southern/West Africa or the Caribbean).

Results: While demographic and HIV characteristics differed by region, the prevalence of hypertension, diabetes mellitus and cardiovascular disease was similar (Table). The prevalence of CKD and ESKD, but not proteinuria, differed by region. In unadjusted analyses, with East African ancestry as reference, West-African ancestry was associated with CKD (HR 1.86 [95%CI 1.17, 2.97] p=0.008) and ESKD (2.02 [1.06, 3.82] p=0.027) but not proteinuria (0.92 [0.67, 1.25] p=0.598). After adjustment for demographic, HIV-associated and renal risk factors, West African ancestry remained associated with CKD (aOR 1.87 [1.09, 3.22] p=0.023) and ESKD (aOR 2.45 [1.21, 4.97] p=0.013). Caribbean ancestry was significantly associated with CKD (aOR 2.23 [1.09, 3.22] p=0.016) but not ESKD (aOR 2.33 [0.98, 5.53] p=0.054) while Southern African ancestry was associated with neither CKD nor ESKD. Among West Africans, the odds of ESKD was greatest among those of Nigerian ancestry (aOR 3.37 [1.57, 7.26] p=0.002).

Conclusion: The prevalence of CKD and ESKD, but not proteinuria, varied significantly among black PWH who have universal access to healthcare in the UK, and was not explained by traditional CKD risk factors. The highest rate of ESKD was observed among those of West African, and particularly Nigerian ancestry, highlighting the need for increased renal vigilance in this cohort.

Table: Demographic and clinical characteristics

		All regions [N=1904]	East Africa (N=408)	Southern Africa (N=565)	West Africa (N=658)	Caribbean (N=273)	P-value
Age (years)	Mean (SD)	48.4 (9.8)	48.8 (9.6)	48.5 (9.8)	47.3 (9.6)	50.4 (10.4)	<0.001
Female gender	N (%)	1088 (57.1)	257 (63.9)	364 (66.6)	342 (52.9)	97 (35.9)	<0.001
Years since HIV diagnosis	Mean (SD)	13.2 (6.4)	15.9 (7.2)	14.2 (5.6)	10.8 (5.5)	12.9 (6.7)	<0.001
CD4- cell count (cells/mm^3)	Median (IQR)	552 (399, 721)	534 (381, 720)	580 (413, 750)	530 (391, 703)	580 (423, 756)	0.002
HIV RNA <50 copies/ml	N (%)	1487 (78.5)	319 (77.4)	455 (80.8)	512 (78.4)	201 (73.9)	0.2
Hypertension *	N (%)	839 (44.4)	174 (43.1)	243 (43.1)	310 (47.3)	112 (41.8)	0.3
Diabetes mellitus *	N (%)	191 (10.2)	45 (11.1)	51 (9.1)	67 (10.3)	28 (10.5)	0.8
Cardiovascular Disease *	N (%)	81 (4.3)	18 (4.4)	20 (3.6)	25 (3.9)	18 (6.7)	0.2
eGFR (mL/min/1.73m^2)	Mean (SD)	96.0 (27.3)	102.2 (27.1)	97.7 (24.6)	93.5 (28.7)	89.6 (27.7)	<0.001
≥90	N (%)	1208 (63.5)	292 (72.6)	379 (67.1)	393 (59.7)	144 (52.8)	
60-89	N (%)	527 (27.7)	90 (22.1)	148 (26.2)	190 (28.9)	99 (36.3)	
15-60	N (%)	89 (4.7)	13 (3.2)	25 (4.4)	33 (5.1)	18 (6.6)	
ESKD (eGFR <15 or RRT)	N (%)	80 (4.2)	13 (3.2)	13 (2.3)	42 (6.4)	12 (4.4)	
uPCR (mg/mmol)	Median (IQR)	8.9 (6.2, 14.0)	9.6 (6.8, 14.0)	8.3 (6.0, 13.8)	8.8 (6.2, 14.8)	9.0 (6.2, 14.7)	0.3
uPCR <15	N (%)	1382 (72.6)	297 (72.8)	417 (73.8)	471 (71.9)	197 (72.2)	
uPCR 15-50	N (%)	325 (17.1)	74 (18.1)	95 (16.8)	109 (16.7)	47 (17.2)	
uPCR >50	N (%)	197 (10.4)	37 (9.1)	53 (9.4)	78 (11.9)	29 (10.6)	

*Hypertension defined as systolic BP >140 mm Hg, diastolic BP >90 mm Hg, or treatment with BP lowering drugs; diabetes mellitus and cardiovascular disease was a self-reported diagnosis

691 FERRITIN AND TRANSFERRIN INDEPENDENTLY REFLECT RENAL FUNCTION IN PEOPLE WITH HIV

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Background: Chronic kidney disease (CKD) remains a serious complication in people with HIV (PWH), despite effective antiretroviral therapy (ART), and early markers of renal injury are needed. Iron homeostasis, involving the iron-storage and delivery proteins ferritin and transferrin, has an emerging role in renoprotection and is dysregulated by HIV and inflammation. Since PWH have persistent inflammation on suppressive ART, we hypothesized that these iron-regulatory proteins are markers of renal injury and/or renal function in PWH.

Methods: Ferritin, transferrin, beta-2-microglobulin, and neopterin were quantified by ELISA in serum or plasma in 94 PWH with available markers of renal function [blood urea nitrogen (BUN), creatinine] and renal outcome (serum albumin) from a large, observational HIV study. Glomerular filtration rate was estimated using the CKD-EPI equation (eGFR). Ferritin and transferrin associations with renal function, injury, and outcome markers were evaluated using Pearson's correlations and multivariable regression models, adjusting for potential confounders.

Results: Study participants included in this analysis were 19% women, 30% black, 9.6% diabetic, and all virologically suppressed [mean age 48±9 years, median nadir CD4 158 cells/μL (interquartile range, IQR 30-263, mean hgb 14.4±2 g/dL]; 63% were on tenofovir. Median ferritin levels were 135 ng/mL (IQR 73-250) and transferrin 314 mg/dL (IQR 268-364). Ferritin was correlated to serum creatinine ($r=0.73$, $p<0.0001$), BUN ($r=0.58$, $p<0.0001$), the eGFR ($r=-0.20$, $p<0.05$), immune activation, renal injury and outcome markers ($r=0.74$ for neopterin, $p<0.0001$; beta-2-microglobulin, $r=0.75$, $p<0.0001$; serum albumin, $r=-0.23$, $p=0.02$), but not to transferrin. Transferrin was weakly correlated to creatinine, eGFR, and serum albumin ($r=-0.23$, 0.30, and 0.21, respectively, all $p<0.05$). Higher serum ferritin and transferrin were each associated with higher (better) eGFR, adjusting for age, black race, hemoglobin, tenofovir use, hypertension, beta-2-microglobulin, and each other ($p=0.037$ for ferritin; $p=0.001$ for transferrin). Adjustment for diabetes had minimal effect on results.

Conclusion: Higher levels of transferrin and ferritin are associated with better renal function in virologically suppressed PWH, independent of inflammation, immune activation, and other factors; these proteins may actively contribute to renal iron homeostasis during ART, dysregulation of which can promote renal injury and CKD.

692 CHANGE IN TRABECULAR BONE SCORE (TBS) AFTER ZOLEDRONIC ACID INFUSION OR TDF SWITCH

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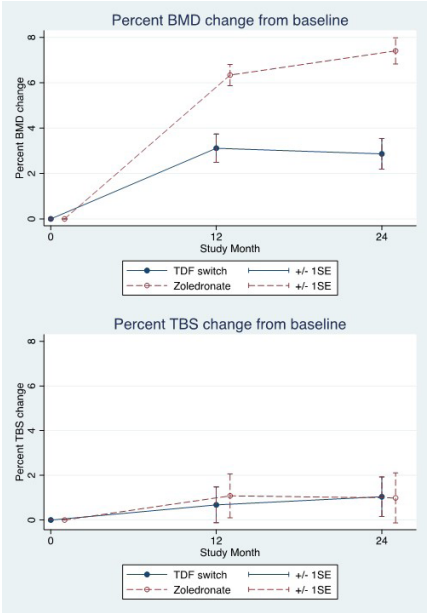
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Background: Significantly greater increase in bone mineral density (BMD) occurred in osteopenic adults on suppressive Tenofovir Disoproxil Fumarate (TDF)-based ART randomized to receive 2 annual infusions of zoledronic acid versus switching off TDF. The aim of this study was to determine the impact of TDF switch versus zoledronic acid on TBS (an indirect measurement of bone microarchitecture and independent predictor of fracture risk in the general population).

Methods: TBS scores were derived from annual lumbar spine dual-energy x-ray absorptiometry (DXA) images following extraction of the raw data using TBS insight software (Medimaps SA, France). TBS was calculated as the mean value of the L1-L4 vertebral images, corrected for weight. Change between the zoledronic acid arm and TDF switch arm over 24 months of follow-up was compared using regression models in a post-hoc, per-protocol analysis.

Results: At baseline, 41.3% of participants had a TBS >1.35 (normal bone microarchitecture) and 17.5% had a TBS <1.2 (degraded bone microarchitecture). The mean (SD) baseline TBS was 1.3 (0.11) for the zoledronic acid group and 1.31 (0.13) for the TDF switch group. The mean (SD) percent increase in BMD in 37 individuals on zoledronate was 6.3 (2.9)% at month (M)12 and 7.4 (3.5)% at M24 while in 38 individuals who switched off TDF it was 3.1 (3.9)% at M12, and 2.9 (4.2)% at M24. The absolute and percent changes in BMD from baseline were significantly different between zoledronate and TDF switch groups ($p<0.001$). In contrast, the mean (SD) increase in TBS was 1.08 (6.11)% at M12 and 0.99 (6.79)% at M24 for the zoledronic acid group compared with 0.68 (5.01)% at M12 and 1.04 (5.47)% at M24 for the TDF-switch group (Figure 1). There was no significant mean (95%CI) difference between groups in percent change in TBS at 24 months (-0.05 [-2.9 to 2.8]).

Conclusion: In this osteopenic population with relatively preserved bone microarchitecture, both TDF cessation and zoledronic acid were associated with small increases in TBS that were not significantly different by randomised arm, unlike the significant increase in BMD. The results are consistent with an increase in BMD due primarily to mineral accretion by both interventions rather than an improvement in bone micro-architecture.



693 LOW BONE MINERAL DENSITY IN OLDER PEOPLE WITH HIV: THE RENAL-BONE AXIS AND ART

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Background: Data on low bone mineral density (BMD) in people with HIV (PWH) are mainly derived from younger adults. We explored the relative contribution of antiretroviral therapy (ART) and alterations in the renal-bone axis to lower BMD in older PWH

Methods: Sub-analysis of the GS-US-104-0423 study, a cross-sectional study of ART-treated HIV-positive men >50 years and post-menopausal women. ART was stratified into 4 groups based on always or never treated with tenofovir disoproxil fumarate (TDF) and/or protease inhibitors (PI): noTDF/noPI, noTDF/PI, TDF/noPI, TDF/PI. In stored blood we analyzed bone turnover markers: osteocalcin (OC), procollagen type 1 amino-terminal propeptide (P1NP) and C-terminal cross-linking telopeptide of type 1 collagen (CTX-1); markers of bone regulation: osteoprotegerin (OPG), surface-bound receptor activator of nuclear factor kappa-B ligand (sRANKL) and phosphatonin (FGF-23), 25(OH) vitamin D and parathyroid hormone (PTH). We analyzed renal tubular markers retinol binding protein (RBP/Cr), carbonic anhydrase III (CA3) and fractional excretion of phosphate (FEPO4) in stored urine. BMD (g/cm_2) at the lumbar spine (LS) and femoral neck (FN) was measured by dual X-ray absorptiometry. The relevant impact of ART exposure and bone/renal markers on BMD was explored using logistic regression adjusted for demographic factors (age, gender, ethnicity, BMI and smoking status)

Results: 247 individuals (median age 57 [IQR 53, 65] years, 47% female, 87% white, time on ART 10 [6, 16] years, CD4 643 [473, 811] cells/mm_3 and 98% with HIV RNA<200c/mL) contributed to the analysis. Prevalence of low BMD (T-score <-1) at LS and FN was 55% and 60%, respectively. RBP/Cr, FEPO4, OC, P1NP, CTX-1 and PTH differed significantly by ART group, with higher values in the TDF

groups. In unadjusted analysis, OC and CTX-1 negatively correlated with BMD-LS and BMD-FN, and RBP/Cr with BMD-FN. In adjusted analyses, compared to the noTDF/noPI group, those on TDF/PI were 4 times more likely to have low BMD-FN and those on TDF and/or PI 3 times more likely to have low BMD-LS (Table, model 1).Further adjustment for the OC, CTX-1 and RBP/Cr had minimal impact on the observed associations (models 2-3)

Conclusion: Exposure to ART rather than levels of bone turnover or renal tubular markers best predicts low BMD in older PWH. Treatment with TDF/PI combined predicted low BMD-FN while TDF with or without PI predicted low BMD-LS. These data do not support routine measurement of biomarkers to predict low BMD in older PWH

Table. Adjusted Odds Ratio and 95% Confidence Intervals derived from logistic regression models exploring the contribution of ART to low BMD.

	1) Adjustment for age, gender, ethnicity, BMI and smoking status		2) Additional adjustment for bone turnover (OC and CTX-1)		3) Additional adjustment for renal tubular dysfunction (RBP/Cr)	
Effect on BMD-FN	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
noTDF/noPI	1		1		1	
noTDF/PI	1.706 (0.735, 3.958)	0.213	1.765 (0.750, 4.156)	0.193	1.717 (0.741, 3.979)	0.208
TDF/noPI	1.791 (0.831, 3.861)	0.137	1.807 (0.827, 3.947)	0.138	1.706 (0.780, 3.732)	0.181
TDF/PI	3.926 (1.615, 9.544)	0.003	3.901 (1.547, 9.838)	0.004	3.647 (1.460, 9.108)	0.006
Effect on BMD-LS	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
noTDF/noPI	1		1		1	
noTDF/PI	3.566 (1.518, 8.377)	0.004	2.962 (1.277, 6.868)	0.011	3.149 (1.385, 7.150)	0.006
TDF/noPI	3.146 (1.456, 6.799)	0.004	3.109 (1.410, 6.856)	0.005	3.305 (1.496, 7.303)	0.003
TDF/PI	3.034 (1.327, 6.939)	0.009	2.349 (1.003, 5.498)	0.049	2.870 (1.234, 6.676)	0.014

694 BONE MINERAL DENSITY IMPROVES IN WOMEN WHO SWITCH FROM TDF/FTC/NNRTI TO ABC/3TC/DTG

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Background: Tenofovir disoproxil fumarate (TDF) is associated with decreased bone mineral density (BMD) which is of particular concern to peri/post-menopausal women. We hypothesized that BMD and renal tubular function would improve in women who switch from a TDF- and NNRTI-containing regimen to abacavir/lamivudine/dolutegravir (ABC/3TC/DTG).

Methods: We conducted a randomized controlled trial (Bone Evaluation in women who Switch from TDF/FTC/NNRTI to Triumeq [BESTT, EudraCT 2015-005297-37]) in which HLA-B5701 negative women aged ≥40 years with HIV RNA <50 copies/mL on TDF/FTC/NNRTI for ≥12 months were randomized 1:2 to continue TDF/FTC/NNRTI or switch to ABC/3TC/DTG for 96 weeks. Primary endpoint was change from baseline in total hip BMD at week 48. Secondary endpoints included changes in lumbar spine BMD, bone turnover, renal tubular function and (post-hoc) weight. Linear regression was used to estimate the mean difference from baseline to week 48 between the two study arms, using multiple imputation with chained equations for missing BMD data.

Results: Ninety-one women (86% black ethnicity, mean [SD] age 50.4 [6.6] years, CD4 cell count 639 [263] cells/mm_3, BMI 30.3 [6.5] kg/m_2) were randomized; 29/32 (91%) in the TDF/FTC/NNRTI vs. 51/59 (86%) in the ABC/3TC/DTG arm continued through week 48. Women who switched to ABC/3TC/DTG maintained viral suppression and experienced improvements in total hip and lumbar spine BMD and proteinuria (Table). No change in vitamin D, parathyroid hormone, bone turnover markers (CTx and P1NP), estimated glomerular filtration rate (eGFR-cystatin C) or fractional excretion of phosphate was observed. Switching to ABC/3TC/DTG was associated with an improved CD4 cell count (adjusted mean difference 74.0 [6.9, 141.2] cells/mm_3, p=0.032) and 1.8kg weight gain vs. no change in those who continued TDF/FTC/NNRTI (adjusted mean difference 1.81 [0.03, 3.59] kg, p=0.046); weight increased >5% from baseline in 37% vs. 0% (p<0.001). Nine participants (15%) discontinued ABC/3TC/DTG for drug-associated adverse events (hypersensitivity, N=2; neuropsychiatric, N=5; other, N=2).

Conclusion: Switching from TDF/FTC/NNRTI to ABC/3TC/DTG resulted in improvements in BMD, proteinuria and CD4 cell count. However, the possible benefits of these need to be balanced against weight gain and treatment-limiting adverse events.

Table

		Baseline mean (95% CI)		Week 48 mean (95% CI)		Adjusted mean difference (95% CI) between arms from baseline to week 48	P-value
		TDF/FTC/NNRTI	ABC/3TC/DTG	TDF/FTC/NNRTI	ABC/3TC/DTG		
BMD total hip	g/cm2	**1.03 (0.98, 1.08)**	**0.96 (0.92, 0.99)**	**1.03 (0.98, 1.08)**	**0.97 (0.94, 1.00)**	**0.01 (0.002, 0.03)**	**0.027**
BMD lumbar spine	g/cm2	**1.07 (1.02, 1.12)**	**1.03 (0.99, 1.07)**	**1.06 (1.02, 1.11)**	**1.05 (1.01, 1.10)**	**0.03 (0.01, 0.05)**	**0.002**
25(OH) vitamin D	nmol/L	40.8 (33.1, 48.4)	49.0 (42.9, 55.1)	37.8 (31.4, 44.2)	47.2 (41.3, 53.1)	3.72 (-2.45, 9.94)	0.235
Parathyroid hormone	ng/L	34.7 (29.3,40.2)	32.6 (27.3,37.7)	35.6 (29.9,41.2)	30.5 (26.6, 34.4)	-3.75 (-9.92, 2.42)	0.230
P1NP	µg/L	61.6 (54.6, 68.7)	68.7 (62.1, 75.3)	59.4 (51.6, 67.1)	58.41 (52.4, 64.5)	-1.81 (-10.86, 7.24)	0.691
CTx	µg/L	0.44 (0.36, 0.51)	0.53 (0.45, 0.62)	0.42 (0.34, 0.50)	0.37 (0.32, 0.42)	-0.06 (-0.15, 0.03)	0.217
eGFR (cystatin C)	mL/min/1.73m2	101.8 (91.2, 112.4)	99.8 (93.1, 106.4)	98.1 (88.5, 107.7)	96.5 (91.1,102.0)	0.36 (-4.42, 5.13)	0.881
PCR	mg/mmol	10.7 (7.1, 14.4)	10.2 (8.1, 12.4)	9.4 (7.0, 11.9)	6.7 (5.6, 7.8)	-0.03 (-0.06, -0.01)	0.003
RBPCR	µg/mmol	2.8 (1.0, 4.5)	2.3 (1.5, 3.1)	2.3 (0.6, 3.9)	1.3 (0.7, 1.9)	-0.79 (-1.92, 0.34)	0.168
FE-PO_4		0.10 (0.07, 0.12)	0.10 (0.08, 0.11)	0.09 (0.07, 0.11)	0.09 (0.07, 0.10)	-0.003 (-0.03, 0.02)	0.792

P1NP= procollagen type 1 N-terminal propeptide; CTx=serum collagen type 1 cross-linked C-telopeptide; eGFR=estimated glomerular filtration rate; PCR=protein/creatinine ratio; RBPCR=retinol-binding protein creatinine ratio; FE-PO4=fractional excretion of phosphate.

BMD was adjusted for age, ethnicity (black vs. other), BMI at baseline, time on TDF, ART (efavirenz vs. other third agent) and BMD at baseline; all other parameters were adjusted for age, ethnicity; BMI at baseline, time on TDF and baseline measurement

695 BONE DENSITY IN ART TREATED HIV+ AND HIV– SUBJECTS IN FOLLOW UP; HIV UPBEAT RESULTS

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Background: Decreases in bone mineral density (BMD) in people with HIV (PWH) have been associated with intiation of antiretroviral therapy (ART) containing tenofovir disproxil fumarate (TDF). With recent introduction of new ART strategies we aimed to explore the effect of switching to non-TDF regimes on BMD.

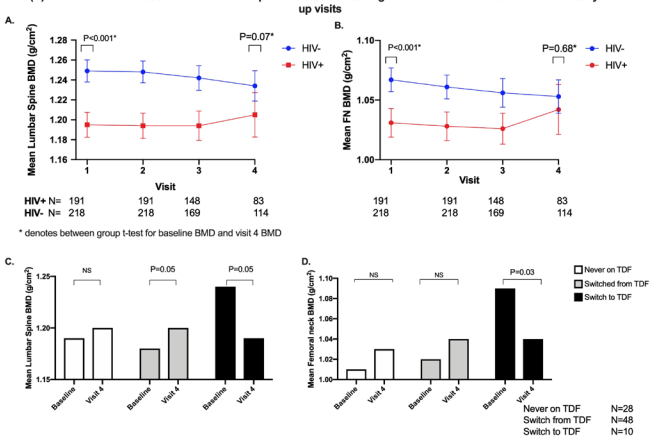
Methods: HIV UPBEAT, a single site, prospective cohort study recruited PWH and a comparable HIV- group from 2011 to 2017. Demographic, clinical, medication history and BMD measured by DXA at lumbar spine (LS) and femoral neck (FN) were recorded at 4 visits over at least 5years. Subjects with at least 2 DXA were included in the analysis. We used linear mixed models to determine predictors of rate of absolute change in BMD adjusting for HIV status, age, gender, ethnicity, BMI and smoking status for the whole cohort and discontinuous change mixed models to assess effect of switching-off TDF in the PWH subgroup, excluding those who switched back to TDF. Data are median[IQR] unless specified

Results: Of 409 subjects, 191(47%) were PWH (62% male, 61% Caucasian, age 40 [34-47] yrs) and 218 were HIV- (45% male, 77% Caucasian, age 42[35-50] yrs). The PWH group were 32% MSM, 18% IVDU and 50% heterosexual, with 11[8,14] yrs since HIV diagnosis and 7.9 [6,10.3] yrs cumulative ART. 76% were on TDF at visit 1 with 48 (28%) subjects switching off TDF over 7.3 [3.7, 9.5] yrs follow-up.

Neither absolute or percentage (%) change in BMD, nor the rate of change of LS or FN BMD differed between PWH and HIV- subjects (absolute % change in BMD; LS 0.15 [-3.48, 3.52] vs -0.62[-3.99, 3.09],P=0.49 and FN 0.63 [-3.69, 4.69] vs -0.55 [-4.26, 3.97],P=0.31, respectively). PWH had a net (although not statistically significant) gain in LS and FN BMD evident in later visits (Fig 1), resulting in no significant difference in LS or FN BMD between groups at visit 4. In PWH, switching off TDF was independently associated with increases in LS BMD +0.004 g/cm_2/yr[0.001, 0.007], P=0.005 but not FN BMD, while those switched to TDF had significant decline in mean FN and LS BMD (Fig 1)

Conclusion: In a contemporary cohort of ART treated PWH change in BMD was similar over time regardless of HIV status, with no between-group difference in BMD at last study follow up. Switching away from TDF was independently associated with increases in LS BMD suggesting reversal of prior reduction in BMD in PWH to levels comparable to the HIV- population

Figure1: Change in BMD at (A) Lumbar Spine and (B) Femoral Neck and mean Bone Mineral Density at (C) Lumbar spine and (D) Femoral Neck in those never on TDF compared to those switching from or to TDF in HIV UPBEAT over study follow up visits



696 INTERSTITIAL LUNG ABNORMALITIES IN PEOPLE LIVING WITH HIV AND UNINFECTED CONTROLS

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Background: Chest computed tomography (CT) findings in people living with HIV (PLWH) remain poorly characterized. We aimed to visually characterize interstitial lung abnormalities (ILAs) in PLWH and uninfected controls and assessed whether these abnormalities are associated with reduced pulmonary function and symptoms.

Methods: ILAs that included focal ground-glass opacity (GGO), reticulation, patchy GGO (<5% of the lung), nondependent GGO and non-dependent reticulation (>5% of the lung), diffuse centrilobular abnormality with GGO, honeycombing, traction bronchiectasis, non-emphysematous cysts, and architectural distortion were assessed by chest CT scans in PLWH from the Copenhagen Comorbidity in HIV-infection (COCOMO) Study and in uninfected controls from the Copenhagen General Population Study (CGPS) who were >40 years. Based on these CT findings we defined four outcome variables as: i) any ILA (any of the above findings), ii) equivocal for interstitial lung disease (ILD), iii) suspicious for ILD, and iv) definite ILD. Multivariate logistic regression was used to determine associations between HIV status, any ILA, equivocal and suspicious for ILD.

Results: Of 754 PLWH (95.4% with full viral suppression), 82 (10.9%) had any ILA, 59 (7.8%) were classified equivocal, 22 (2.9%) as suspicious and only one (0.1%) as definite ILD. Of 470 uninfected controls, these numbers were 36 (7.7%, p=0.079), 33 (7%, p=0.684), 4 (0.9%, p=0.025) and 0 (0%, p=1). In multivariate analysis adjusting for age, sex, ethnicity and pack-years of smoking, HIV infection were associated with aORs of 1.82 (95%CI: 1.18-2.88), 1.35 (95% 0.85-2.21) and 5.15 (95%CI: 1.72-22.2) for any ILA, equivocal and suspicious ILD, respectively. PLWH with suspicious ILD only seemed to have slightly lower forced vital capacity (FVC%) predicted (86.5% vs. 92.5%, p=0.052) and increased respiratory symptoms (cough 25% vs 12.5%, p=0.163; dyspnea 9.1% vs 8.3%, p=1), although not reaching statistical significance. We found no associations between current and nadir CD4+ T cells counts and any of the outcomes considered.

Conclusion: HIV infection was independently associated with ILAs. Moreover, the proportion of individuals with radiographic findings suspicious of ILD was higher in PLWH. Whether these ILAs may develop into more recognizable disease states over time is unknown but warrants ongoing investigation.

697 IMPLEMENTATION OF A LUNG CANCER SCREENING INITIATIVE IN HIV-INFECTED SUBJECTS

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Background: Low-Dose Computed Tomography (LDCT) screening has shown to decrease mortality in at-risk individuals. While HIV-infected individuals exhibit approximately a two-fold higher risk of lung cancer compared to the general population, the role of LDCT in this population remains controversial. We report the results of a lung screening program with LDCT in HIV-infected individuals.

Methods: HIV-infected individuals on follow-up in a tertiary hospital were offered LDCT for lung cancer screening. Inclusion criteria were: 45 years or years or older, 30 pack-year history of smoking, quit smoking in the previous 15 years, and absence of previous lung cancer diagnosis. We registered the following radiological data: presence of lung nodules, pathological lymph nodes, coronary atherosclerosis, aortic dilatation, bone marrow attenuation, lung emphysema, and non-nodular lung opacities.

Results: A total of 141 patients underwent LDCT of whom 86% were men and 14% were women. The median age was 57 years (54-60), 87 (62 %) had positive HCV antibodies, median nadir CD4 count was 179 (75-305), current CD4 count was 666 (403-911), HIV RNA count <20 copies/mL in 138 (97.1%) subjects. The median pack-year was 34 (25-41), 122 (82%) were active smokers. Radiological abnormalities were common, including pulmonary emphysema in 90 patients (64%), lung non-nodular opacities in 29 (21%), lymph nodes >1cm in 10 (7%), aortic dilation in 4 (2.8%), and radiological bone marrow attenuation in 21 (15%). Lung nodules were found in 52 subjects (37%); <4mm in 21 (15%), 4-8mm in 18 (13%) and >8mm in 13 (9%).
Lung cancer was diagnosed in 5 cases, yielding a prevalence of 3.6%. Histological examination revealed 4 cases of squamous cell carcinoma and 1 adenocarcinoma. Compared to the rest of our cohort, patients with lung cancer were of similar age (56.5 [53.5-59.5] years), had a lower CD4 nadir count (71 [4-105] cells/uL), lower current CD4 counts (352 [242-517] cells/uL), and higher median pack-year (71 [50-91]).

Conclusion: In this program of lung cancer screening with LDCT in HIV-infected individuals we found a high prevalence of lung cancer (3.6%). These results indicate that people living with HIV with additional risk factors for lung cancer are a target population for screening programs.

698 DIMENSIONS OF SLEEP HEALTH: IMPACT ON QUALITY OF LIFE OF PEOPLE WITH AND WITHOUT HIV

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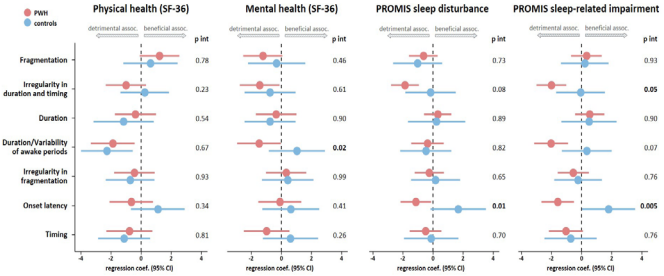
Background: Poor sleep quality can affect physical, mental and emotional function and has been frequently reported in people with HIV (PWH). We explored dimensions of sleep health, derived from objectively-measured sleep/wake activity, and their associations with health- and sleep-related quality of life (QoL) in PWH and lifestyle-matched controls.

Methods: A subset of PWH (18-49 and ≥50 yo) and HIV-negative controls (≥50 yo) participating in the POPPY study wore an actigraphy device for 7 days/nights. Physical and mental QoL, sleep-related impairment (perceptions of daytime functional impairment associated with sleep) and disturbance (perceptions of sleep quality) were derived from the SF-36 and PROMIS questionnaires. Exploratory factor analysis of 27 actigraphy variables was performed and 7 dimensions of sleep health were obtained. Linear regression was used to test associations of sleep dimensions with HIV-status and QoL measures (separately in PWH and controls) and whether they differed by HIV-status. All analyses accounted for age, gender and ethnicity.

Results: The 343 PWH and 117 HIV-negative controls were predominantly male (87% and 68%) with a median (IQR) age of 57 (52-62) and 61 (57-66) years, respectively. The 7 actigraphy-derived dimensions of sleep health were fragmentation, irregularity in duration/timing, sleep duration, duration/variability of awake periods (after initial sleep), irregularity in fragmentation, onset latency and timing. None of these significantly differed between PWH and controls (all p's>0.1). In PWH, longer duration and/or greater variability

of awake periods was associated with poorer physical (p=0.01) and mental (p=0.04) health and greater sleep-related impairment (p<0.001). Greater irregularity in duration/timing and longer onset latency were both associated with greater sleep-related impairment (p<0.001 and p=0.004) and disturbance (p<0.001 and p=0.03). Irregularity in duration/timing was also associated with poorer mental health (p=0.03). Associations were generally similar to those seen among the HIV-negative controls; only the associations of onset latency and sleep-related QoL appeared to differ (p-interaction=0.01 and 0.003, Figure).

Conclusion: We found seven dimensions of sleep health based on objective actigraphy measures. Whilst these dimensions have differential impacts on self-reported health, the effects are generally similar between people with and without HIV. These findings could inform targeted strategies to improve sleep health and, in turn, QoL of PWH.



699 HIV IS ASSOCIATED WITH WORSE PULMONARY DIFFUSING CAPACITY INDEPENDENT OF EMPHYSEMA

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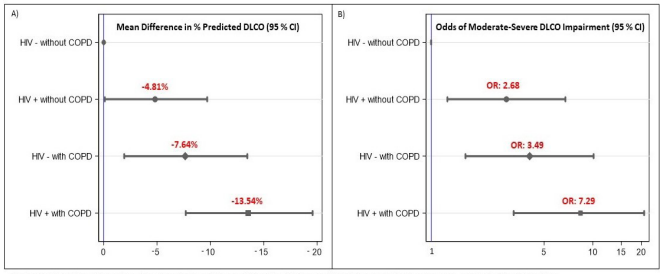
Background: HIV is associated with accelerated decline in lung function and increased risk for Chronic Obstructive Pulmonary Disease(COPD). Recently there has been more focus on the Diffusing Capacity of the Lungs for Carbon Monoxide(DLCO), a marker of gas transfer. Studies note that HIV is associated with lower DLCO. While increased emphysema and COPD likely contribute to the DLCO impairment observed, there may be other factors that drive this association. We aimed to 1)Describe the association between HIV and DLCO independent of emphysema severity and 2)Identify the joint influence of HIV and COPD on DLCO impairment.

Methods: We utilized data from the Study of HIV in the Etiology of Lung Disease(SHIELD) in Baltimore, MD. SHIELD characterized COPD, and early lung disease, among 229 HIV+(67%) and 110 HIV- participants, with lung function testing and Chest CT imaging. COPD was defined as post-bronchodilator FEV1/FVC<0.70. Emphysema severity was defined by % emphysema on CT. To examine the contribution of HIV to DLCO impairment, linear and logistic regression models were generated with % predicted DLCO(corrected for hemoglobin, age, sex) and odds of moderate-severe DLCO impairment(<60% predicted) as primary outcomes. Models were adjusted for race, emphysema, FEV1% predicted(to account for differences in COPD sampling across group), smoking status, pack-years, and injection drug use. Models were also stratified by COPD status.

Results: Participants had a median age of 50.9(+/- 4.84), 235(69%) were male, 131(39%) had COPD. Of those with HIV 86(38%) had detectable viremia. After adjusting for confounders, including emphysema, HIV was associated with lower DLCO(β -3.69%; P=0.02) and higher odds of significant DLCO impairment(Odds Ratio 1.93; P=0.01). Among HIV+ participants, we did not see effect modification by CD4 count or viremia. When analyzed by COPD status(figure), a higher percentage of those with HIV and COPD(69.3%) had significant DLCO impairment versus COPD alone(54.2%)(P<0.01). Even among those without COPD, HIV was independently associated with lower DLCO(β -4.81%; P=0.04) and significant impairment(OR 2.68; P=0.01).

Conclusion: HIV was associated with DLCO impairment independent of emphysema severity on CT and COPD. Our data also suggest a potentially additive influence between HIV and COPD on DLCO impairment. Future studies should investigate the other factors, including pulmonary vascular disease, that may contribute to DLCO impairment among persons living with HIV.

Figure*. The relationship between HIV,COPD status and DLCO impairment A) represents mean difference (95% Confident Interval(CI)) in DLCO % predicted for differing groups and B) represents odds ratio (OR [95% CI]) of moderate to severe DLCO impairment (<60% predicted) compared to HIV negative participants without COPD. Note panel B is displayed with a log scale.



*Adjusted for Race, Education, Smoking History (Current Smoking Status and Pack Years), % CT Emphysema, and Injection Drug Use

700 HIV AS A RISK FACTOR FOR INCIDENT PULMONARY HYPERTENSION

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Background: HIV is associated with prevalent pulmonary hypertension (PH). However, PH incidence based on echocardiographic measures of pulmonary artery systolic pressure (PASP) in both HIV-infected and uninfected persons remains unstudied. We hypothesized that HIV-infected individuals have higher PH incidence rates and risk versus uninfected individuals and that markers of poor HIV viral suppression would further elevate PH risk.

Methods: This analysis used data from the Veterans Aging Cohort Study (VACS), an electronic health record cohort of HIV-infected veterans matched 1:2 to uninfected controls on age, sex, race/ethnicity, clinical site, and enrollment year. We evaluated 3677 VACS participants (N=1188 HIV+) referred for echocardiography with reported PASP measures at/below 35mmHg. We estimated PH incidence rates by HIV status using Poisson regression; HIV-infected individuals were further stratified by CD4 cell count and HIV viral load at the time of their first echocardiogram (baseline). We then performed Cox proportional hazards regression to estimate risk of incident PH in HIV-infected individuals as a whole, by CD4 cell count, and by HIV viral load versus uninfected. Adjusted models included age, sex, race/ethnicity, prevalent heart failure, chronic obstructive pulmonary disease, body mass index, and eGFR as covariates. PH incidence was defined as the presence of at least one subsequent echocardiogram with PASP above 35mmHg. Individuals with a single echocardiogram or follow-up PASP measures at/below 35mmHg were censored at date of death or end of follow-up (9/30/2015).

Results: Over 97% of the cohort was male with an average age of 58 years. Nearly half of the cohort was African American; another 40% was white. Median follow-up time was 3 years (Q1, Q3: 1, 7). PH incidence rates were higher among HIV-infected veterans versus uninfected veterans (Table). Accordingly, PH risk was 50% higher in HIV-infected individuals compared to uninfected; highest risk was observed in individuals with low CD4 cell counts and/or unsuppressed HIV viral load (Table). We also observed increased PH risk in African Americans versus white individuals (HR=1.38 [1.08, 1.76]).

Conclusion: HIV is independently associated with higher PH incidence after adjusting for risk factors. Low CD4 cell count and high HIV viral load contribute to the increased risk of incident PH among HIV-infected veterans. Race may also contribute to differences in incident PH.

Group	N	PH Events	Rate/1000PY [95% CI]	Unadjusted HR [95% CI]*a*	Adjusted HR [95% CI]*a,b*
HIV-Uninfected	2489	176	17.6 [15.2, 20.4]	1.00	1.00
HIV+	1188	106	24.0 [19.9, 29.1]	1.36 [1.07, 1.73]	1.50 [1.17, 1.93]
HIV+ by CD4 Cell Count					
HIV+, CD4≥500	359	29	22.3 [15.5, 32.0]	1.36 [0.92, 2.01]	1.44 [0.97, 2.13]
HIV+, 200≤CD4<500	424	29	18.4 [12.8, 26.4]	1.18 [0.82, 1.69]	1.28 [0.88, 1.86]
HIV+, CD4<200	181	19	32.9 [21.0, 51.7]	1.83 [1.16, 2.89]	2.34 [1.48, 3.70]
HIV+, Missing CD4*c*	224	29	30.5 [21.2, 43.9]	---	---
HIV+ by Viral Load					
HIV+, VL<500	712	50	20.1 [15.3, 26.6]	1.29 [0.97, 1.72]	1.38 [1.03, 1.85]
HIV+, VL ≥500	257	26	26.7 [18.2, 39.2]	1.54 [1.02, 2.31]	1.81 [1.21, 2.71]
HIV+, Missing VL*c*	219	30	31.4 [22.0, 44.9]	---	---

CI = confidence interval; HIV = human immunodeficiency virus; HR = hazard ratio; PH = pulmonary hypertension; PY = person years; VL = HIV viral load
a all hazard ratios are compared to HIV-uninfected veterans
b adjusted for age sex, race/ethnicity, prevalent heart failure, COPD, body mass index, and estimated glomerular filtration rate
c missing category used only for calculation of incidence rates. For models, missing CD4 cell counts and HIV viral loads were imputed

701 START OR SWITCH OF INTEGRASE INHIBITORS ON DEPRESSIVE SYMPTOMS IN WOMEN WITH HIV

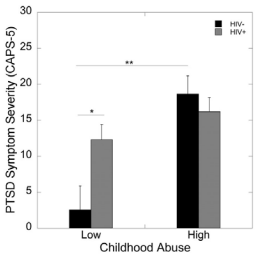
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Background: Depressive symptoms are associated with use of some antiretroviral therapy (ART) agents. Recently, concerns regarding neuropsychiatric symptoms with integrase strand transfer inhibitor (INSTI) use have been raised. We examined INSTI-associated changes on the profile of depressive symptoms in women with HIV (WWH).
Methods: Women's Interagency HIV Study (WIHS) participants who started or switched to INSTI-based ART and had two consecutive records (one before and one after the start/switch) with a completed Center for Epidemiologic Studies Depression Scale (CES-D) were included in the present analysis. We examined the adverse effects of INSTI start or first switch as a drug class on subscale-level (interpersonal, somatic, negative and positive affect) CES-D symptoms using linear mixed effects models adjusting for relevant covariates (e.g., age, race, substance use, body mass index, HIV RNA). Subsequent models examined each of the INSTIs separately.
Results: 1036 WWH, median age 48 (interquartile range 36, 60) years, 697 (67%) black, non-Hispanic were included in the analysis. Twenty-one percent were INSTI starts (30% raltegravir [RAL]; 29% elvitegravir [EVG]; 41% dolutegravir [DTG]) and the remainder of observations were switches to INSTI-based regimens (35% RAL; 27% EVG; 38% DTG). The majority of switches were from a protease inhibitor (PI) (56%) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (34%) based regimen. Overall, INSTI use was not associated with subscale changes in depressive symptoms after start/switch. Similarly, start/switch to individual INSTIs did not affect depressive symptoms. When analysis was restricted to those who switched to INSTIs from any ART, again no effects on depressive symptoms were observed. Similarly, switch from a NNRTI-based or PI-based regimen to any INSTI or individual INSTIs did not impact depressive symptoms. Starting any INSTI on the other hand improved positive affect, when stratified by INSTI type EVG but not RAL or DTG improved positive affect (p=0.004).
Conclusion: Among WWH, switching to INSTI based therapy did not have an impact of depressive symptoms. Initiation of INSTIs did result in improvement in positive affect symptoms and this was predominantly driven by EVG use.

702 PTSD SYMPTOMS AND HYPERAROUSAL INFLUENCED BY CHILDHOOD TRAUMA IN WOMEN WITH HIV

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Background: Lack of knowledge about HIV interactions with posttraumatic stress disorder (PTSD) may limit generalizability of treatment strategies for patients with HIV and PTSD. In addition, childhood trauma is a risk factor for PTSD.
Methods: African American women (18-65 yrs) recruited from Women's Interagency HIV Study (WIHS) in Atlanta, GA (n=91, 30 without HIV, 61 with HIV (WWH)), provided informed consent, and underwent interviews to capture trauma exposure and PTSD symptoms for DSM-5. Psychophysiological hyperarousal was assessed by skin conductance (SC) at baseline and during CAPS-5 using mobile eSense SC Level App. ANOVAs controlled for income and HIV viral load.
Results: Rates of adult and childhood trauma did not differ by HIV serostatus (p's>0.05). Sociodemographic variables were similar among groups: age (p=0.19); education (p=0.24); employment (p=0.84). Income level was greater in WWH (p=0.02). Within WWH, the median CD4 count was 652 and 82% had undetectable viral loads. PTSD symptom severity was influenced by interaction of HIV serostatus and childhood trauma (p=0.018; eta2=0.07; Fig 1). HIV was associated with greater PTSD symptoms only with low childhood trauma (p=0.016; eta2=0.07). There was no impact of HIV status on PTSD symptoms in women with high childhood trauma (p=0.46). HIV serostatus interacted with childhood trauma to impact baseline arousal (p=0.05; eta2=0.17) and reactivity to trauma reminders (p=0.015; eta2=0.25). Higher childhood trauma in uninfected women associated with greater baseline SC compared to uninfected women with low childhood trauma (p=0.05; eta2=0.15). Childhood trauma did not impact baseline SC in WWH (p=0.69). HIV associated with lower baseline SC in women with high childhood trauma (p=0.08; eta2=0.14). In women with low levels of childhood trauma, psychophysiological response to trauma reminders was lower in WWH compared to uninfected women (p=0.06; eta2=0.15). In women exposed to high childhood trauma, HIV associated with augmented reactivity to trauma reminders (p=0.06; eta2=0.15).
Conclusion: Taken together, these findings suggest HIV impacts PTSD symptoms and hyperarousal in women dependent on childhood trauma. Given that HIV status impacts PTSD symptoms as well as baseline and trauma reminder-evoked SC response, the current data have high clinical relevance for treating PTSD in WWH.



703 DYSREGULATED SYNTHESIS OF NEUROTRANSMITTERS IN METHAMPHETAMINE USERS LIVING WITH HIV

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Background: Elevations in the kynurenine/tryptophan (K/T) ratio are only partially reversed by effective treatment, linked to neuropsychiatric disorders, and predict faster clinical HIV progression. However, relatively less is known about the mechanisms of HIV-associated increases in the phenylalanine/tyrosine (P/T) ratio, which disrupts catecholamine synthesis (e.g., dopamine). This 15-month longitudinal study examined whether co-occurring stimulant use and HIV-associated pathophysiologic processes predict greater K/T and P/T ratios even after adjusting for detectable HIV viral load.
Methods: In total, 110 sexual minority men (i.e., gay, bisexual, and other men who have sex with men) living with HIV were enrolled in a randomized controlled trial. All participants had biologically confirmed, recent methamphetamine use via urine or hair toxicology screening. Peripheral venous blood samples were collected at baseline, 6, 12, and 15 months. Marginal, generalized linear mixed models were constructed to identify predictors of the time-varying K/T and P/T ratios. Generalized Estimating Equations were used to test the predictors of screening positive for clinical depression using the Centers the Epidemiologic Study of Depression scale (scores > 16).
Results: The majority of participants were racial/ethnic minorities (57%) and middle-aged (mean = 43.2 years; SD = 8.9). At baseline, the median baseline CD4+ T-cell count was 646 cells/mm$_3$ (Interquartile Range = 428 – 816) and 26% had a detectable HIV viral load (> 40 copies/mL). As shown in the Table, greater time-varying sCD14 and detectable viral load were independent predictors of a higher K/T ratio in adjusted analyses. On the other hand, greater proviral HIV DNA at baseline and time-varying sCD14 as well as time-varying reactive urine toxicology results for stimulants (i.e., methamphetamine or cocaine) independently predicted an increased P/T ratio. Time-varying reactive urine toxicology results for stimulants (Adjusted Odds Ratio = 2.26, 95% CI: 1.06-4.80, p = 0.043) but not the time-varying K/T or P/T ratios were significantly associated with screening positive for clinical depression.
Conclusion: HIV persistence and stimulant use are independent risk factors for dysregulated catecholamine synthesis. Findings support the need for targeted pharmacologic treatments to mitigate dysregulated catecholamine synthesis in those who co-occurring HIV and stimulant use.

Table 1. Predictors of dysregulated neurotransmitter synthesis in people living with HIV who use methamphetamine (N = 110).

Variables	Dysregulated Neurotransmitter Synthesis Outcomes			
	Kynurenine/Tryptophan (K/T) Ratio		Phenylalanine/Tyrosine (P/T) Ratio	
	Unadjusted (β)	Adjusted (β)	Unadjusted (β)	Adjusted (β)
Age (years)	0.010	0.016	0.002	-0.004
Time Points (continuous)	0.004	0.025*	-0.005	0.023
Proviral HIV DNA[1]	-0.025	-0.071	0.305****	0.330****
Lipopolysaccharide Binding Protein (LBP)[1]	0.173*	0.048	0.051	-0.088
Soluble CD14 (sCD14)	0.210****	0.132*	0.173**	0.109
Protease Inhibitor (PI)	-0.047	0.055	-0.037	0.117
Efavirenz	-0.640*	-1.010**	-0.529	-0.209
Detectable Viral Load	0.326**	0.741****	0.082	-0.195
ART Adherence ≥ 90%	-0.016	-0.042	-0.045	0.093
Recent Stimulant Use	-0.105	-0.078	0.199	0.524***

[1]Measured at baseline only and entered in the model as a time-invariant covariable ; * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001; Unadjusted models included only time points as continuous variable (baseline, 6, 12, and 15 months) and age in years. Adjusted estimates from generalized linear mixed models including all variables shown.

704 EXERCISE-INDUCED EPIGENETIC CHANGES IN MUSCLE DIFFER BY HIV SEROSTATUS

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Background: Exercise is an effective intervention for improving physical function among aging persons. Whether persons with HIV (PWH) experience the same benefits of exercise, and whether mechanisms underlying exercise effects are unique to HIV is not well understood.

Methods: Sedentary PWH (16 baseline; 14 paired) and controls (18 baseline; 15 paired), all men, aged 50 to 75 underwent biopsy of the vastus lateralis prior to and following 24 weeks of supervised cardiovascular and resistance exercise training. Skeletal muscle DNA methylation was quantified on MethylationEPIC BeadChip 850K array (Illumina), normalized and adjusted for batch effects. Linear models were fit for methylation values to test for the association of HIV status or exercise, adjusted for age and race/ethnicity to generate differentially methylated positions (DMPs). DMPs were then used to identify differentially methylated regions (DMRs) between pre- and post-exercise intervention for PWH and controls using Comb-p and adjusted for multiple comparisons. Pathway analysis was performed using Ingenuity.

Results: Pre-exercise, 983 DMPs differed between PWH and controls. Top canonical pathways included gas signaling (p=3.5E-3), IL-1 signaling (p=6.9E-3) and androgen signaling (p=1.3E-2). Post-exercise, 237 DMPs differed between PWH and controls, enriching neuroinflammation signaling (p=5.0E-3) and interferon pathways (p=1.6E-2). Exercise induced 209 genome-wide significant DMRs in PWH; top enriched canonical pathways included amytrophic lateral sclerosis signaling (p=1.3E-6), glutamate receptor signaling (p=1.1E-3), phosphatase and tensin homolog deleted on chromosome 10 (PTEN) signaling (p=3.7E-3), glial-cell-line-derived neurotrophic factor family ligand-receptor interactions (p=3.6E-3), and fibroblast growth factor signaling (p=5.1E-3). In controls, exercise training induced 75 genome-wide significant DMRs, enriching pathways associated with cyclins and cell cycle regulation (p=1.6E-3), telomerase signaling (p=3.4E-3), alanine degradation/biosynthesis (p=5.7xE-3), and hippo signaling (p=1.8E-3).

Conclusion: Epigenetic responses to exercise differed by serostatus: PWH experienced changes in DNA methylation status of genes involved in oxidative damage, mitochondrial function, angiogenesis, and metabolism while controls experienced changes in cell cycle, proliferation, protein synthesis and immune senescence.

705 EFFECTS OF HIV, AGE, AND SEX ON SKELETAL MUSCLE MASS AND DENSITY

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Background: Lower muscle density due to ectopic fat in skeletal muscle is associated with worse physical function. Muscle density declines with antiretroviral therapy (ART) initiation; both density and area decline with increasing age in persons with HIV, though few women have been studied. We examined the effects of age, sex, and HIV serostatus on muscle density to understand potential mechanisms of impaired physical function.

Methods: Men and women with and without HIV in the musculoskeletal substudies of the Multicenter AIDS Cohort Study (BOSS) and Women's Interagency HIV Study (MSK) were included. Participants underwent L4-L5 computed tomography scans to quantify total density (Hounsfield Units, HU) and area (centimeters2) of four trunk muscle groups. We identified factors associated with muscle density and area using generalized linear regression models.

Results: 387 men (198 HIV) and 184 women (118 HIV) had available CT scans. Among men, mean age was 64, 20% were black, 13% current smokers, and 19% were obese (BMI ≥30 kg/m_2). Among women, mean age was 50, 51% were black, 53% current smokers, and 44% were obese. All with HIV were on ART. Older age, female sex, and obesity were associated with lower muscle density in all 4 muscle groups; HIV serostatus was associated only with lower psoas density (table). Black race was associated with greater muscle density of nearly all muscle groups. No interaction between sex and HIV serostatus was observed. In sex-stratified models, HIV infection was significantly associated with lower psoas density in men (-1.8 [SE 0.54]HU, p=0.01) but not women (-1.0 [0.8]HU, p=0.19). Muscle area was lower with older age (effect range:-0.22 to -0.6 cm_2) and female sex (-6.0 to -3.1), but greater with obesity (range:1.5 to 5.4), all p≤0.02; no race effect was detected. HIV serostatus was associated with greater lateralis (1.0 [0.4],p=0.02) and paraspinal (0.8[0.4],p=0.03) but lower psoas (-0.6[0.2], p=0.01) area. Similar to density, in sex-stratified models, the association between HIV serostatus and area was only in men.

Conclusion: Older age and being a woman was associated with smaller and fattier muscle, while obesity was associated with larger and fattier muscle. Detrimental effects of HIV on the psoas density and area, particularly among men, may have important implications on balance, trunk stability, and mobility.

	Muscle Density (Hounsfield units, HU)			
	Lateralis	Rectus	Psoas	Paraspinal
Age (per year)	-0.3 (0.07)**	-0.4 (0.1)**	-0.3 (0.04)**	-0.6 (0.06)**
Race: (vs. White)				
Black	3.0 (0.9)**	1.5 (1.4)	2.3 (0.6) **	3.2 (0.9)**
Other	2.6 (1.3)*	1.7 (2.0)	0.4 (0.8)	1.2 (1.3)
Female (vs. Male)	-5.3(1.3)**	-13.9 (1.9)**	-3.8 (0.8)**	-10.8 (1.2)**
HIV-infected (vs. uninfected)	0.1 (0.7)	-1.3 (1.0)	-1.6 (0.4)**	0.5 (0.7)
BMI (vs. <25 kg/m^2)				
25-30	-4.0 (0.8)**	-3.4 (1.2)**	-0.9 (0.5)	-2.0 (0.8)*
30+	-10.7 (0.9)**	-10.5 (1.3)**	-1.8 (0.5)**	-4.3 (0.9)**

Results presented as effect (standard error): * p<0.05, ** p<0.01

706 CONSISTENT STATIN USE DOES NOT AFFECT AGE-ASSOCIATED GAIT SPEED AND STRENGTH DECLINES

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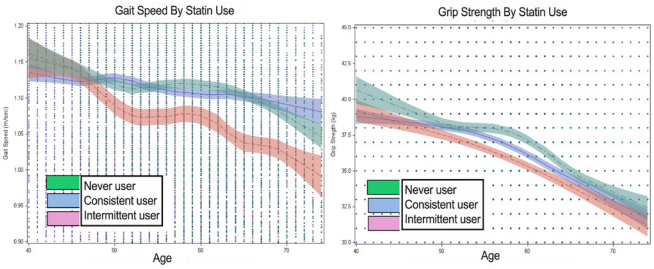
Background: Statin use decreases inflammation and reduces cardiovascular events, and may be useful among persons with HIV, who have increased risk of cardiovascular (CV) events. Other benefits are unclear; some studies suggest that statins benefit physical function despite myalgias as a common side effect. We compared age-associated changes in physical function among men with or without statin use in the Multicenter AIDS Cohort Study.

Methods: Men 40-75 years old with ≥2 measures of gait speed or grip strength (baseline=2007) were included. Consistent statin use was defined as use at ≥80% of visits. Gait speed was measured on a 4-m course and grip strength by handheld dynamometer. Generalized estimating equations included an interaction term for statin group and age; models were further adjusted for demographics, HIV status, and CV risk factors.

Results: Among 2021 men, median age was 52 (IQR 46,58) years; 68% were white, 27% black non-Hispanic, and 60% were overweight/obese. 636 were consistent (51% with HIV), 398 intermittent (61% HIV), and 987 never statin users (49% HIV). Duration of follow-up was 8.5 years (IQR 4.4, 10.4). Baseline gait speed was 1.12 m/sec (IQR 0.99, 1.25) and grip strength 38 kg (IQR 32, 44). Unadjusted changes in gait and grip are shown in the Figure. After adjusting for baseline, demographics, and CV risk factors, gait speed declined at -0.0028 m/s per year of age among all men, with no significant difference in gait speed decline among consistent vs never users (-0.0002 [-0.002, 0.0016], p=0.87). Intermittent users had a steeper gait speed decline over time vs never users (-0.0028 [-0.0048, -0.0007], p=0.007). Similar effects were seen with statin group and grip strength, with similar strength changes over time among

consistent vs never users (-0.062 [-0.17, 0.041], p=0.24), but tended to decline more among intermittent users (-0.109 [-0.22, 0.007], p=0.07). HIV serostatus was not associated with gait speed (-0.002 [-0.0162, 0.0123) or grip strength (-0.212 [-0.997, 0.574]; p≥0.60). Although pain was strongly associated with gait and grip decline, severe baseline pain did not confound the association between statin use and physical function.

Conclusion: Consistent statin use had no apparent effect on declines in gait and grip strength, suggesting no statin-associated impairments in physical function in this population.



707 PREVALENCE OF PHYSICAL-FUNCTION IMPAIRMENT AND FRAILTY IN MIDDLE-AGED PWH

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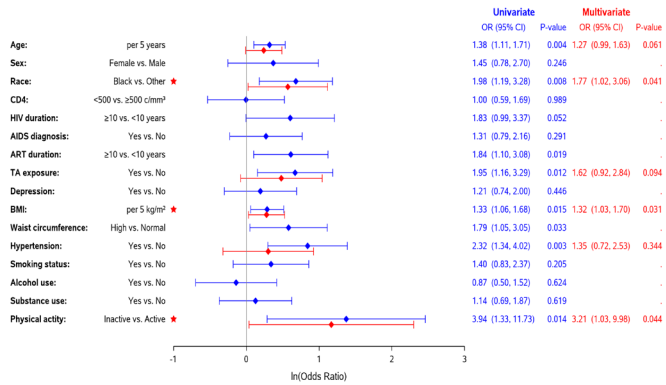
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Background: People with HIV (PWH) are at risk for accelerated development of physical function impairment and frailty with increasing age; both of which are associated with increased risk of falls, hospitalizations and mortality. We evaluated the prevalence of physical function impairment and frailty, and their association with demographics, clinical characteristics and risk factors among middle-aged PWH with low to moderate cardiovascular risk.

Methods: At enrollment, REPRIEVE (A5332) participants were 40-75 years of age, on stable antiretroviral therapy (ART) with CD4+ count >100 cells/mm$_3$, cardiovascular risk score ≤15%, excluding diabetes if LDL cholesterol ≥70 mg/dL; those concurrently enrolled into the physical function substudy A5361S (PREPARE) between 2017-2018 at US sites were evaluated at baseline. The evaluations included Short Physical Perfomance Battery (SPPB; 10x repeated chair stand, balance, 4-m walk), frailty phenotype, Duke Activity Status Index (DASI) and Rapid Eating and Activity Assessment for Patients (REAP). Physical function impairment was defined as a composite SPPB score ≤10. Associations between covariates and physical function impairment were evaluated using logistic regression.

Results: Among the 266 participants, the median age was 51 (Q1, Q3: 46, 55) years; 81% were male; 47% white, 45% Black; 18% Hispanic. The median CD4+ count was 610 (437, 840) cells/mm$_3$; 93% had HIV-1 RNA <50 copies/mL; 28% hypertension; 38% were overweight (BMI 25 to <30 kg/m$_2$), 30% obese (BMI ≥30 kg/m$_2$); 33% had high waist circumference (>102 cm in men, >88 cm in women); 89% were physically inactive (REAP). 37% (95% CI: 31%, 43%) had physical function impairment; 6% (4%, 9%) were frail and 42% pre-frail; 31% reported not being able to perform one or more instrumental activities of daily living (DASI). Older age, Black race, ≥10 years on ART, history of thymidine analog (TA), greater BMI, high waist circumference, hypertension and physical inactivity were associated with physical function impairment in univariate analyses (figure). Black race, greater BMI and physical inactivity remained associated with physical function impairment in the multivariate model.

Conclusion:
Physical function impairment and pre-frailty were common among middle-aged PWH; greater BMI and physical inactivity are important modifiable factors that may prevent further decline in physical function with aging.



Odds ratios (OR) and confidence intervals (CIs) are shown in log scale for visual purposes.

708 CAUSE-SPECIFIC HOSPITALIZATION TRENDS AMONG NORTH AMERICAN PERSONS WITH HIV 2005-2015

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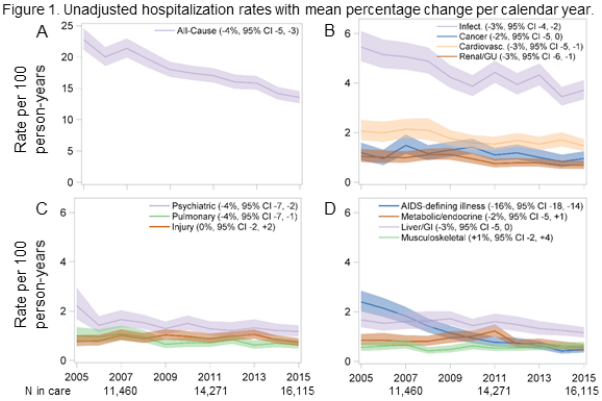
Background: Hospitalization rates among persons with HIV (PWH) may be changing due to demographic and antiretroviral (ARV) therapy changes. Early 2000s evidence suggested hospitalization rates among PWH were increasing for renal, pulmonary, and cardiovascular disease (CVD), possibly due to long-term HIV infection or ARV toxicity. To characterize recent hospitalization trends, we examined all-cause and cause-specific hospitalization rates among US and Canadian PWH 2005–2015.

Methods: Among patients ≥18 in care (≥1 CD4 or HIV RNA in a year) in 6 dynamic cohorts in NA-ACCORD 2005–2015, we categorized primary hospital discharge diagnoses with modified Clinical Classifications Software. We calculated all-cause and cause-specific annual hospitalization rates and used Poisson regression with GEE to estimate rate ratios for linear calendar time trends, unadjusted and adjusted for sex, race/ethnicity, HIV risk factor, and time-updated age, CD4, and HIV RNA.

Results: Of 27,347 patients, 81% were male, 33% Black, 52% MSM, and 13% with IDU history. From 2005 to 2015, median (IQR) age increased from 43 (38, 50) to 49 years (39, 57), CD4 count from 389 (243, 568) to 579 cells/μL (385, 786), and proportion with HIV RNA <400 copies/mL from 54% to 86%. Over 126,468 person-years (PY) of follow-up, 21,946 hospitalizations occurred. From 2005 to 2015, the annual all-cause hospitalization rate per 100 PY decreased from 22.8 (21.1, 24.6) to 13.5 (12.6, 14.5), with a mean annual change of -4% (-5, -3) [Fig. 1A]. Non-AIDS infection (25%), CVD (10%), liver/gastrointestinal (8%), psychiatric/substance use (8%), non-AIDS cancer (6%), and AIDS-defining illness (ADI, 6%) were the most common discharge diagnosis categories. Crude rates decreased for all categories except injury, endocrine, and musculoskeletal, which had no change (Fig. 1B-D). In adjusted models, rates decreased for CVD (-4%; CI -6, -2) and ADI (-8%; CI -11, -6) and were stable for other categories, including renal (-1%; CI -4, +2) and pulmonary (-2%; CI -5, +1).

Conclusion: Crude hospitalization rates decreased during 2005–2015 for most diagnostic categories. Preventing and treating non-AIDS infection, the most common hospitalization cause, remains important in HIV patient management. Adjusted decreases in CVD and ADI hospitalizations may be due to improvements in viral suppression, immunologic status, and outpatient care. Adjusted rates did not increase for organ systems potentially susceptible to cumulative damage from long-term HIV infection or ARV toxicity.

Figure 1. Unadjusted hospitalization rates with mean percentage change per calendar year.



709 MODIFIABLE RISK FACTORS AND INCIDENT CKD AND CVD AMONG HIV+ AND HIV– PATIENTS

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Background: HIV increases the risk of chronic kidney disease (CKD) and cardiovascular disease (CVD), but whether the association of preventable or treatable ("modifiable") risk factors with incident CKD or CVD is similar in people with HIV (PWH) and uninfected people is unknown.

Methods: We evaluated the association of modifiable risk factors with incident CKD (sustained eGFR <60 ml/min/1.73m$_2$) and CVD (hospitalized CHD, unstable angina or stroke) among adult (≥21 years) PWH and HIV-uninfected patients ("uninfected", age, sex, race/ethnicity, medical center, and calendar year matched 1:10) from Kaiser Permanente (KP) California (Northern and Southern) and Mid-Atlantic States (DC, MD, VA) healthcare systems during 2000-2016. We excluded patients with prior known CKD or CVD. Modifiable risk factors included diabetes mellitus, hypertension, dyslipidemia, smoking (ever documented history) and alcohol use disorder. We compared adjusted rate ratios (RRs) separately for each risk factor and outcome by HIV status using Poisson regression with terms for HIV status, risk factor of interest, and HIV*risk factor interaction. Models additionally adjusted for sociodemographic characteristics (time-updated age, sex, race/ethnicity, socioeconomic status, insurance type, KP region), years of KP membership, obesity (BMI>25), drug use disorder, CKD (for CVD), CVD (for CKD).

Results: Among 38,545 PWH and 384,658 uninfected without prior CKD, there were 3,084 and 10,257 incident CKD events, with rates of 1.7 and 0.5 per 100 person-years, respectively. Among 38,757 PWH and 384,404 uninfected without prior CVD, there were 1,227 and 10,039 incident CVD events, with rates of 0.6 and 0.4 per 100 patient-years, respectively. All modifiable risk factors had a stronger association with CKD among uninfected compared with PWH in adjusted models (all p<0.001; Table). Alcohol use disorder and dyslipidemia appeared protective for CKD among PWH. For CVD, dyslipidemia (p<0.001) and smoking (p=0.06) were stronger risk factors among uninfected compared with PWH.

Conclusion: All modifiable risk factors evaluated had a stronger association with CKD, and dyslipidemia and smoking a stronger association with CVD, among uninfected than PWH. Some risks appear protective for CKD among PWH, potentially due to successful treatment for those, and require further study. Mitigation of risks is important but may have a greater effect on CKD and CVD among uninfected people.

Table. Association of modifiable risk factors with CKD and CVD among PWH and uninfected adults

			P value comparing RR by HIV status
CKD:	**PWH**	**HIV-**	
Adjusted Rate Ratio (95% CI) for risk factors by HIV status			
Alcohol Use Disorder History	0.80 (0.72, 0.89)	0.99 (0.93, 1.05)	p=0.0006
Diabetes Mellitus	1.02 (0.93, 1.22)	2.37 (2.27, 2.48)	p<0.0001
Dyslipidemia	0.71 (0.66, 0.76)	1.62 (1.54, 1.70)	p<0.0001
Hypertension	1.31 (1.21, 1.41)	4.44 (4.21, 4.68)	p<0.0001
Smoking History	0.94 (0.87, 1.01)	1.20 (1.15, 1.25)	p<0.0001
CVD:			
Adjusted Rate Ratio (95% CI) for risk factors by HIV status			
Alcohol Use Disorder History	1.09 (0.94, 1.26)	1.19 (1.12, 1.26)	p=0.26
Diabetes Mellitus	1.47 (1.29, 1.68)	1.54 (1.47, 1.61)	p=0.54
Dyslipidemia	1.23 (1.10, 1.39)	1.58 (1.51, 1.66)	p=0.0001
Hypertension	1.79 (1.60, 2.01)	1.96 (1.87, 2.05)	p=0.14
Smoking History	1.24 (1.11, 1.40)	1.40 (1.34, 1.45)	p=0.06

Models adjusted for: demographics (updated age, sex, race/ethnicity, socioeconomic status, insurance type), drug use disorder history, years of KP membership, drug abuse (ICD code), CKD (for CVD), CVD (for CKD) and obesity (BMI>25) , and the modifiable risk factors smoking, diabetes mellitus, hypertension, alcohol use disorder, and dyslipidemia, including interaction term for that risk

710 BASELINE AND ACQUIRED COMORBIDITIES IN PATIENTS INITIATING ART IN THE HOPS, 2008-2018

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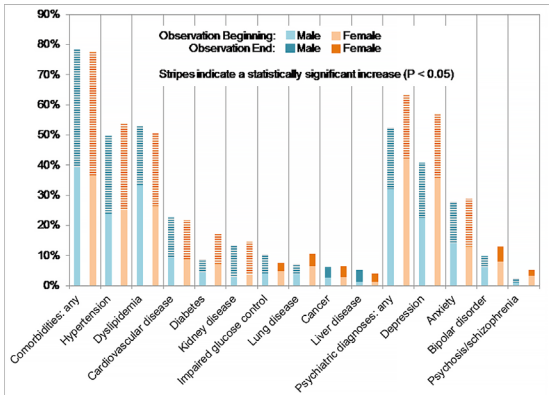
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Background: Among persons living with HIV (PLWH), the presence of physical and psychiatric comorbidities at baseline and the rate at which they develop may be related to aging, metabolic changes, medication, or socioeconomic factors.

Methods: We analyzed antiretroviral therapy (ART)-naïve participants in the HIV Outpatient Study (HOPS) initiating ART from 2008-2018 with ≥2 tests of CD4 counts since ART initiation by demographic factors, HIV risk activity, ART type and comorbid conditions: lipid disorders, diabetes, cardiovascular disease (CVD), cancer and mental health diagnoses at ART-start until last HOPS encounter. Yates-corrected chi-square analyses were used to test for changes in burden of comorbidity by sex during observation. Poisson regression was used to compare outcomes by sex, adjusted by age, race, payor, and individual person-time observation.

Results: There were 1236 participants, with 982 (79%) males and 254 (21%) females, median age 36 years, 66% non-white, 44% publicly insured, 53% with smoking history, and 33% with substance use history. The baseline CD4 count was 379 cells/mm$_3$ for men vs. 360 cells/mm$_3$ for women. Women were more likely to be older, Black or Hispanic, with public insurance, seen at a public clinic, with high school education or less (all P<0.05). Participants were followed for a median of 4.9 years, with men followed for a median of 4.6 years (interquartile range [IQR]=2.4-7.1), and women followed for a median of 6.1 years (IQR=3.1-8.3). Compared with baseline, there were statistically significant temporal increases for multiple comorbidities among men and women, including for dyslipidemia, hypertension, CVD, renal disease, diabetes, depression, and anxiety at last HOPS encounter (all P<0.05). At the end of observation, women were more likely than men to have a diagnosis of diabetes (Rate Ratio: 1.50, 95% Confidence Interval: 1.01-2.23); no associations of other comorbidities with sex were found.

Conclusion: Certain medical and psychiatric comorbidities are already present in persons initiating ART therapy in the past 10 years. There is a predominance of acquired metabolic comorbidities such as dyslipidemia, as well as psychiatric conditions that will complicate the long term management of persons living with HIV. With aging, PLWH who start ART experience a significant increase in the burden of physical and psychiatric non-HIV comorbidities over time that warrants continued surveillance, prevention, and treatment.



711 WOMEN WITH HIV HAVE HIGH OVERALL BURDEN AND EARLY ACCRUAL OF NON-AIDS COMORBIDITIES

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Background: HIV infection may accelerate aging-related comorbidity development. The incidence of non-AIDS comorbidities (NACM) in women with HIV (WWH) is poorly characterized.
Methods: WWH and HIV- women in active follow-up in the Women's Interagency HIV Study (WIHS) in 2009 (when >80% of WWH used antiretroviral therapy (ART)) or onward were included, with outcomes measured through March 31, 2018. Age, demographic and clinical covariates, and prevalent NACM were determined at enrollment. We used Poisson regression to estimate incidence rate ratios (IRR) comparing accrual of incident NACM by HIV serostatus and age using partially adjusted (age, HIV) and fully adjusted (age, HIV, covariates) models.
Results: There were 3129 women (2239 HIV+, 890 HIV-) with 36,589 person-yrs (PY) of follow-up. At enrollment, median age was 37yrs, 65% were black, 47% currently smoked, and median body mass index was 28 kg/m_2. WWH had a median CD4 count of 484 cells/mm_3, 69% were on ART and 45% were virologically suppressed. Of 10 NACM evaluated, mean NACM count at enrollment was higher among WWH vs HIV- women (1.4 vs 1.2, p=0.006), though only prevalent liver disease (26% vs 16%, p<0.001) and psychiatric illness (26% vs 21%, p=0.003) differed significantly by HIV serostatus.
In partially adjusted models, incident NACM burden was greater in WWH vs HIV- women (0.20/PY vs 0.16/PY; IRR 1.21, 95% CI 1.13-1.29) and increased with age regardless of HIV serostatus (p<0.0001). Incidence was higher in WWH vs HIV- women for (IRR; 95% CI): chronic kidney (3.14; 1.80-5.49), liver (2.56; 1.85-3.54), psychiatric (1.38; 1.02-1.86), hyperlipidemia (1.36; 1.14-1.62) and bone disease (1.35; 1.14-1.58). The incidence of hypertension, diabetes, cardiovascular, lung disease and non-AIDS cancer did not differ significantly by HIV serostatus.
In fully adjusted models, incident NACM burden was significantly higher among WWH vs HIV- women in most age strata (Figure, HIV*age interaction p=0.046). Women <25yrs had the greatest IRR at 1.50 (95% CI 1.21-1.87) vs those 25-29 (1.32; 1.10-1.58), 30-34 (1.24; 1.09-1.42), 35-39 (1.12; 1.00-1.25), 40-44 (1.03; 0.92-1.16), 45-49 (1.28; 1.07-1.53), 50-54 (1.18; 0.95-1.46), ≥55 (1.38; 1.04-1.84).
Conclusion: WWH have higher baseline and incident NACM burden than HIV- women. Incident differences were most dramatic among women aged <25yrs, a group for whom routine comorbidity screening is lacking. More data are needed to inform best practices for NACM screening and management in WWH, particularly young women.

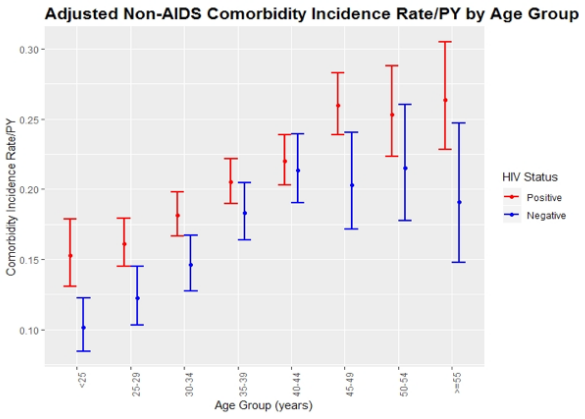


Figure. Incident non-AIDS comorbidity burden per person-year (PY) stratified by HIV serostatus and baseline age, adjusted for HIV, age, HIV*age interaction, study enrollment wave, race, body mass index, income, residence, marital status, education and use of tobacco, alcohol and crack/cocaine.

712 PERSISTENT LOW-LEVEL VIREMIA IS ASSOCIATED WITH NONINFECTIOUS COMORBIDITIES

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Background: Despite improved life expectancy with antiretroviral therapy (ART), persons living with HIV (PLWH) have higher rates of noninfectious comorbid diseases (NCDs) than do uninfected individuals. Chronic inflammation and immune activation due to persistent low-level viral replication may contribute to the heightened risk of NCDs among some PLWH. We characterized the risk of several NCDs among PLWH with undetectable plasma viral load, persistent low-level viremia (pLLV), and viral failure in the African Cohort Study (AFRICOS).
Methods: AFRICOS is an ongoing cohort enrolling participants in 12 clinics in Uganda, Kenya, Tanzania, and Nigeria. Clinical assessments, including HIV viral load testing, are completed every six months. Participants without an NCD at baseline were included in these time-to-event analyses. PLLV was defined as at least two consecutive visits with a detectable viral load <1000 copies/mL. We examined four different NCDs: elevated blood pressure (any single systolic pressure >139, diastolic >89 mmHg, or use of anti-hypertensive medications), hypercholesterolemia (total cholesterol >199 mg/dL or lipid-lowering medications), dysglycemia (any non-fasting glucose >199 mg/dL or fasting glucose >99 mg/dL), and renal insufficiency (estimated glomerular filtration rate <60). We also evaluated the presence of any one or more of these NCDs as a dichotomized outcome variable. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard modeling. Models were adjusted for study site, education, ART regimen, and age.
Results: As of June 1, 2019, 2,872 PLWH were enrolled of which 1,773 did not have an NCD at baseline and were included in these analyses. The majority of participants were female (58%) and between 18-39 years (61%) with 12% >50 years at enrollment. Over the course of follow up, 623 (35%) participants developed any NCD, including 261 (15%) who developed elevated blood pressure, 359 (20%) hypercholesterolemia, 176 (10%) dysglycemia, and 28 (2%) renal insufficiency. Participants with pLLV developed any NCD sooner than their virally-suppressed counterparts (HR 1.49 [95% CI 1.24-1.80]). Similar associations were observed for most of the individual NCDs evaluated (Table).
Conclusion: PLLV was significantly associated with NCDs in this population. Targeting viral suppression below the limit of detection on clinical HIV viral load assays may reduce the risk of non-infectious complications of HIV.

Table: Unadjusted and adjusted hazard ratios for viral load category and noninfectious comorbidities

		Unadjusted Hazard Ratio	95% Confidence Interval	Adjusted Hazard Ratio[1]	95% Confidence Interval
Any Noninfectious Comorbid Disease	Virally Suppressed	Ref		-	
	Persistent Low-level Viremia	**1.50**	**1.26-1.79**	**1.49**	**1.24-1.80**
	Viral Failure	1.14	0.87-1.50	0.97	0.73-1.28
Elevated Blood Pressure	Virally Suppressed	Ref		-	
	Persistent Low-level Viremia	**1.44**	**1.12-1.85**	**1.50**	**1.16-1.95**
	Viral Failure	1.14	0.77-1.69	1.09	0.73-1.62
Hypercholesterolemia	Virally Suppressed	Ref		-	
	Persistent Low-level Viremia	**2.49**	**1.6-3.81**	**1.74**	**1.11-2.73**
	Viral Failure	1.68	0.88-3.20	1.03	0.53-2.00
Dysglycemia	Virally Suppressed	Ref		-	
	Persistent Low-level Viremia	**3.07**	**1.77-5.34**	**1.96**	**1.07-3.57**
	Viral Failure	2.05	0.86-4.91	0.91	0.37-2.21
Renal Insufficiency	Virally Suppressed	Ref		-	
	Persistent Low-level Viremia	1.35	0.67-2.74	1.40	0.67-2.92
	Viral Failure	0.95	0.29-3.09	0.77	0.23-2.56

Statistically significant values (p<0.05) are shown in **bold**.
[1]Adjusted for ART regimen, age at visit, education, and study site

713 FACTORS ASSOCIATED WITH PSORIASIS: THE INDEPENDENT ROLE OF HLA-B*5701

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Background: Psoriasis is a T cell-mediated inflammatory disease with genetic factors involved in its aetiopathogenesis. In non-HIV population, HLA-B*5701 has been associated with a higher risk of psoriasis. The aim of this study was to study demographic and immunovirological characteristics associated with psoriasis and to assess whether HLA-B*57:01 is associated with psoriasis among patients living with HIV (PLHIV) followed in a large French multicenter cohort.
Methods: All PLHIV followed up in the Dat'AIDS cohort with an available result for HLA-B*57:01 available were included. Patients with psoriasis were identified by the presence of corresponding ICD-10 codes corresponding to this disease in the database. Logistic regression models were used to identify associations between psoriasis (outcome variable) and explanatory variables.
Results: Among the 31 076 PLHIV with available HLA-B*57:01 result included in the Dat'AIDS cohort from 2000 to 2018, the prevalence of psoriasis and HLA-B*57:01 were 2.25% and 4.73%, respectively. In multivariate analysis, male gender (OR 1.81 [95% CI, 1.46 – 2.24], p<10-4), positive HLA-B*57:01 (OR 2.66 [95% CI, 2.12 – 3.33], p<10-4), nadir CD4 cell count < 200/mm_3 (OR 1.41 [95% CI,

1.19 – 1.67], p<10-4) and positive HCV serology (OR 1.45 [95% CI, 1.20 – 1.76], p<10-4) were significantly associated with higher risk of psoriasis. To be born in West and Central Africa (OR 0.15 [95% CI, 0.10 – 0.25], p<10-4), in the Caribbean islands (OR 0.14 [95% CI, 0.05 – 0.45], p=0.0008) and in Latin America (OR 0.31 [95% CI, 0.14 – 0.69], p=0.004) was associated with lower risk of psoriasis compared to patients born in mainland France. Psoriasis preceded HIV diagnosis in 115 patients (19.6%), was concomitant in 119 patients (20.3%), and developed more than one year after in 352 patients (60.1%). For 114 patients (16.3%), the chronology was unknown. Patients in whom psoriasis preceded HIV diagnosis were significantly more often HLA-B*57:01 positive than the patients in whom the psoriasis was concomitant or occurred after HIV diagnosis.

Conclusion: PLHIV carrying HLA-B*57 01 have around 3-fold risk of psoriasis. Such association might provide a possible explanation for the observed differences in psoriasis prevalence between ethnic groups.

714 IMPACT OF ANTIRETROVIRAL THERAPY INITIATION ON EPIGENETIC AGING AND TELOMERE LENGTH

Clinical: (M) Other Complications of HIV Infection and Antiretroviral Therapy

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Background: Epigenetic age (EA) is an accurate predictor of biological age based on changes in DNA methylation. We investigated how changes in T cell subtypes after antiretroviral therapy (ART) initiation impact on EA, epigenetic age acceleration (EAA) and blood telomere length (TL).

Methods: We analyzed 114 randomly selected participants in the NEAT001/ANRS143 clinical trial before and 96 weeks (W96) after initial ART introduction. Whole blood DNA methylation profiles were assayed via Illumina Infinium MethylationEPIC BeadChips. Data were preprocessed using Noob normalization. The EA and estimated abundance of leukocyte subsets were obtained from the advanced analysis for blood tissue using the Horvath´s DNA methylation Age Calculator. We estimated three EAA measures: universal (AgeAccel), extrinsic (EEAA) and intrinsic (IEAA). We measured telomere length (TL) with multiplex qPCR.

Results: At baseline (BL), male: 88%, mean chronological age: 39.2 years, Caucasian: 80%, HIV-1 RNA: 4.7 $\log_{10}$ c/ml, and mean CD4+ and CD8+ (flow cytometry): 311 and 954 cells/µl. At W96, 96% had HIV-RNA <50 c/ml and mean CD4+ and CD8+ were 564 and 845 cells/µl. At BL, EA positively correlated with chronological age (rho: 0.891, p<0.001) while TL correlated negatively (rho: -0.490; p<0.001). Mean EA at BL and W96 was 47.5 and 47.6 years respectively. Age advancement (EA minus chronological age) significantly improved after ART initiation (BL: 8.3 vs W96: 6.5 years, p=0.007). Compared with BL, two measures of mean EAA slowed at W96 (AgeAccel: -1.49 years, p=0.011; EEAA: -4.02 years, p<0.001), while IEAA did not change (0.03 years, ns). EAA decreased in 71.05% (AgeAccel) and 78.07% (EEAA) of participants. At W96, EA correlated negatively with CD4+/CD8+ ratio by flow cytometry, estimated CD4+, naïve CD4+ and naïve CD8+, and positively with estimated CD8+CD28-CD45RA- T cells and NKs. Mean TL change at W96 was 0.034 (T/S). At W96 TL correlated positively with CD4+/CD8+ ratio by flow cytometry, estimated abundance of total CD4+, naïve CD4+ and naïve CD8+ and negatively with estimated abundance of CD8+CD28-CD45RA- and NKs (Table).

Conclusion: EA stabilized and EAA slowed in the majority of patients after starting ART. However, an age advancement of 6.5 years persisted after the first two years of successful ART. The reversal of epigenetic aging and the increase in blood TL caused by ART initiation are likely driven by changes in T cell subtypes toward less differentiated phenotypes.

Cell type	Rho (p-value)	
	EA	TL
$CD4^+$ T cell	-0.250 (0.007)	0.297 (0.001)
$CD4^+$ naïve T cell	-0.454 (<0.001)	0.426 (<0.001)
$CD8^+$ T cell	0.038 (0.688)	-0.026 (0.783)
$CD8^+$ naïve T cell	-0.582 (<0.001)	0.402 (<0.001)
$CD8^+CD28^-CD45RA^-$	0.353 (<0.001)	-0.377 (<0.001)
CD4/CD8	-0.240 (0.011)	0.251 (0.008)
B-cell	0.007 (0.937)	0.015 (0.874)
Plasmablast	0.039 (0.676)	-0.112 (0.236)
Natural Killer	0.329 (<0.001)	-0.306 (<0.001)
Monocyte	0.109 (0.251)	-0.057 (0.546)
Granulocyte	-0.101 (0.282)	0.039 (0.673)

Table. Correlations between estimated abundance of leukocyte subsets, CD4/CD8 ratio (flow cytometry) and epigenetic age (EA) and telomere length (TL) at week 96.

715 IN VITRO IMPACT OF TAF ON MITOCHONDRIAL FUNCTION IN IMMUNE CELLS

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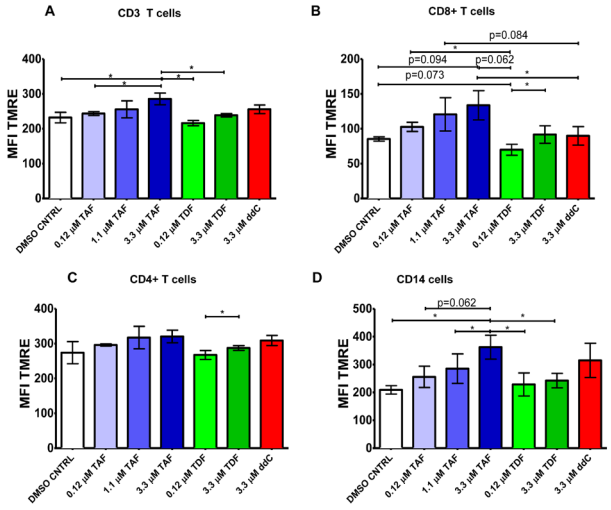
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Background: Mitochondrial dysfunction has been involved in toxicity of antiretrovirals such as Zalcitabine (ddC). Markedly lower plasma levels of tenofovir (TFV) are thought to lead to the more favorable bone and renal safety profile of tenofovir alafenamide (TAF) compared to tenofovir disoproxil fumarate (TDF). It is unknown whether an increase in intracellular levels of the active metabolite, tenofovir-diphosphate (TFV-DP) with TAF (compared to TDF) may alter mitochondria. This study was designed to address whether TAF affects in vitro mitochondrial membrane potential (MMP), a direct measure of the state of energization of the mitochondria, in peripheral blood mononuclear cells (PBMCs).

Methods: PBMCs were isolated from healthy 18-40 years old participants (n=10). PBMCs were incubated for 2-hour with TDF and/or TAF at concentrations that model clinically relevant plasma exposure. ddC was used as positive control. We used flow cytometry and the dye Tetramethylrhodamine ethyl ester (TMRE) to quantify the MMP in immune cells. Wilcoxon tests were used for statistical comparison between groups.

Results: After 2 hours of in vitro exposure of PBMCs to 0.12-3.3 µM TAF, TDF and ddC, 3.3 µM ddC and 0.12, 3.3 µM TDF did not affect the median fluorescence intensity (MFI) of TMRE in CD3+, CD4+, CD8+ T cells and CD14+ cells compared to DMSO control. 3.3 µM TAF increased the MFI of TMRE in CD3+ T cells and in CD14+ monocytes compared to DMSO control ($p<0.05$). 3.3 µM TAF increased the MFI of TMRE in CD8+ T cells compared to ddC ($p<0.05$). 2 hours of in vitro exposure of primary PBMCs to 0.12-3.3 µM TAF did not affect the MFI of TMRE in CD4+ T cells and increased the MFI of TMRE compared to TDF in CD3+ T cells and CD14+ monocytes (Figure).

Conclusion: We did not find any evidence of in vitro mitochondrial toxicity (reduction in MMP) with TAF. TAF may increase in vitro the MMP in resting PBMC as early as 2 hours. This concentration dependent effect was more prominent in monocytes compared to T cells. The clinical relevance of these in vitro findings is unknown. The effect of TAF on mitochondrial function in chronic treated HIV should be further explored in patients switching from TDF to TAF regimens.



716 INFLAMMATION AND MITOCHONDRIAL DYSFUNCTION NOT NRTIs DRIVE EVENTS IN ACTG A5241

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Background: ACTG A5241 (OPTIONS Study) randomized individuals experiencing treatment failure to omit or add nucleoside reverse transcriptase inhibitors (NRTIs) to a regimen that had a cumulative activity of 2 or more active antiretroviral agents. There were more deaths and clinical events observed in those randomized to add NRTIs. We hypothesized that clinical events were associated with markers of inflammation and mitochondrial dysfunction.

Methods: Cohort study of 174 participants enrolled in OPTIONS (N=413) selected randomly and enriched to include those with clinical events (death, AIDS defining opportunistic infections and non-AIDS clinical events). Protein levels relating to inflammation (IL-6, TNFr1, TNFr2, sCD14, CRP, Insulin) or mitochondrial dysfunction (NADH dehydrogenase [C1], FGF21 and GDF15) were measured by Luminex and ELISA, respectively at baseline, weeks 24 and 48 and evaluated for their association with the composite endpoint of clinical events. At baseline sampling, all participants were taking a failing regimen of NRTIs plus protease inhibitors. The statistical analysis included univariate parametric (t-tests) and non-parametric tests (Wilcoxon test) with selected variables analyzed using linear and generalized linear models.

Results: 174 participants were evaluated with a median age of 47 years, 40% women; 43% Black, 20% Hispanic/Latino, 36% white. There were 58 participants with clinical events and 116 participants without clinical events of whom 35% vs. 36% were randomized to omit NRTIs, respectively. At baseline, sCD14 (555,263 vs 448,584 pg/mL, P=0.03); CD4 count (148 vs. 209 cells/mm_3, P=0.03); CD4:CD8 ratio (0.16 vs 0.22, P=0.02) and VACS Index (46 vs. 33, P=0.02) were significantly different in those who subsequently experienced a clinical event. At baseline, there were no significant differences in the two groups NADH dehydrogenase activity, FGF-21, GDF-15, IL-6, TNFr1, TNFr2, insulin or HIV RNA levels. Censoring for those with clinical events before weeks 24 or 48, FGF-21, sCD14, CD4, CD4:CD8 ratio and VACS index were significantly different at weeks 24 and 48 (Table). Analyses were similar when adjusted for randomization to omit or add NRTIs. Only sCD14 remained significant on multivariate analyses at baseline, week 24 or week 48 (Odds ratio, 1.0).

Conclusion: Severity of illness, biomarkers of inflammation and mitochondrial dysfunction were associated with clinical events. Randomization to omit or add NRTIs was not associated with clinical events. sCD14 identifies a group at higher risk of developing clinical events.

Table of Median Values of Week 24 and 48 Measures

	Week 24			Week 48		
	Clinical Event (N=52)	No Event (N=116)	P value	Clinical Event (N=49)	No Event (N=116)	P value
Baseline CD4 (cells/mm³)	***164***	***209***	***0.04***	***149***	***209***	***0.04***
Baseline CD4:CD8 ratio	***0.17***	***0.23***	***0.02***	***0.17***	***0.23***	***0.01***
Baseline VACS Index	***43.5***	***33.0***	***0.03***	***43.5***	***33.0***	***0.03***
Baseline HIV RNA (copies/mL)	18,344	16,284	0.45	20,400	16,284	0.40
sCD14 (pg/mL)	***545,042***	***387,479***	***<0.001***	***572,375***	***363,165***	***0.002***
IL-6 (pg/mL)	5.27	5.27	0.36	5.27	5.27	0.18
TNFr1 (pg/mL)	1,617	1,302	0.13	1,672	1,364	0.06
TNFr2 (pg/mL)	65.59	61.22	0.66	63.48	57.76	0.46
FGF-21 (pg/mL)	***146.49***	***102.20***	***0.02***	***169.56***	***123.93***	***0.04***
GDF-15 (pg/mL)	1,959	1,828	0.84	2,030	1,801	0.45
CRP (mg/L)	1.02	0.89	0.73	1.27	0.78	0.89

717 IMPACT OF TREAT-ALL GUIDELINES ON TB INCIDENCE AMONG PLWH IN RIO DE JANEIRO, BRAZIL

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Background: Antiretroviral therapy (ART) substantially lowers tuberculosis (TB) risk, and implementation of universal ART ("treat all") guidelines therefore has the potential to reduce TB burden among people living with HIV (PLWH). We evaluated the impact of treat all guidelines on TB incidence and mortality in Rio de Janeiro, Brazil.

Methods: Brazilian guidelines recommended ART for patients with CD4≤500 from 2010-2013 and treatment for all starting in 2014. We included all PLWH entering public sector care in Rio from 2010-2016 with follow-up through 2017, excluding those with prevalent TB. We used national electronic registries to obtain data on CD4s, viral loads, TB diagnoses, ART prescriptions, and deaths; and joined databases using probabilistic linkage. We followed patients from entry into care until TB diagnosis, death, or administrative censoring at 2 years. We calculated incidence rates (IR) per 100 person-years (pys) and the 2-year cumulative hazard (CH) of 1) TB and 2) TB/death prior to and following implementation of treat all guidelines, stratified by baseline CD4 and ART status.

Results: 16,552 PLWH entered care from 2010-2016; 5,675 (34%) were female and median age was 34 years (IQR 27-43). Baseline CD4 was ≤500 in 6,902 (42%), >500 in 4,013 (24%), and unknown in 5,637 (34%). Overall, 8,446 (51%) started ART, 248 (1.5%) developed TB, and 893 (5.4%) died within 2 years. IR by entry year are shown (Table). There was a 22% reduced rate of TB (IR ratio 0.78, 95% CI 0.61-0.99) and TB/death (IR ratio 0.78, 95% CI 0.69-0.88) post treat all compared with pre treat all. The 2-year CH of TB and TB/death declined between periods for those with unknown baseline CD4s (TB: 2.2% vs 1.7%, p=0.14; TB/death: 7.2% vs 5.4%, p=0.01) but did not decline for those with CD4≤500 (TB: 1.8% vs 1.9%, p=0.82; TB/death: 10.8% vs 10.1%, p=0.49) or CD4>500 (TB: 0.6% vs 0.7%, p=0.78; TB/death: 2.4% vs 2.1%, p=0.50). ART was associated with a 66% reduced rate of TB (IR ratio 0.34, 95% CI 0.22-0.52) and TB/death (IR ratio 0.34, 95% CI 0.28-0.42) in the pre treat all period; in the post treat all period, ART was associated with a 17% reduced rate of TB (IR ratio 0.83, 95% CI 0.59-1.17) and a 44% reduced rate of TB/death (IR ratio 0.56, 95% CI 0.47-0.67).

Conclusion: Risk of TB and death fell in the treat all era in Rio but remains high. ART coverage must increase, and additional interventions, including TB preventive therapy, should be scaled-up to reduce TB morbidity and mortality.

Table. Incidence of TB and TB or death among persons newly entering public sector care in Rio de Janeiro, 2010-2016

Entry into care		TB cases	TB or death	Person-years	IR of TB per 100 pys (95% CI)	IR of TB or death per 100 pys (95% CI)
Pre Treat All	2010	36	165	3,906	0.92 (0.66-1.28)	4.22 (3.63-4.92)
	2011	31	139	3,907	0.79 (0.56-1.13)	3.56 (3.01-4.20)
	2012	39	142	3,790	1.03 (0.75-1.41)	3.75 (3.18-4.42)
	2013	37	162	4,574	0.81 (0.59-1.12)	3.54 (3.04-4.13)
Post Treat All	2014	45	192	5,165	0.87 (0.65-1.17)	3.72 (3.23-4.28)
	2015	38	175	5,567	0.68 (0.50-0.94)	3.14 (2.71-3.65)
	2016	22	122	3,621	0.61 (0.40-0.92)	3.37 (2.82-4.02)

Abbreviations: TB, tuberculosis; IR, incidence rate; pys, person-years; CI, confidence interval

718 ESTIMATING TB TRANSMISSION IN PRIMARY CARE CLINICS IN TB/HIV HIGH-BURDEN SETTINGS

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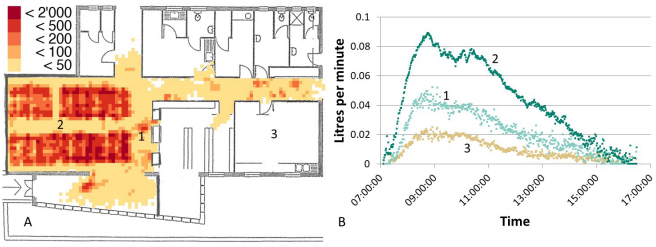
Background: Tuberculosis (TB) transmission is difficult to measure and its drivers are not well understood. We piloted a novel approach using clinical, environmental and position-tracking data to study the risk of TB transmission in a primary care clinic in Cape Town, South Africa.

Methods: We collected risk factors for airborne transmission during 4 weeks on workdays in August 2019. Patient data included characteristics and number of patients, waiting times and anonymous patient movements using video sensors. Environmental data included indoor carbon dioxide levels (CO2 in parts per million [ppm]), relative humidity (RH, associated with Mycobacterium tuberculosis (Mtb) survival in the air), frequency and intensity of patients' coughing using sound recording (analyses ongoing), and number of Mtb particles in the air using bio-aerosol sampling devices (molecular detection; analyses ongoing). We calculated rebreathed air volume (RAV) based on people density and CO2 levels (indicating airborne transmission). We defined three areas in the clinic: registration desk (1, see figure), waiting room (2), and TB treatment room (3).

Results: 14,795 people visited the clinic. The median number visiting per day was 706 (interquartile range [IQR] 622-803), with a median time of 12.4 min (IQR 11.2-13.7) spent in the waiting room. Density of people was highest in the waiting room (see figure). Overall, the median CO2 level was 623 ppm (IQR 501-751); higher in the morning, compared to midday and afternoon (715 vs. 668 vs. 485; p<0.001). The median RAV was 40 L/day (IQR 18-77); higher in the waiting room compared to the registration area and TB room (69 vs. 26 vs 12 L/day; p<0.001). The ventilation rate (air change) was relatively high with 11.2 l/h per person (typical value for bedrooms: 5.0l/h per person). The proportion of patients' time spent above 1,000 ppm CO2 indicating poor ventilation was 10% (typical outdoor value: around 400 ppm). The median RH was above 65% in 32% of time. We are in the process of combining these data with clinical data, cough recordings and the number of Mtb particles in the air to construct a mathematical TB transmission model.

Conclusion: This pilot study documents the feasibility of a novel approach to the control of TB in a high-risk transmission setting. Mathematical modelling will allow us to identify factors driving the risk of TB transmission and to evaluate interventions such as separating patient flows or improving ventilation.

Figure: A: Floor plan of the primary care clinic in Cape Town, South Africa. Density of visiting patients per minute during the study period using a video sensor tracking system; B: Mean shared rebreathed air volume (RAV, in L per minute) during the day at the registration desk (1), waiting room (2), and TB treatment room (3).



719 ALARMING TUBERCULOSIS RATE AMONG PWID IN VIETNAM

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Background: Vietnam belongs to the 30 high TB burden countries according to WHO, with an annual TB incidence of 129/100.000. A few reports suggested that PWID had increased TB rate, most likely due to high HIV prevalence in this key population (eg. 27% in Haiphong, 2 million inhabitant city, Vietnam). The record of a high numbers of deaths due to TB during the implementation of large project aiming at ending HIV transmission among PWID in Vietnam, prompted the evaluation of the TB rate in this population.

Methods: We implemented a cross-sectional assessment of active TB during a follow-up visit of 2 open cohorts of HIV-negatives and HIV-positives PWID in Hai Phong. Cohort participants were recruited through 2 community-based Respondent-Driven-Sampling surveys carried out at 1 year interval (N=1383 and 1451, respectively). Adult PWID with heroin detected in urine and recent injection skin marks were available. During a cohort follow-up visit, community-based organization (CBO) members systematically assessed TB symptoms using a standardized questionnaire. If any symptom was recorded, then a Chest X-Ray (CXR) was done at the local TB hospital, followed by a Xpert® MTB/RIF test on sputum if the CXR was abnormal.

Results: Among the 581 HIV positives and 672 HIV-negative participants expected, 484 and 457 PWID completed their cohort visit. Overall, 93% were males, their median age was 42 years; 75% and 51% were using methadone, respectively. Among HIV-positives, 90% were on ART and 82% had a viral load < 1000 copies/mL, with a median CD4 count of 472 cells/µL. Among the 451 HIV-positive PWID screened for TB, 293 (65%) had a least one symptom, 84/253 (33%) had an abnormal CXR, and among the 38 who had a Xpert® MTB/RIF result available, 8 were positive. Assuming all PWID who dropped from the screening cascade had no TB, the conservative TB prevalence was 1.8% [0.6; 3.0]. Very similar figures were found among HIV-negative PWID, with 7 active TB cases for a TB prevalence of 1.6% [0.4; 2.8].

Conclusion: In this high TB burden setting, the active TB prevalence among PWID is more than 10 times higher than the annual TB incidence in the general population, with no increased risk due to HIV. This very high TB rate suggests transmission of M. tuberculosis within PWID. Urgent interventions targeting PWID are required to reach the objective of ending the TB epidemic.

720 PREVALENCE OF TB SYMPTOMS, DIAGNOSIS, AND TREATMENT AMONG HIV PATIENTS NOT ON ART

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Background: Current WHO guidelines recommend that HIV-positive patients who report >1 symptom of tuberculosis (TB) require further investigation for TB disease prior to antiretroviral treatment (ART) initiation. This requirement for ruling out active TB before initiating ART may preclude same-day treatment initiation for many patients who do ultimately not have TB, and, by requiring extra clinic visits, contributes to loss-to-follow-up. We compared the prevalence of TB symptoms, which can delay ART initiation, to the prevalence of TB diagnosis and treatment in intervention arm patients enrolled in the Simplified Algorithm for Treatment Eligibility clinical trials (SLATE I and II) in South Africa and Kenya.

Methods: We used intervention arm screening data to describe prevalence of TB symptoms (cough, weight loss, fever, night sweats), diagnosis, and treatment in patients presenting for HIV care not currently on ART in South Africa (n=594) and Kenya (n=240). Data for SLATE I and II in South Africa were combined.

Results: 38%(95%CI:32-44%) of patients in Kenya and 41%(37-45%) in South Africa had >1 symptom of TB when presenting for HIV care. 70% of patients in both countries who presented with >1 TB symptom were tested for TB disease. 13%(7-22%) tested positive for TB in Kenya and 6%(4-10%) tested positive in South Africa. All 27 patients who tested positive for TB disease in both countries reported having >3 symptoms. In both countries, patients with TB symptoms had lower CD4 counts at study enrollment than did those with no symptoms of TB (Kenya: median 152 cells/mm$_3$(IQR:64-329) vs. 357(191-632); South Africa: 205(104-391) vs. 351(172-513)). The lowest median CD4 counts were recorded among those with active TB disease (Kenya 124(12-150); South Africa 193(56-223)). Among the 493 asymptomatic patients in SLATE I and II, 4(3%) of patients in Kenya and 151 (44%) of patients in South Africa were tested for TB. One patient tested positive for TB in South Africa and commenced TB treatment; no adverse events (e.g. immune reconstitution inflammatory syndrome) were reported.

Conclusion: Among 234 patients with WHO-defined TB symptoms, 88% did not have TB but experienced an unnecessary delay in ART initiation. Requiring TB test results for all symptomatic patients prior to ART initiation, without consideration of symptom number or severity, should be reconsidered.

Table. Self-reported TB symptoms, TB diagnosis, and TB treatment uptake among patients who screened out due to TB symptoms in the intervention arms of the SLATE I and SLATE II trials.

Variable (n, % responding yes)		Kenya (SLATE I) (N = 240)	South Africa (SLATE I and II) (N = 594)
Screened for TB		240 (100)	594 (100)
1 or more TB symptom reported		90 (38)	245 (41)
Symptoms reported (n)	Cough (current)	75 (83)	147 (60)
	Fever	53 (59)	65 (27)
	Night sweats	56 (62)	73 (30)
	Weight loss	72 (80)	172 (70)
Number of symptoms reported (n)	1 symptom	13 (14)	125 (51)
	2 symptoms	18 (20)	59 (24)
	≥3 symptoms	59 (66)	61 (25)
TB test performed in symptomatic patients		63 (70)	171 (70)
Positive TB tests among symptomatic patients		12 (13)	15 (6)

721 HOUSEHOLD AIR POLLUTION INCREASES RISK FOR PULMONARY TB IN HIV-INFECTED ADULTS

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Background: Millions of deaths related to household air pollution (HAP), pulmonary tuberculosis (PTB), and HIV occur annually in low income countries. However, little is known about the influence of HAP on PTB risk among people living with HIV (PLHIV).

Methods: We conducted a case-control study among PLHIV at four clinics in eastern Democratic Republic of Congo (DRC) from March 2018 to February 2019. Cases were ≥18 years old, with recent (≤5 years) or current PTB. Controls were age- and sex-matched PLHIV with neither recent nor current PTB. During home visits, HAP exposure was assessed using a validated International Multidisciplinary Programme to Address Lung Health and TB in Africa (IMPALA) questionnaire. Personal carbon monoxide (CO) exposure was assessed using the EasyLog USB CO Lascar Monitor, and volatile organic compound exposure using Radiello® passive-diffusive sampler. Urinary 1 hydroxypyrene and S-phenyl-mercapturic acid were measured. Bacteriologic confirmation of PTB (sputum smear or Xpert MTB/RIF positive), CD4 count, and antiretroviral treatment (ART) history were extracted from medical records. Conditional multivariate logistic regression was performed to assess independent associations between HAP and PTB.

Results: We recruited 435 cases and 842 controls. Median age (IQR) 41 years (33-50), 76% female. Overall median 24h-personal average CO was 5.3 [2.3-10.6] parts per million (ppm). After adjusting for sociodemographic covariates, tobacco smoking, median CD4 count, and duration on ART, each 1 ppm increase in average 24h CO exposure was positively associated with PTB (adjusted odds ratio, aOR; 95% confidence interval, CI: 1.5; 1.01-2.23). Average 24h CO level stratification by quintiles yielded a concentration dependent increase in the odds of PTB from the lowest [0.1-1.9 ppm], to highest quintile [12.3-76.2 ppm] (aOR 4.64; 95%CI: 1.04-20.65) (Fig. 1). Furthermore, for women, each additional hour spent cooking over wood fire was associated with increased odds of PTB (aOR 2.76; 95% CI: 1.02-7.47).

Conclusion: Personal CO exposure and time spent cooking over wood fire (among women) were independently associated with increased odds of PTB among PLHIV in eastern DRC. Longitudinal studies are needed to confirm our findings and inform comprehensive strategies to reduce the triple burden of HAP-TB-HIV.

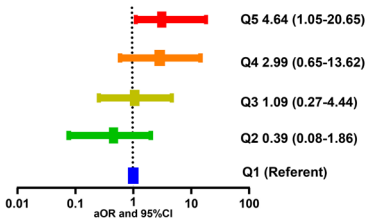


Fig. 1. Forest plot on log scale of average 24h-personal CO exposure by quintile and risk of pulmonary tuberculosis in adults living with HIV displaying a concentration dependent increase pattern, Eastern Democratic Republic of Congo.

722 ALCOHOL USE IS ASSOCIATED WITH INCIDENT TB INFECTION IN HIV+ AND HIV– UGANDAN ADULTS

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Background: Globally, an estimated 10% of TB disease is attributable to alcohol use. Alcohol users may be at increased risk of TB disease as a result of spending more time in social venues (e.g. bars) where TB transmission is high, however the relationship between alcohol use and incident TB infection is unknown.

Methods: We assessed this association in a longitudinal cohort of tuberculin skin test (TST) negative adults nested in the SEARCH study (NCT:01864603) in Eastern Uganda. Baseline (2015-16) TSTs were placed in 2,940 adults participating in a household survey, enriched for persons living with HIV. Participants with no TST induration were eligible for TST testing a year later. Our primary outcome, incident TB infection, was defined as a change in TST induration from 0mm to >5mm if HIV+ or >10mm if HIV- at reassessment. Alcohol use was assessed using the Alcohol Use Disorders Test-C (AUDIT-C). Exposure variables were: (1) any alcohol use (AUDIT-C>0) vs. no use and (2) hazardous use (AUDIT-C >3 for women, >4 for men) vs. non-drinking/ non-hazardous use. We calculated odds ratios using generalized estimating equations and used inverse probability weighting to account for incomplete measures. All models were adjusted for age, gender, household wealth, HIV status, and household TB contact.

Results: One-year follow-up TSTs were completed in 1,047 (58%) of the 1,814 adults with a negative TST at baseline. Among those who completed TSTs, 84 (8%) reported alcohol use, 36 (3%) reported hazardous alcohol use, 269 (26%) were living with HIV, and 21 (2%) reported a household TB contact in the year prior. At follow-up, 177 (17%) met our definition of incident TB infection. Incident TB infection was more common in persons who reported any alcohol use compared to no use (27% vs. 16%) and alcohol use was positively associated with incident TB infection (aOR 2.0, 95% CI: 1.0-3.8, p=0.04). Hazardous alcohol use was associated with incident TB infection (aOR 2.8, 95%CI: 1.1-7.1, p=0.03) compared non-drinkers/non-hazardous drinkers. There was no association between incident TB infection and HIV status or having a household TB contact.

Conclusion: In this longitudinal cohort of adults in Uganda, incident TB infection was high, positively associated with alcohol use at any and hazardous levels, and not associated with HIV-status or a known household TB contact. TB prevention efforts that focus on reducing transmission in venues shared by drinkers may decrease the latent TB reservoir in this TB risk group.

723 TUBERCULOSIS EVALUATION AMONG HIV-POSITIVE PATIENTS ON ANTIRETROVIRAL THERAPY

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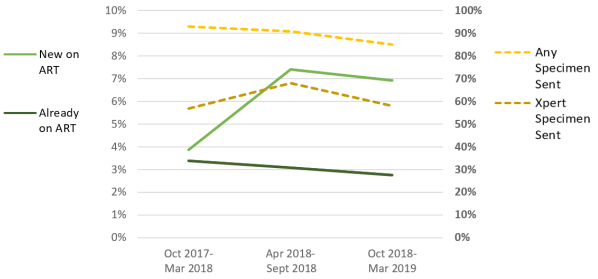
Background: The World Health Organization estimates nearly 500,000 cases of tuberculosis (TB) among people living with HIV (PLHIV) go unreported each year. Among PLHIV, four-symptom TB screening (cough, fever, weight loss, and night sweats) is recommended at every clinical encounter, followed by sputum testing with Xpert MTB/RIF for positive screens. We assessed TB screening programs in countries supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR).

Methods: We analyzed TB screening and diagnostic testing data collected at PEPFAR-supported sites during October 2017–March 2019. Countries reporting TB screening data with ≥90% completeness were included. Using pooled and country-specific data, we determined the proportion of patients screened for TB symptoms and those who screened positive among PLHIV newly initiating ART vs those already receiving ART at the time of screening. We also determined the proportion of patients with a positive TB screen who had TB diagnostic testing, including Xpert MTB/RIF.

Results: Of 30 countries reporting TB screening data, we included 20. Of the 8,337,799 PLHIV already receiving ART, 7,273,266 (87%) were screened at least once for TB symptoms in the most recent biannual reporting period. In the same period, the pooled rate of positive TB symptom screens was 2.6% (7.0% among ART-naïve PLHIV vs 2.3% among those already receiving ART). Median country-specific rates of positive TB screening results were 2.5% (interquartile range [IQR], 1.7%–5.8%) overall (ART-naïve PLHIV, 7.4% [IQR: 5.8%–13.8%]; PLHIV already receiving ART, 2.1% [IQR, 1.5%–5.3%]). Since 2017, the rate of positive TB screens globally has increased from 3.9% to 6.9% among ART-naïve PLHIV and has decreased to 2.8% from 3.4% among those already receiving ART. Among all PLHIV with a positive TB screen result, 85% had sputa sent for diagnostic testing (58% for Xpert MTB/RIF testing); trends in specimen testing decreased over the analysis period.

Conclusion: The proportion of ART-naïve PLHIV with a positive TB screen result is increasing but remains lower than expected for high-burden settings. We identified gaps in TB diagnostic services: roughly 1 in 6 PLHIV with TB symptoms does not receive diagnostic testing. Our findings suggest that improved TB screening and GeneXpert-based TB testing will be crucial in improving progress.

Figure 1. Pooled trends in positive tuberculosis symptom screens and diagnostic testing across sites supported by the U.S. President's Emergency Plan for AIDS Relief



724 TUBERCULOSIS PREVENTIVE TREATMENT IN NEW VS EXISTING ANTIRETROVIRAL THERAPY PATIENTS

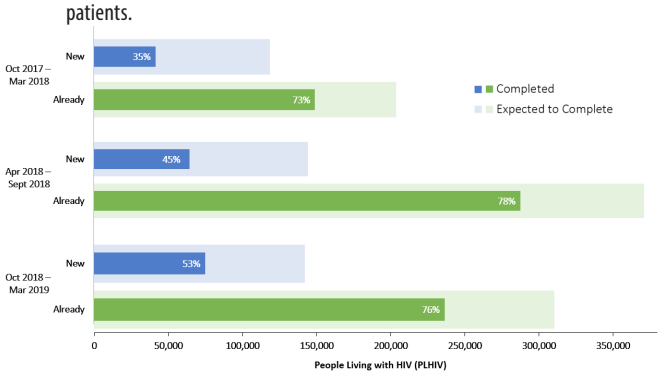
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Background: Tuberculosis (TB) preventive treatment (TPT) has been shown to drastically reduce mortality among people living with HIV (PLHIV). The World Health Organization recommends TPT for all PLHIV without contraindications or active TB disease. Accordingly, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) is committed to providing TPT to the eligible 14 million PLHIV currently supported by this program. In 2017, PEPFAR-supported programs began biannual reporting on TPT among all new and existing antiretroviral (ART) patients.

Methods: We conducted a descriptive analysis of TPT completions and expected completions (i.e. those initiated on TPT in the previous six-month reporting period) in PEPFAR-supported sites during 2017–2019. Countries with >90% TPT data completion were included for analysis. We calculated the proportion of PLHIV who completed TPT of those that initiated in the previous reporting period. We then determined the proportion that initiated TPT in the previous reporting period and the proportion that completed TPT among all eligible PLHIV on ART (based on negative TB symptom screen), disaggregated by those newly initiating ART versus already receiving ART in the reporting period.

Results: Nineteen of twenty-nine countries were retained for analysis. In the most recent reporting period (October 2018—March 2019), number of PLHIV eligible for TPT based on negative TB symptom screen ranged from 555—981,037 per country. Among eligible patients newly initiating ART, only 33% were initiated on TPT, and only 17% completed TPT. Among eligible patients already receiving ART, only 8% were initiated on TPT and only 6% completed a course. Since October 2017, overall TPT completion among all PLHIV that initiated in the previous reporting period increased from 59% to 69%. During the same time, among those already receiving ART, completion increased from 73% to 76%; completion was consistently lower (35–53%) in those newly initiating ART (Figure 1).

Conclusion: Programmatic data suggests TPT implementation remains low. Only one in six eligible patients who were newly initiated on ART completed a course of TPT in the most recent data. A marginal increase in completion rates was observed among those newly initiating ART; however, overall, completion rates remained consistently higher among those already receiving ART. Accelerated efforts will be necessary to provide TPT to all eligible PLHIV by reducing barriers to TPT initiation and completion among both new and existing patients.



725 POTENTIAL IMPACT OF LATENT TUBERCULOSIS IN PEOPLE LIVING WITH HIV

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Background: Approximately 28% of the human population harbour Mycobacterium tuberculosis (MTB), with more than 90% of infected individuals not developing disease. Recent findings in the animal model suggest that latent MTB infection (LTBI) may have symbiotic effects by protecting against MTB-unrelated infections via activation of the innate immune system. So far, potential interactions of LTBI in HIV-infected individuals have not been investigated.

Methods: We included all participants of the Swiss HIV Cohort Study (SHCS) with at least one documented MTB test. LTBI was defined as either a positive skin reactivity test or a positive IGRA test; patients who developed active MTB were excluded. Logistic regression was used to analyse the frequency of the most common opportunistic infections and laboratory conditions between patients with and without LTBI. Linear regression was used to detect differences in the setpoint viral load between patients with and without LTBI. In multivariable models we corrected for baseline demographic characteristics, i.e., year of HIV diagnosis, HIV transmission group and ethnicity. In the analysis of opportunistic diseases, we corrected as well for the CD4 nadir.

Results: Out of 13675 patients tested for MTB, 1027 (7.7%) had a LTBI and 316 (2.3%) developed active MTB. Patients with LTBI had significantly lower odds of having oral candidiasis (univariable (UV) odds ratio (OR)=0.31, p<0.0001; multivariable (MV) OR=0.61, p<0.0001) and oral hairy leukoplakia (UV OR=0.36, p<0.0001; MV OR=0.72, p=0.028) as compared to MTB uninfected patients. For other opportunistic diseases, the significant interaction with LTBI disappeared in the MV model (Figure). LTBI was associated with a reduced setpoint viral load (UV=0.27, 95%-confidence interval=[0.35,0.20], log-reduction; MV=0.24 [0.32,0.18]).

Conclusion: The finding that LTBI is independently associated with a reduced risk for oral candidiasis and oral hairy leukoplakia points towards a yet not appreciated interaction between LTBI and other infections. In addition, a significant reduction of the setpoint viral load in asymptomatic HIV-infected individuals suggests a more complex interaction between MTB infections and HIV than previously assumed. In conjunction, these findings potentially suggest

that LTBI in humans also might have an activating effect on the innate immune system as was proposed in the mouse system.

Association of latent tuberculosis and opportunistic diseases

■ unadjusted ■ adjusted: HIV transmission group, ethnicity, year of HIV diagnosis, CD4 nadir

	no TB	LTBI	p unadj	p adj
Oral candidiasis	27.85%	10.71%	< 0.0001	< 0.0001
Oral hairy leukoplakia	13.25%	5.16%	< 0.0001	0.0279
HIV-related thrombocytopenia	6.53%	3.99%	0.0015	0.6912
Esophageal candidiasis	9.03%	4.58%	< 0.0001	0.5260
Herpes zoster multidermatomal or relapse	11.34%	6.82%	< 0.0001	0.3242
Pneumocystis pneumonia	8.96%	3.41%	< 0.0001	0.1817
HIV-related encephalopathy	3.23%	0.97%	0.0001	0.1004
Kaposi sarcoma	4.61%	2.04%	0.0002	0.6152
Cerebral toxoplasmosis	2.83%	0.88%	0.0004	0.5374
Recurrent bacterial pneumonia	2.81%	1.07%	0.0014	0.6085

726 GEOGRAPHIC AND INDIVIDUAL RISK FACTORS FOR TB OR DEATH IN THE BRIEF-TB TRIAL (A5279)

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Background: The BRIEF TB trial (A5279, NCT01404312) demonstrated non-inferiority of one-month of isoniazid and rifapentine (1HP) versus nine months of isoniazid (9H) for TB prevention. We explored differences in rates of the primary outcome by demographic, clinical, and geographic factors in a pre-planned secondary analysis.

Methods: BRIEF TB enrolled 3000 adults and adolescents with HIV infection in 10 countries who were followed for at least 3 years. The primary endpoints were TB or death from TB or an unknown cause. We analyzed risk of reaching an endpoint by baseline factors, including sex, race, tuberculin skin test (TST)/ interferon-gamma release assay (IGRA) status, CD4 count, country of residence, and time-dependent receipt of antiretroviral therapy (ART). We performed a multivariate Cox proportional hazards analyses of factors associated with experiencing a primary endpoint and tested two-way interactions between each factor and treatment.

Results: Rates of TB or death from TB or an unknown cause varied by country, with incidence rates per 100 person years of 0 (Brazil and US), 0.48 in South Africa, 0.50 in Botswana, 0.54 in Kenya, 0.57 in Peru, 0.58 in Thailand, 0.89 in Zimbabwe, 1.33 in Malawi and 1.4 in Haiti. Half of participants were on ART at baseline, 75% 1 year post-entry, 83% 2 years post-entry, and 93% by end of study. Primary endpoint rates were higher in individuals with lower CD4 counts, who were not on ART, and who had a positive TST or IGRA at baseline. In the Cox proportional hazards analysis (Table), reaching an endpoint was significantly associated with baseline CD4 count, TST/IGRA positivity, and BMI, but not with time-dependent ART status, age, sex, or treatment assignment. There remained unexplained heterogeneity between countries when added to the model (not shown), but estimates of other covariates were similar in both models.

Conclusion: TB risk was greater for those with lower CD4 counts, lower BMI, and a positive TST/IGRA test at baseline. There was considerable heterogeneity by country of residence, indicating that local TB transmission patterns likely affect TB risk. 1HP represents an exciting new strategy for preventing TB in people living with HIV.

Table. Multivariate Cox proportional hazards analysis of factors associated with experiencing an endpoint of TB or death due to an unknown cause.

Covariate	Hazard Ratio	Lower 95% Wald Confidence Limit	Upper 95% Wald Confidence Limit
Time-Dependent ART: Started ART vs. Not Started ART	0.562	0.288	1.096
Treatment: 9H vs. 1HP	1.119	0.680	1.844
Age: Per 1 Year Increase	1.009	0.986	1.034
Sex: Female vs. Male	1.580	0.946	2.641
CD4 count: Per 10 Cell Increase	0.978	0.965	0.991
BMI: Per 1 Unit Decrease	1.070	1.009	1.135
IGRA/TST: Positive vs. Not Positive at Entry	1.949	1.312	3.356

727 ADJUSTED ANALYSIS OF EFFECT OF IPT ON ADVERSE PREGNANCY OUTCOMES IN WOMEN WITH HIV

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Background: IMPAACT P1078 is a randomized non-inferiority study designed to compare safety of starting isoniazid preventive therapy (IPT) in pregnant women with HIV during pregnancy or after delivery. Previous unadjusted analyses showed that IPT during pregnancy increased the odds of the composite outcome of fetal demise, pre-term delivery (PTD), low birth weight (LBW) or congenital anomaly, but not individual outcomes. In this analysis we compared adverse pregnancy outcomes between study arms adjusting for important covariates.

Methods: HIV-infected pregnant women from 8 countries with TB incidence >60/100,000, were randomly assigned, with their infants, to initiate 28 weeks of IPT either during pregnancy (immediate) or at 12 weeks after delivery (deferred). Inclusion criteria were gestational age ≥14-34 weeks; weight ≥35 kg; no grade ≥2 liver enzyme elevations, acute hepatitis or Grade ≥1 peripheral neuropathy; no findings suggestive of TB; and no recent exposure to active TB cases. The composite and individual adverse pregnancy outcomes of interest and covariates are described in Table.1. Logistic regression of these outcomes were performed, stratified by gestational age (14-<24 vs 24-34 weeks).

Results: This secondary analysis included 925 mother-infant pairs with pregnancy outcome data. All mothers were receiving antiretrovirals and 581(63%) had study entry HIV RNA<LLQ. The adjusted odds of fetal demise, PTD, LBW or congenital anomaly (composite outcome 1) were 1.68 times higher among women on immediate IPT compared to deferred IPT (95% CI=1.19, 2.38; P=0.003). The odds of fetal demise, PTD, LBW or neonatal death (composite outcome 2) were 1.59 times higher among women on immediate IPT compared to deferred IPT (95% CI=1.12, 2.26; P=0.009). The odds of early neonatal death, fetal demise, PTD, or LBW (composite outcome 3) were 1.70 times higher among women initiated on immediate IPT compared to deferred IPT (95% CI=1.20, 2.42; P=0.003). The odds of LBW were 1.68 times higher among women on immediate IPT compared to deferred IPT (95% CI=1.10, 2.59; P=0.018). There was no evidence that immediate IPT had an effect on PTD, perinatal or neonatal mortality alone.

Conclusion: Adjusted analysis on the first composite outcome is consistent with previously reported unadjusted analysis, and shows that IPT effect on LBW outcome is significant. The results contextualize the risk/benefit ratio for IPT in pregnant women with HIV on ARVs living in high TB burden settings.

Table 1: Summary of adverse pregnancy outcomes by treatment group

Outcome	Immediate INH	Deferred INH				
	n / Total n (%)	*n / Total n (%)*	*Unadjusted OR (95% CI)*	*Unadjusted P*	*Adjusted OR (95% CI)*[1]	*Adjusted P*
Composite 1: Fetal demise[2], preterm delivery, low birth weight, or congenital anomaly	106/449 (23.6)	78/460 (17.0)	1.51 (1.09, 2.10)[3]	0.013	1.68 (1.19, 2.38)	0.003
Composite 2: Fetal demise, preterm delivery, low birth weight, or neonatal death (<28 days)	105/450 (23.3)	78/459 (17.0)	1.48 (1.07, 2.06)	0.018	1.59 (1.12, 2.26)	0.009
Composite 3: Fetal demise, preterm delivery, low birth weight, or early neonatal death (<7 days)	105/450 (23.3)	73/459 (15.9)	1.61 (1.15, 2.24)	0.005	1.70 (1.20, 2.42)	0.003
Perinatal death 1: Fetal demise or neonatal death (<28 days)	23/459 (5.0)	20/459 (4.4)	1.18 (0.64, 2.17)	0.60	1.18 (0.63, 2.22)	0.60
Perinatal death 2: Fetal demise or early neonatal death (<7 days)	21/459 (4.6)	13/459 (2.8)	1.67 (0.83, 3.38)	0.15	1.73 (0.84, 3.57)	0.14
Low birth weight (<2500 grams at birth)	62/430 (14.4)	46/446 (10.3)	1.46 (0.97, 2.20)[3]	0.07	1.68 (1.10, 2.59)	0.018
Preterm delivery (<37 weeks gestational age at delivery)	48/442 (10.9)	40/458 (8.7)	1.27 (0.82, 1.98)[3]	0.28	1.40 (0.89, 2.21)	0.15

[1]OR=Odds ratio; CI=Confidence Interval; Adjusted for covariates with p < 0.25 in univariate analysis. The following covariates were considered: study arm, maternal age at delivery, ARV regimen, CD4 count, HIV RNA < Lower Limit of Quantitation (LLQ), HBsAG positive, Hepatitis C serology, IGRA status at study entry, Mid upper arm circumference (MUAC), twins, current smoker, food insecurity, non-infectious pregnancy complication, infectious pregnancy complication, and maternal hospitalization.

[2]Includesspontaneous abortion

[3]Previously reported

728 HIGH LEVELS OF ALCOHOL USE ASSOCIATED WITH LATENT TB INFECTION IN HIV-POSITIVE ADULTS

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Background: HIV infection and heavy alcohol use are risk factors for tuberculosis (TB) disease, but it is unknown if TB infection varies by level of alcohol use among people living with HIV (PLWH). We examined associations between level of alcohol use and tuberculin skin test (TST) positivity among PLWH with heavy alcohol use, to inform TB prevention.

Methods: We evaluated adults screened (2018-19) for enrollment in an ongoing randomized controlled trial of economic incentives to reduce heavy alcohol use and improve isoniazid preventive therapy (IPT) completion in HIV/TB+ drinkers in rural Uganda. Adults had TSTs placed if they were HIV+ on ART ≥6 months, reported no history of TB or IPT, endorsed hazardous drinking and had a positive urine ethyl glucuronide test (alcohol biomarker). Alcohol use was measured by the Alcohol Use Disorders Identification Test-C (AUDIT-C). Hazardous use was a score ≥3 if female and ≥4 if male and was stratified into medium (AUDIT-C 4-5 men/3-5 women), high (6-7) and very high (8-12) levels. Positive TST was defined as induration ≥5mm 48-72 hours after placement; TST results outside the testing window were excluded. We conducted logistic regression with robust standard errors to evaluate associations between drinking levels and TST-positivity, adjusting for age, sex, and study site.

Results: Among 729 HIV+ hazardous drinkers who underwent TST placement, 617 (85%) returned for TST reading on time. Among those with TST results, 217 (35%) were TST-positive, 452 (73%) were male, median age was 40 years (IQR 32-48) and median AUDIT-C score was 6 (IQR 5-8). Drinking levels were: 42% medium, 31% high and 28% very high. TST-positivity by drinking level was: medium 31%, high 33%, very high 45%. In the multivariate model, very-high level use was significantly associated with TST- positivity compared to medium level drinking (aOR 1.61, 95%CI: 1.03-2.50, p=0.04). High level drinking had a non-significant association with TST-positivity compared to medium level use (aOR 1.05, 95%CI: 0.69-1.59, p=0.83).

Conclusion: Very high-level alcohol use was associated with increased TST-positivity among a cohort of PLWH. Potential mechanisms of increased TB infection are unclear but may include more time spent in high transmission environments (e.g. bars) or high-risk social networks. Our findings suggest higher prevalence of latent TB may be a contributor to drinkers' higher risk of TB disease. These results underscore the importance of advancing TB prevention efforts for HIV+ drinkers.

729 PRAGMATIC DOSING RECOMMENDATIONS OF RIFAPENTINE-CONTAINING REGIMENS FOR LATENT TB

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Background: Two short-course regimens containing rifapentine (P) and isoniazid (H) have demonstrated efficacy in preventing tuberculosis (TB) disease: 1 month of daily H and P (1HP) and 3 months of weekly H and P (3HP). Weight-based dosing of both drugs is recommended in adults and children; however, dosing algorithms (weight band or mg/kg) are not aligned for the two drugs nor with available formulations (P=150 mg; H=100 mg), over-complicating implementation. Further, pharmacokinetic (PK) rationale for dosing P by weight is lacking in adults. Here, we provide PK evidence supporting flat (non-weight based) P dosing in adults and simplified weight band dosing in children, easily implementable with current formulations.

Methods: A population PK model of P was established based on PK data from 9 clinical studies (n=863 adults). The impact of weight, HIV, age and other factors on PK were examined using nonlinear mixed effect approaches. For H in adults and P and H in children, previously published models were used. Dosing simulations were performed with current and proposed regimens for 1HP (adults only) and 3HP using established PK models. PK metrics (eg, time above MIC, AUC) were compared by regimen and relevant patient factors (eg, HIV status, weight).

Results: Weight-based dosing of P in adults is not justified by population PK and results in lower P exposures in low weight individuals who receive smaller doses. Flat P dosing (600 mg in 1HP or 900 mg in 3HP) would ensure equal exposure across adults of all sizes. However, stratification by HIV status may be warranted. HIV+ patients require at least 30% higher P doses to account for reduced bioavailability (ie, 1200 mg P weekly in HIV+ produces similar exposures as 900 mg P weekly in HIV-). In children, aligning H and P weight bands delivered equal exposures to the current guidelines and utilized available formulations (Table 1). Future coformulation of 300/300 HP in a child-friendly tablet could further simplify therapy. For H, dosing stratification by NAT2 genotype is justified, when possible, as it is the main driver of drug exposure discrepancies, not weight.

Conclusion: 3HP dosing recommendations can be simplified to improve implementation without compromising clinical efficacy. Further, flat dosing of P in adults should be recommended to avoid underexposure in low weight people and HIV+ adults need 30% higher P doses to match exposures in HIV- adults.

Table 1. Proposed dosing chart for 3HP.

	Rifapentine (P)		Isoniazid (H)	
	Number of tablets[1]	Dose	Number of tablets[2]	Dose
Children aged 2-14 years:				
10-15 kg	2	300 mg	3	300 mg
16-23 kg	3	450 mg	5	500 mg
24-30 kg	4	600 mg	6	600 mg
≥ 31 kg	5	750 mg	7	700 mg
Adults and children 15 years and older:				
<50 kg	6	900 mg	2	600 mg
≥ 50 kg	6	900 mg	3	900 mg

3HP = 3 months of weekly rifapentine and isoniazid. [1]150 mg tablet. [2]100 mg tablet (child) and 300 mg tablet (adult).

730 INCREASED HLA-DR EXPRESSION IN MONOCYTES OF PERSONS WITH HIV AND LATENT TB INFECTION

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Background: Persistent monocyte activation contributes to the increased risk of end-organ complications in persons with HIV (PWH). Whether Mycobacterium tuberculosis (Mtb) coinfection has an effect on monocyte activation in PWH is unknown. We hypothesized that there would be greater monocyte activation phenotypes in PWH with Mtb coinfection.

Methods: Cross-sectional study within a cohort of HIV-infected and -uninfected participants enrolled at the Joint Clinical Research Centre in Kampala, Uganda. Participants were ≥45 years with at least one traditional cardiovascular disease risk factor. PWH had to be on stable antiretroviral therapy with HIV viral load ≤1,000 copies/mL within the 6 months prior to study entry. Participants completed a TB questionnaire and had a QuantiFERON TB (QFT) test. Latent TB infection (LTBI) was defined by a positive QFT and no TB symptoms. Prior active TB was defined by self-report and/or medical records review. Persons without evidence of Mtb infection had a negative QFT, no TB symptoms, and denied prior TB. Fresh blood samples were stained with monocyte subset markers (CD14, CD16), CD62p, CD69, CX3CR1, HLA-DR, and tissue factor, and examined with flow cytometry.

Results: We included 125 participants (83 PWH and 42 without HIV) with flow cytometry data and defined TB status in this analysis. Median CD4 count was 556 cells/uL in PWH. PWH had a higher frequency of total monocytes (4.3% vs 3.2%; p<0.001) and inflammatory monocyte subset (15.5% vs 11.7%; p=0.016) compared to those without HIV. Among PWH, prior TB was associated

with increased frequency of total monocytes compared to LTBI (5.1% vs 3.7%; p=0.013), but not when compared to PWH without Mtb infection. HLA-DR density on all monocyte subsets was higher in PWH with LTBI or prior TB compared to PWH without Mtb infection (Table). In multivariable regression, a higher frequency of inflammatory monocytes remained associated with HIV infection after adjusting for TB status, age, sex, cholesterol, and diabetes mellitus (log-%, b=0.37; p=0.019). Among PWH, a higher density of HLA-DR on monocytes remained associated with LTBI or prior TB in adjusted modeling (log-MFI; b=1.17; p<0.001).

Conclusion: Inflammatory monocytes are expanded in HIV infection. LTBI and prior active TB were associated with increased HLA-DR expression on all monocyte subsets in PWH, which indicates increased immune activation in the setting of Mtb and HIV coinfection.

Table. Density of HLA-DR on circulating monocytes among PWH by TB status (n=83) [a]

HLA-DR MFI [b]	No *Mtb* infection (n=40)	LTBI (n=18)	Prior active TB (n=25)	*p* value [c]
Total Monocytes	0.45 (0.1 – 1.2)	1.38 (0.9 – 3.3) [d]	1.48 (0.38 – 2.9) [d]	0.002
Classical subset	0.55 (0.1 – 1.2)	1.77 (0.9 – 4) [d]	1.73 (0.7 – 2.5) [d]	0.002
Inflammatory subset	1.57 (0.1 – 3.6)	3.77 (2.1 – 6.6) [d]	3.9 (1.4 – 7) [d]	0.005
Patrolling subset	0.83 (0.1 – 2.7)	2.6 (1.5 – 9) [d]	3.2 (1 – 8) [d]	0.009

[a] Data presented as median and interquartile range in parenthesis.
[b] MFI=Median fluorescence intensity.
[c] *p* value of Kruskal Wallis test.
[d] Indicates that there was a significant difference ($p<0.05$) on HLA-DR MFI between this group and the no *Mtb* infection group using the Mann-Whitney-Wilcoxon test.

731 INTRAVENOUS BCG VACCINATION IN SIV+ MACAQUES CONFERS HIGH-LEVEL PROTECTION AGAINST TB

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Background: The only licensed vaccine to prevent tuberculosis (TB) is BCG, a live attenuated M. bovis strain, given intradermally (ID) to infants at birth. While BCG ID confers protection against disseminated TB infection, it has more limited protection against pulmonary TB in adolescents and adults. Vaccination with BCG has been limited in HIV+ persons due to safety concerns related to BCG dissemination, even though TB is the major cause of morbidity and mortality in this population. BCG vaccine safety and efficacy can be assessed in macaques in the setting of SIV and M. tuberculosis (Mtb) infection. Recently, intravenous (IV) BCG was shown to prevent Mtb infection and disease in rhesus macaques and was associated with a sustained increase in lung T cells. Here, we used our established model of SIV/Mtb coinfection of Mauritian cynomolgus macaques (MCM) to determine whether IV BCG would be safe and effective at protecting chronic SIV+ macaques from TB.

Methods: We infected MCM intrarectally with SIVmac239. Five months later, they were vaccinated IV with 8x107 CFU BCG. Beginning 4 weeks later, vaccinated animals were treated with an 8-week regimen of isoniazid/rifampin/ethambutol (HRE) to prevent potential disseminated BCG as well as to determine whether this BCG exposure period was sufficient to confer protection. Four weeks after stopping HRE treatment and 12 weeks after BCG IV, animals were challenged with low-dose (~10 CFU) Mtb Erdman via bronchoscope. Control animals consisted of SIV+ unvaccinated and SIV- vaccinated MCM that were all challenged with Mtb.

Results: Administration of BCG IV in SIV+ MCM resulted in a notable spike in plasma SIV followed by natural reestablishment of viral control. Even prior to HRE treatment, SIV+ MCM exhibited no signs of disseminated BCG. Flow cytometry of BAL revealed a rapid and sustained increase in mycobacteria-specific, cytokine-producing T cells in airways following BCG vaccination in both SIV+ and SIV- animals. Following TB challenge, 18F-FDG PET/CT imaging showed rapid TB progression in unvaccinated, SIV+ animals but complete absence of inflammation in 6 of 7 BCG IV-vaccinated SIV+ MCM. Remarkably, necropsy at 12 weeks after Mtb challenge showed the protected animals to be free of TB and without culturable bacilli in their tissues.

Conclusion: These data show that IV BCG is safe, immunogenic, and extraordinarily protective in SIV+ macaques.

732 EARLY BACTERICIDAL ACTIVITY OF MEROPENEM (+ AMOX/CLAV) WITH & WITHOUT RIFAMPIN FOR TB

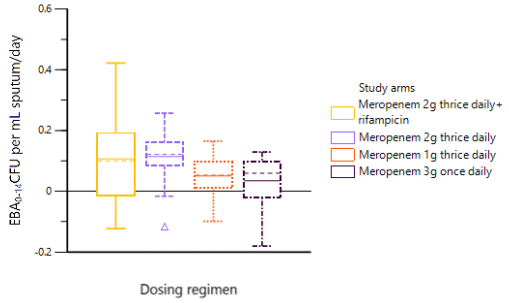
Veronique De Jager[1], Ahmed A. Abufathi[2], Hannelise Feyt[1], Nikhil Gupte[3], Naadira Vanker[1], Grace Barnes[4], Elana Van Brakel[1], Eric Nuermberger[4], Susan E. Dorman[5], Elin M. Svensson[6], Andreas H. Diacon[1], Kelly E. Dooley[4], for the COMRADE Study Team
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Background: A dose finding study was conducted to measure the early bactericidal activity (EBA) of meropenem and amoxicillin/clavulanate, with or without rifampicin, in patients with pulmonary tuberculosis.

Methods: In this Phase 2A RCT, patients with sputum smear-positive pulmonary TB were randomized to receive 14 days of: Meropenem 2g TID plus Rifampicin 20 mg/kg (Arm C); Meropenem 2g TID (Arm D); Meropenem 1g TID (Arm E) or Meropenem 3g QD (Arm F). All received Amoxicillin/Clavulanate. Overnight sputum was collected on days 0, 1, 2, 3, 4, 6, 8, 10, 12, 14. The mean daily fall in $\log_{10}$colony forming units (CFU) of M. tuberculosis per mL of sputum over 14 days of treatment (EBA0-14CFU) was calculated. Intensive PK sampling over 8h was performed on Day 13. PK data were analyzed in R and WinNonlin. EBA0-14 CFU were calculated as [baseline $\log_{10}$CFU/mL – $\log_{10}$CFU/mL at day 14]/14.

Results: Sixty patients were recruited in Cape Town, South Africa. Mean (range) age was 36.8 years (19.9-62.7), 75% were male, and 23.3% were HIV-positive. Mean AUC0-24 for regimens C, D, E, and F, were 573, 555, 289, and 315 h*mg/L, respectively; C_{max} were 133, 134, 68.1, and 179 mg/L, respectively. Over 14 days, mean (95% CI) EBA0-14CFU were 0.11 (0.03-0.18), 0.11 (0.06-0.17), 0.05 (0.01, 0.09), and 0.03 (-0.01, 0.08), in Arms C, D, E, and F, respectively (Figure). Over the first 2 days of treatment, mean EBA0-2CFU were 0.39; 0.11; 0.14; and 0.02, in regimens C, D, E, and F, respectively.

Conclusion: Meropenem exhibits linear dose-dependent PK, and rifampicin does not impact its exposures. Addition of Rifampicin to Meropenem and Amoxicillin/Clavulanate increased early EBA (EBA0-2) but did not significantly increase 14-day EBA. 14-day EBA was significantly higher with Meropenem doses of 2g thrice-daily (total daily dose of 6g) than with total daily doses of 3g. With total daily doses of 3g, given once-daily or in divided doses, 14-day EBA was negligible, and similar. The activity of Meropenem against drug-resistant strains remains to be explored.



733 EFFECT OF RIFAMYCINS ON PRETOMANID EXPOSURE IN PATIENTS WITH PULMONARY TB

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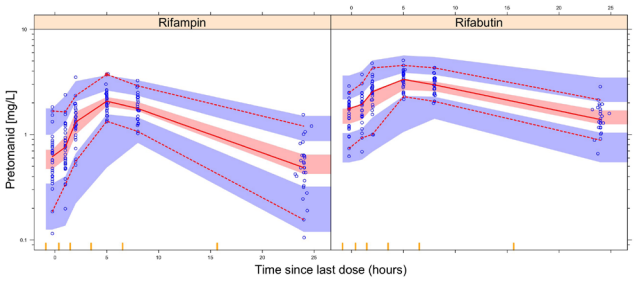
Background: Pretomanid is a novel anti-TB nitroimidazole that was granted FDA approval for treatment of XDR TB this year. It may be a useful drug for treatment shortening for drug-sensitive TB, if delivered with other potent sterilizing drugs. Pretomanid is 20% metabolized by CYP3A4 isoenzyme. In healthy volunteers, rifampicin reduced pretomanid AUC by 66% (from 13.7 vs. 42.5 mg•h/L) but there are no data in patients to guide pretomanid and rifamycin co-administration.

Methods: APT (Assessing Pretomanid for Tuberculosis) is a phase IIB RCT assessing the safety and efficacy of pretomanid added to first-line drugs over 12 weeks among patients with TB. Arm 1 received pretomanid 200 mg (Pa) plus isoniazid (H), rifampin (R), pyrazinamide (Z) for 8 weeks, followed by PaHR (weeks 9-12); Arm 2 received PaHRbZ for 8 weeks, followed by PaHRb (weeks 9-12); Arm 3 received standard therapy. This interim PK analysis includes 57

patients from Arms 1 and 2. PK samples were collected prior to and 1, 2, 5, 8, and 24 hr post-dose on day 14 and a standard meal was provided.

Results: A one-compartment model with first-order elimination and transit compartment absorption fitted the data well. Allometric scaling using body weight was applied to clearance (CL) and volume of distribution. Patients taking rifampin had 44 % reduction in AUC compared to rifabutin. The individual median estimates of C_{max} were 2.15 and 3.40 mg/L for rifampin and rifabutin, respectively. For the AUC0-24, the values were 29.9 and 58.9 mg•h/L. CL was 20% higher in men than women.

Conclusion: As part of a multidrug regimen, co-administration of pretomanid with rifampin increases the CL substantially compared to rifabutin. However, exposures in the rifampin arm in our study were similar to those seen in patients taking 200mg of pretomanid alone, without food (AUC of 36 mg•h/L). Though pretomanid co-administered with rifabutin is more likely to maintain exposure levels equal to or exceeding regimens that do not contain rifamycins, the reduced exposure with rifampin is less pronounced when given with food and may still permit co-administration.



VPC = visual predictive check
The circles represent the original data, the dashed and solid lines are the 5th, 50th, and 95th percentiles of the original data, while the shaded areas are the corresponding 95% confidence intervals for the same percentiles, as predicted by the model. An appropriate model is expected to have most observed percentiles within the simulated confidence intervals.

734 CLINICAL PHARMACOKINETICS AND TOXICODYNAMICS OF LINEZOLID IN THE NIX-TB TRIAL

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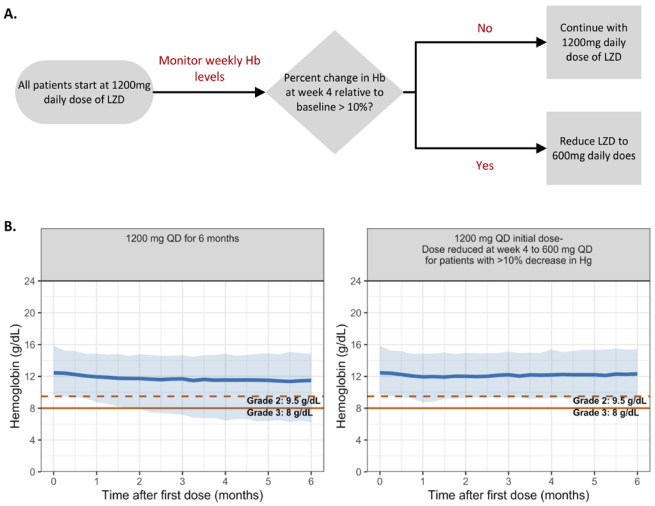
Background: FDA recently approved a high dose linezolid (LZD) containing regimen in combination with pretomanid and bedaquiline (BPaL) for treatment of extremely drug resistant-tuberculosis (XDR-TB). WHO also prioritized LZD for the treatment of DR-TB. Use of LZD is associated with significant toxicities, but limited data is available on optimal dosing and best clinical practices for LZD. We performed population pharmacokinetic (PK)-toxicodynamic modeling and simulation to quantify PK/toxicity relationships of LZD as part of a 6-month BPaL regimen from the NiX-TB study.

Methods: Data was available for 88 patients; all initially administered 1200 mg LZD daily (BID or QD schedules). Dose adjustments of LZD were allowed per discretion of the investigator to manage LZD toxicity. LZD PK profiles that accounted for individual dosing histories were predicted from the PK model and linked to safety profiles. Delayed PK/toxicity response models described suppression of platelets (PLT) and hemoglobin (Hb). A proportional odds model described graded peripheral neuropathy (PN) rates over time. Final models were used to simulate and compare PK and safety outcomes following daily doses of 1200 mg LZD as well as alternative dosing regimens.

Results: LZD PK was described by a two-compartment model with nonlinear clearance. At 1200 mg QD and 600 mg BID nonlinearity was mild with steady-state average concentrations of 11 and 9.8mg/L. Hb and PLT suppression and PN were each significantly ($p<0.001$) related to LZD PK. Hb production was largely suppressed for LZD concentrations above 7.7mg/L, consistent with anemia reported for ~40% of subjects. Simulations indicated that the median time to onset of severe anemia was 9 weeks and Hb values at baseline and week4 might predict severe anemia (ROC AUC=0.91) better than LZD PK troughs (0.56). A greater than 10% decrease in Hb levels at week 4 had maximum sensitivity and specificity to predict severe anemia and a dose reduction to 600 mg QD for these patients prevented 65% of severe anemia cases. For PN, simulations showed reversal by 3 months for most patients following dose reductions or termination, with the more aggressive adjustments better minimizing longer durations. The significant PK/PLT effect was small, consistent with thrombocytopenia reported in only 6% of subjects.

Conclusion: QD and BID dosing had comparable toxicity. PN is reversible and week 4 Hb levels can be used to guide early dose adjustments to prevent anemia.

Management strategy to predict and prevent severe anemia cases.
A. Decision tree algorithm for the proposed management strategy to predict severe anemia cases, defined as Division of Microbiology and Infectious Disease Grade 3 or greater anemia toxicity (Hb levels < 8 g/dL). B. Simulated hemoglobin profiles following 1200 mg QD dose of linezolid for full 6-months of treatment (left panel) and following implementation of anemia toxicity management strategies for initial 1200 mg QD dose (right panel). Solid blue lines represent the typical patient (median of 500 simulations) and the shaded areas the 90% prediction interval. Red dashed line represents Grade 2 toxicity threshold (hemoglobin levels < 9.5 mg/L) and red solid line represents Grade 3 toxicity threshold (hemoglobin levels < 8 mg/L).



735 HIV VIROLOGICAL OUTCOMES DURING TENOFOVIR ALAFENAMIDE AND RIFABUTIN COADMINISTRATION

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Background: Tenofovir alafenamide (TAF) absorption may be decreased during rifabutin (RFB) therapy due to induction of P-glycoprotein. Current USA HIV guidelines therefore recommend against coadministration of TAF and RFB. Based on expert opinion, some centres have administered TAF containing HIV regimens with RFB; however, clinical outcomes have not been assessed.

Methods: Retrospective observational study of all individuals at UC San Diego who received a TAF containing HIV regimen coadministered with RFB for ≥1 month between April 2016 and July 2019. The primary outcome was defined as documented HIV VL ≤200 copies/ml after initiating TAF/RFB therapy or maintenance of viral suppression (≤200 copies/ml) for participants already established on antiretroviral therapy (ART) prior to TAF/RFB coadministration. Cases with suspected virological failure were further evaluated for potential alternate causes other than TAF/RFB interaction.

Results: 23 patients were included in the analysis. Demographics and HIV related variables are shown in table 1. The majority of patients (78.3%) received RFB 300mg daily and all patients received TAF 25mg daily. Thirteen patients (56.5%) were being treated for mycobacterium tuberculosis, 5 (21.7%) for mycobacterium avium complex, and 5 for other mycobacterium infections. The median duration of TAF and RFB overlap was 33 weeks (IQR 12-44 weeks). Of the 6 patients with baseline viral load ≤200 copies/mL, 4 maintained viral load ≤200 copies/mL through the duration of TAF and RFB overlap. One patient stopped ART during treatment and the other was also receiving chemotherapy for cancer. Of the 17 patients with viral load >200 copies/mL at baseline, 14 (82.4%) achieved viral load ≤200 copies/mL. Of the patients with end of treatment data, 77.8% had a viral load ≤200 copies/mL at the end of TAF and RFB overlap. Mean change in CD4 count from baseline to end of treatment was +105 cells/uL (95% CI -16 -227).

Conclusion: Despite a predicted decrease in TAF absorption when coadministered with RFB, the majority of individuals achieved or maintained HIV suppression during TAF/RFB therapy. This data supports further study of TAF and RFB coadministration in HIV and mycobacterial infection.

Table 1:

Median Age (IQR)	36 (30-49)
Female, n (%)	6 (26.1)
Race, n (%)	
White	8 (34.8)
Black	1 (4.3)
Asian	1 (4.3)
Other/Unknown	13 (56.5)
Ethnicity, n (%)	
Hispanic	13 (56.5)
Non-hispanic	10 (43.5)
Median baseline CD4 count, cells/uL (IQR)	36 (36-112)
Viral load <200 copies/mL at baseline (%)	6 (26.1)
Median baseline viral load, copies/mL (IQR)	74461 (71-279220)
On antiretrovirals at baseline, n (%)	10 (43.5)
Documented resistance to at least 1 ARV class, n (%)	9 (39.1)
Additional ARVs	
Integrase inhibitor	19 (82.6)
Protease inhibitor	2 (8.7)
Integrase + Protease inhibitor	2 (8.7)

736 DRUG-RESISTANCE MUTATIONS AND TUBERCULOSIS MORTALITY IN HIGH-BURDEN COUNTRIES

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Background: Strategies to control Mycobacterium tuberculosis (Mtb) drug resistance include universal access to quality-controlled drug resistance (DR) testing coupled with aligned treatment regimens and patient centred treatment support. We examined the impact of drug resistance mutations (DRM) on mortality in HIV+ and HIV- patients with TB in eight high-burden countries.

Methods: We included 247 HIV+ and 335 HIV- adult patients diagnosed with TB in Kenya, South Africa, Democratic Republic of the Congo, Nigeria, Côte d'Ivoire, Peru and Thailand; 60 patients died during treatment. Sampling was stratified by HIV status and on-site DR diagnosis, as determined by locally available tests (Xpert/LPA and/or culture). Whole genome sequences (WGS) were scanned for high-confidence DRM. We compared the DR profiles diagnosed at sites with the DRM from WGS to identify the most common mutations and the DR missed locally. We used logistic regression to examine their association with mortality during TB treatment, adjusted for sex, age and HIV status. We ran a separate model for each DRM with frequency >20 and for combined groups of rare DRM. The reference group consisted of TB patients with pan-susceptible Mtb based on WGS.

Results: The most common mutations in our sample were S315T, S450L, L79S, C-15T, M306V, D435V, M306I and K43R (details in Table 1). While DR to rifampicin (RIF) was missed only in 2% of cases, DR to isoniazid (INH) was missed in 25% of cases and for all other drugs in >70% cases. The DRM individually associated with the largest increase in mortality were S315T with OR 3.7 (95%CI: 2.2-6.5), D453V with OR 3.8 (95%CI: 1.7-8.4) and L79S with OR 4.13 (95%CI: 2-8.5). The OR for groups of rare DRM conferring resistance to RIF, ethambutol (EMB) and all second-line drugs were also statistically significant, ranging from 2.9 to 4.5. Results were similar in HIV+ and HIV- patients.

Conclusion: We identified several DRM associated with increased mortality in TB patients from eight high-burden countries. Many of the conferred DR were missed by local DR tests, potentially leading to an inadequate treatment. Our results highlight the critical need of rapid molecular point-of-care DR tests that cover a broader range of DRM and thus could contribute to more effective treatment and reduced mortality among patients with MDR TB.

Table 1: Description of most common DRM and groups of rare DRM, number (%) of missed DR and odds ratios for death during the TB treatment.

Mutation	Gene	Drug resistance	No. with DRM	No. missed DR* (%)	Mortality OR#	95% CI	P
S450L	rpoB	RIF	84	2 (2%)	0.84	(0.38, 1.86)	0.667
D453V	rpoB	RIF	42	0 (0%)	**3.79**	**(1.70, 8.44)**	**0.001**
any other RIF	rpoB	RIF	74	3 (4%)	**3.83**	**(2.06, 7.10)**	**<0.001**
S315T	katG	INH	152	33 (22%)	**3.74**	**(2.15, 6.50)**	**<0.001**
C-15T	fabG1	INH, ETH	43	13 (30%)	2.02	(0.87, 4.66)	0.100
any other INH	katG, inhA, fabG1	INH	44	15 (34%)	1.57	(0.63, 3.94)	0.336
M306V	embB	EMB	43	31 (72%)	1.33	(0.53, 3.36)	0.543
M306I	embB	EMB	39	31 (80%)	1.71	(0.67, 4.39)	0.261
any other EMB	embB, embA	EMB	40	38 (95%)	**4.43**	**(2.07, 9.47)**	**<0.001**
L79S	gidB	SM	49	48 (98%)	**4.13**	**(2.01, 8.49)**	**<0.001**
K43R	rpsL	SM	35	23 (66%)	1.76	(0.69, 4.50)	0.235
any other SM	gidB, rpsL, rrs	SM	41	33 (81%)	**3.51**	**(1.73, 7.12)**	**0.001**
any other ETH	ethA, inhA, fabG1	ETH	45	45 (100%)	**2.92**	**(1.34, 6.37)**	**0.007**
any FQ	gyrA	FQ	21	15 (71%)	**4.50**	**(1.62, 12.4)**	**0.004**
any injectable	eis, rrs, tlyA	AK,CAP,KAN	16	14 (88%)	**3.93**	**(1.30, 11.9)**	**0.016**
any PZA	pncA	PZA	15	15 (100%)	**4.52**	**(1.47, 13.9)**	**0.008**

* DR missed by local resistance testing but found in *Mtb* whole genome sequences

OR adjusted for age, sex and HIV status

INH, isoniazid; PZA, pyrazinamide; RIF, rifampicin; SM, streptomycin; AK, amikacin; CAP, clarithromycin; KAN, kanamycin; EMB, ethambutol.

737 CSF TB BACILLARY LOAD PREDICTS 2-WEEK MORTALITY IN HIV-ASSOCIATED TB MENINGITIS

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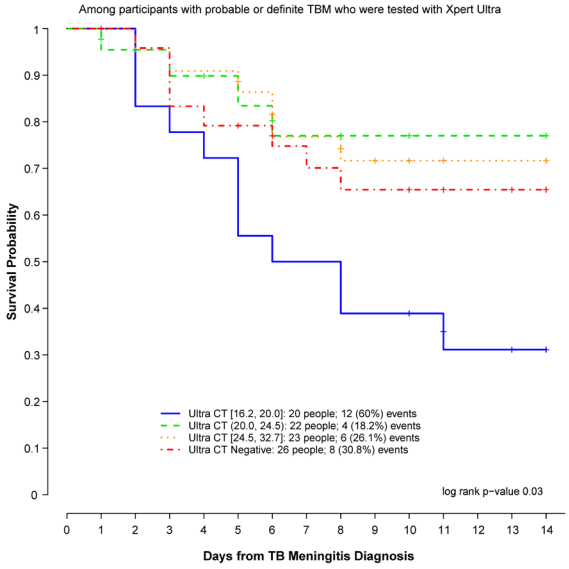
Background: Tuberculous meningitis (TBM) carries a ~40% in-hospital mortality in HIV-positive persons and neurologic sequelae are frequent among survivors. WHO has recommended GeneXpert MTB/RIF Ultra (Ultra), a fully automated PCR assay, as the initial TBM diagnostic test. TB bacillary load can be estimated by PCR Cycle threshold (Ct) values, which represent the number of PCR cycles required for probe signal to reach a detection threshold (low Ct value = high bacillary load). Based on PCR Ct values and configuration of probe positivity, Ultra reports 5 semi-quantitative categories of: trace, very low, low, medium and high. We aimed to explore whether CSF TBbacillary load (by Ct value or semi-quant category) is associated with mortality.

Methods: We prospectively enrolled 107 HIV+ Ugandans with TBM from April 2015 to August 2019. Ultra semi-quant category and Ct tertiles were separately analysed as predictors of 2-week mortality. We investigated associations between Ct and baseline clinical and CSF parameters.

Results: Subjects in the lowest Ct tertile (i.e. highest bacillary load) had 60% 2-week mortality; significantly worse than the intermediate (18%) and highest (26%) Ct tertiles and Ultra-negative (31%) probable TBM cases (Figure, p=0.03). Using the reported Ultra semi-quant category, subjects with medium-low semi-quant category also trended toward worse 2-week survival (50%) compared to very low (27%), trace (27%) and negative (31%) categories but was not statistically significant (p=0.25). Participants with negative Ultra results (probable TBM) had evidence of CSF inflammation and a high mortality (31%), suggesting a bacillary load undetectable by Ultra is not associated with improved survival. TB bacillary load was not associated with focal neurological deficit but a high bacillary load was associated with higher CSF lactate levels (p=0.04).

Conclusion: High CSF TB bacillary load, as measured by Ultra Ct, is associated with over 2-fold higher 2-week mortality in HIV-associated TBM, being a better predictor than the reported Ultra semi-quant category. This is the first study to investigate Ultra Ct values and TBM outcomes and raises the possibility of Ultra Ct values being used to identify patients at greatest risk of death and who may benefit from enhanced supportive care or intensified TBM treatment.

Figure. Two-week Mortality by Xpert MTB/RIF Ultra PCR Cycle Threshold (Ct) level



738 MORTALITY IN ADULT HIV/MDR-TB BY ART USE: INDIVIDUAL PATIENT DATA META-ANALYSIS

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Background: HIV is associated with increased mortality during treatment for multidrug-resistant tuberculosis (MDR-TB), but factors affecting this risk have been difficult to identify because of low MDR-TB incidence in any one setting. We examined how the use of HIV anti-retroviral therapy (ART) and effective antitubercular medications modify mortality among adults with MDR-TB and HIV using a large, multi-country database.
Methods: We conducted a individual patient data meta-analysis (IPD) from studies published between 2009 and 2018 of adults from 40 countries/regions with MDR-TB, systematic drug susceptibility testing for fluoroquinolones (FQ) and second-line injectables (SLI), and known HIV status who were not lost to follow-up. Data included clinical and demographic characteristics, use of ART, and ever-use of antitubercular medications (grouped according to World Health Organization (WHO) categorizations). The primary outcome was death, compared to treatment success, treatment failure, and relapse. Patients without HIV were compared to HIV+ (all), HIV+/on ART, and HIV+/no or unknown ART using logistic regression after exact matching on country-level income, SLI and FQ resistance and after propensity score matching on age, sex, site, year of treatment initiation, previous TB treatment, directly observed therapy, and acid-fast-bacilli-smear positivity to obtain adjusted odds ratios (aORs) and 95% confidence intervals (CI).
Results: Of 10,044 patients, 3,215 (32%) were HIV-infected, 2,504 (25%) were HIV+/on ART, 6,068 (60%) were males, 9,615 (96%) had only pulmonary TB, and 1,611 (16%) had extensively drug-resistant TB. The aOR of death for those with HIV (all) vs HIV-negative patients was 2.4 (2.1-2.8), and varied according to ART use (1.8 [1.5-2.2] for HIV+/on ART vs 4.6 [3.0-7.1] for HIV+/no or unknown ART) (Table). Among persons with HIV, aORs for death were lowest for HIV+/on ART, HIV+ patients receiving at least 5 effective drugs, and HIV+ patients on WHO Group A drugs (later generation FQs, bedaquiline and/or linezolid) (Table).
Conclusion: In a large, diverse population of HIV-infected adults with MDR-TB, HIV-infection is associated with an increased adjusted odds of death during MDR-TB treatment, but use of ART and more effective antitubercular drugs lowers the odds. Access to ART and effective antitubercular drugs should be urgently pursued for those with HIV/MDR-TB.

Table: Stratified analysis of the association between HIV and death among patients with MDR-TB[1]

	Incidence of death among all HIV- (n/N)	Incidence of death among HIV+ (n/N)	Adjusted OR for death HIV+ all vs HIV- (95% CI) [1]	Incidence of death among HIV+ on ART (n/N)	Adjusted OR for death HIV+ on ART vs HIV- (95% CI) [1]	Incidence of death among HIV+ not on ART/Unknown ART (n/N)	Adjusted OR for death HIV+ not on ART/Unknown ART vs HIV- (95% CI) [1]
All patients	889/6829	979/3215	**2.4 (2.1, 2.8)**	673/2504	**1.8 (1.5, 2.2)**	305/710	**4.6 (3.0, 7.1)**
Received any WHO Group A drug							
Yes	571/4961	615/2399	**2.1 (1.7, 2.6)**	529/2209	**1.9 (1.5, 2.3)**	86/190	**6.6 (3.1, 14.1)**
No	318/1868	364/816	**2.3 (1.7, 3.1)**	145/296	1.3 (0.9, 2.0)	219/520	**3.7 (2.5, 5.4)**
Received at least 5 effective drugs							
Yes	195/2118	145/743	**2.1 (1.3, 3.4)**	123/659	**1.7 (1.1, 2.7)**	22/84	**3.4 (1.1, 10.2)**
No	694/4711	834/2472	**2.6 (2.1, 3.2)**	551/1846	**2.0 (1.6, 2.5)**	283/626	**4.7 (3.0, 7.2)**
Received any Group A drug AND Received at least 5 effective drugs							
Yes	160/1757	122/652	**1.9 (1.1,3.1)**	109/613	**1.8 (1.1,2.8)**	13/39	-
No	729/5072	857/2563	**2.7(2.2,3.3)**	565/1892	**2.0 (1.6, 2.4)**	292/671	**4.6 (3.0, 6.8)**

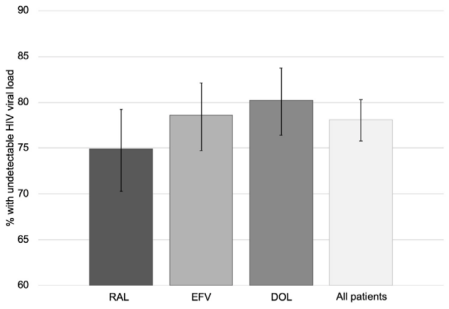
1-Model is propensity score matched for age, sex, site, year, past treatment, DOT, AFB smear. Exactly matched for income, SLI resistance, FQ resistance

739 CD4 COUNT AND VIRAL LOAD DYNAMICS UNDER DIFFERENT ART REGIMENS IN HIV/TB COINFECTION

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Background: Tuberculosis (TB) is still a leading cause of morbidity and mortality among people living with HIV (PLHIV). Although it is widely accepted that the use of antiretroviral treatment (ART) reduces the risk of death among HIV-TB coinfected patients, studies comparing the efficacy of different ART regimens in this population are scarce
Methods: Retrospective cohort using real life data collected by the Brazilian Ministry of Health HIV program. We included all HIV-TB coinfected patients aged ≥18 years-old who had a first ART delivery up to 6 months after TB notification, with regimens containing lamivudine + tenofovir combined with either Efavirenz (EFV), Raltegravir (RAL) or Dolutegravir (DOL) between Jan 2017-Dec 2018. We analyzed the percentage of undetectable (<200 copies/ml) HIV viral load (VL) and mean change in CD4+T cell counts at 90-180 days after ART initiation in each treatment group adjusted for sex, age, social vulnerability index and baseline values of CD4+T cell counts and HIV VL
Results: 1427 HIV-TB coinfected patients were included. Patients were mostly young (84% <50 years old), males (79%), of black/mixed color (48%). Baseline HIV VL was >10,000 for most patients (79%), and CD4+T cell counts were <200/mm_3 for 71% of the sample. Overall, 78.1% of HIV-TB coinfected patients had HIV VL<200/ml at 90-180 days after ART initiation (95% CI 75.8-80.3); CD4+ T cell increment at 90-180 days after first ART prescription was 148 cells/mm_3 (SD 156), with mean increment of 156, 139 and 154 cells/mm_3 among patients receiving RAL, EFV and DOL, respectively.
We found no statistically significant differences in the percentage of undetectable HIV VL or CD4+T cell count increment at 90-180 days after ART initiation according to ART regimen in univariable models or after adjustment for potential confounders
Conclusion: Although studies comparing different ART regimens in PLHIV without TB suggest that VL suppression is achieved more frequently and faster with regimens containing integrase inhibitors when compared to those with EFV, we failed to find similar results among patients with TB. Our findings are relevant in reassuring that RAL and DOL can replace EFV for HIV-TB coinfected patients. This is of greater importance for HIV-TB coinfected patients with EFV resistance mutations or significant intolerance

Figure 1: Percentage and 95% confidence intervals of HIV-TB coinfected patients with undetectable HIV VL in a blood sample collected 90-180 days after the first ART prescription, according to ART regimen



740 SUBOPTIMAL TUBERCULOSIS TREATMENT COMPLETION: A MULTICENTER OBSERVATIONAL STUDY

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Background: Standard anti-tuberculosis (TB) treatment includes two months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by four months of isoniazid and rifampicin. To meet the WHO target for reduction in TB deaths by 2025, programs must strive for 90% TB treatment completion. Treatment discontinuation due to treatment toxicity or other reasons may interrupt the course of treatment and decrease effectiveness.
Methods: This 4-year (2015-2019), multicenter, prospective cohort study in Brazil included culture-confirmed, drug-susceptible, pulmonary TB patients who started standard TB treatment. All participants were followed for > 9 months from enrollment and were categorized into three groups: (I) treatment discontinuation – treatment interruption before 6 months, default, or loss to follow-up prior to treatment completion, (II) treatment completion within 9 months, and (III) treatment completed, but duration >9 months.
Results: Among 797 patients included, 592 (74%) completed their first-line treatment regimen, 161 (20%) had early treatment discontinuation, and 44 (6%) were on first-line treatment longer than 9 months. Compared to patients who

completed treatment, those who discontinued were more likely PLWH (32% vs 14% p<0.01), younger (median age 34 vs 36, p=0.06), and male (80% vs 64%, p<0.01). Overall, the reasons for treatment discontinuation were death (28, 17%), treatment abandonment/loss to follow up (92, 57%), treatment toxicity (9, 6%), resistance detection (7, 4%), or other/unknown reasons (18, 11%). Compared to those without HIV, PLWH were more likely to discontinue due to toxicity (15% vs 1%) and death (33% vs 10%), but less likely to discontinue due to abandonment/loss to follow up (46% vs 62%) and resistance (0% vs 6%). PLWH who discontinued treatment were less likely to be on ART at baseline than PLWH who completed treatment within 9 months (29% vs 50%, p=0.01). CD4 count and viral load were similar among PLWH in all three groups. Patients who received treatment for >9 months, were similar to those who completed treatment within 9 months regarding sex, but were older (median age 43 vs 36, p<0.01) and more likely PLWH (27% vs 14%, p=0.02) – rates of ART at baseline were similar between the treatment completion groups.

Conclusion: This study highlights suboptimal TB treatment completion rates, due primarily to death and loss to follow-up. This reinforces the need for early ART initiation and better-tolerated TB treatment regimens, particularly in PLWH.

Table 1. Group characteristics

		Early treatment discontinuation (<6 months)	Treatment completion (up to 9 months)	Not treatment completion (>9 months)
		N = 161	N = 593	N = 43
Age[1]		35.7 ±14.3	37.9 ±14.1	44.7 ±15.4
Sex	Male	128 (79.5%)	378 (63.7%)	24 (55.8%)
HIV status	Positive	52 (32.2%)	84 (14.2%)	12 (28%)
Treatment Length[2]		88.5 (59-180)	186 (181-201)	310 (294-361)

[1]years, mean ± SD
[2]median in days. IQR

741 N-ACETYLCYSTEINE FOR ANTI-TB DRUG-INDUCED LIVER INJURY: A RANDOMISED CONTROLLED TRIAL

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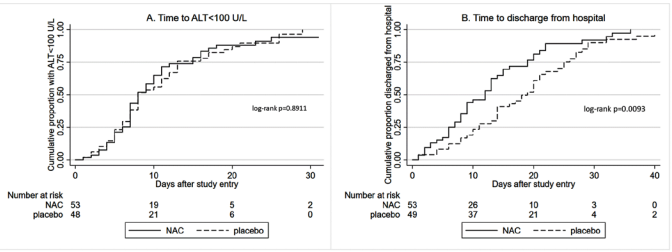
Background: First-line anti-tuberculosis (TB) therapy can cause liver injury. N-Acetylcysteine (NAC) is widely used in patients with paracetamol toxicity and there is limited evidence of benefit in liver injury due to other causes.

Methods: We conducted a randomised, double-blind, placebo-controlled trial to assess whether intravenous NAC improves liver recovery in adult patients admitted to hospital with first-line anti-TB drug induced liver injury (AT-DILI), diagnosed by alanine transaminase (ALT) ≥3 times upper limit of normal (ULN) with hepatitis symptoms or ALT ≥5 times ULN if asymptomatic. NAC was dosed as per paracetamol toxicity guidelines. The primary endpoint was the time for ALT to fall below 100 U/L. Secondary endpoints included duration of hospitalisation, in-hospital mortality and adverse events. We compared time to ALT<100 U/L and time to discharge from hospital using Kaplan-Meier analyses and log-rank tests. We included all participants who commenced NAC/placebo infusion in the analysis.

Results: Fifty- three participants received NAC and 49 placebo. Mean age was 38 years (SD±10), 58 (57%) were female and 89 (87%) were HIV positive, 40 (45%) of whom were on antiretroviral therapy. Median serum ALT and total bilirubin at presentation were 462 U/L (IQR 266-790) and 56 mmol/L (IQR 25-100) respectively. There was no difference in the time to ALT <100 U/L (figure 1A), with a median of 7.5 days (IQR 5.5 -11) and 8 days (IQR 5 -13) in the NAC and placebo arms respectively. Hospital stay was shorter in participants who received NAC (figure 1B), log rank p=0.0093; median hospital stay was 9 days (IQR 6-15) in the NAC arm and 18 days (IQR 10-25) in the placebo arm. Mortality was 14% and did not differ by study arm. The infusion was stopped early due to an adverse reaction in 5 participants, all of whom were receiving NAC (nausea and vomiting in 3, anaphylactoid reaction in 1 drip site pain in 1).

Conclusion: NAC did not shorten time to ALT< 100 U/L in participants with AT-DILI. However, NAC significantly reduced duration of hospital stay. NAC may reduce morbidity and hospitalisation costs in patients hospitalized with AT-DILI. Larger clinical trials are needed to confirm this finding.

Figure 1. Cumulative estimates of time to ALT<100 U/L and time to hospital discharge in participants with AT-DILI randomised to NAC or placebo



742 HIV, TUBERCULOSIS, AND CHRONIC LUNG DISEASE AMONG KENYAN ADULTS

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Background: People living with HIV (PLWH) are at increased risk for non-communicable diseases such as chronic lung disease (CLD) and also remain at risk for pulmonary opportunistic infections including tuberculosis (TB) that may contribute to the development of CLD. We hypothesized that prior active TB would independently increase the risk for CLD and sought to determine whether HIV modifies the relationship between TB and CLD.

Methods: This is a cross-sectional, interim analysis of a cohort of PLWH with well controlled HIV and uninfected adults in Kisumu, Kenya, enrolled from 12/2018 through 10/2019. All participants underwent standardized spirometry and a validated respiratory specific questionnaire. Prior active TB and pneumonia were based on self-report. Multivariable logistic regression was used to evaluate cofactors of CLD as defined by spirometry: obstructive, restrictive, and impaired (a composite of obstructive and/or restrictive patterns). Effect modification was evaluated by an interaction term between HIV and impaired lung function.

Results: We have enrolled 474 participants (79% of target sample size), 246 PLWH and 228 uninfected. PLWH are more likely to report prior active TB (28% vs 4%, p<0.0001) and pneumonia (28% vs 19%, p=0.008). Impaired lung function is more common in PLWH compared to uninfected participants (21% vs 14%, p=0.07). Of those reporting prior TB, a similar proportion of PLWH and uninfected adults had impaired lung function (36% vs 30%, respectively; p>0.05). In multivariable analyses, prior TB was associated with impaired lung function among all participants (aOR 3.1, 95% CI 1.7-5.7, p=0.004) (Table). In separate multivariable analyses, prior TB was also associated with obstructive spirometry (aOR 2.7, 95% CI 1.3-5.8, p=0.009). An interaction between HIV and impaired spirometry was not statistically significant.

Conclusion: In adjusted models, impaired lung function was not significantly associated with HIV but was strongly associated with prior active TB, which was more common in PLWH. Prior TB was also more likely to be associated with an obstructive as opposed to restrictive pattern. TB may potentially account for a greater prevalence of CLD in PLWH, but we did not find evidence for an interaction between HIV and TB in the risk for impaired spirometry in this ongoing cohort. Future work should investigate mechanisms and potential management strategies that could mitigate the risk of impaired lung function in those with prior TB.

Table. Multivariable [a] analyses of cofactors of impaired lung function [b], and of either obstruction or restriction

	Impaired lung Function aOR (95% CI)	p-value	**Obstruction** aOR (95% CI)	p-value	**Restriction** aOR (95% CI)	p-value
HIV	1.03 (0.58-1.8)	0.91	0.77 (0.38-1.5)	0.46	1.9 (0.67-5.5)	0.24
Prior TB	**3.1 (1.7-5.7)**	**0.004**	**2.7 (1.3-5.8)**	**0.009**	2.3 (0.78-6.6)	0.12
Prior pneumonia	1.6 (0.92-2.8)	0.09	1.6 (0.79-3.0)	0.19	1.8 (0.67-4.4)	0.24
Smoking [c]	1.3 (0.47-3.5)	0.55	2.0 (0.64-5.6)	0.21	--	--
Female gender	**1.9 (1.1-3.4)**	**0.03**	1.7 (0.86-3.5)	0.13	2.3 (0.87-6.8))	0.10
Age	1.0 (0.99-1.0)	0.18	1.0 (0.97-1.0)	0.98	**1.1 (1.0-1.1)**	**0.02**
BMI	0.97 (0.92-1.0)	0.38	0.96 (0.90-1.0)	0.36	1.1 (0.97-1.1)	0.17
Kerosene use [d]	1.1 (0.65-2.0)	0.66	1.4 (0.70-2.6)	0.36	0.80 (0.25-2.2)	0.67
Wood use [d]	1.0 (0.57-1.8)	0.98	0.93 (0.47-1.8)	0.84	0.99 (0.35-2.9)	0.99

Abbreviations: CI, confidence interval; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal (predicted per Global Lung initiative 2012; aOR, adjusted odds ratio
[a] Adjusted for HIV status, prior TB, prior pneumonia, smoking (current or former), gender, age, BMI, kerosene use, and wood use
[b] Impaired lung function is a composite of: Obstruction (FEV1/FVC<LLN), Restriction (FEV1/FVC ratio normal, FVC<80% predicted), or both (FEV1/FVC<LLN and FVC<80% predicted)
[c] Current or prior smoking. Smoking was initially included in the restriction model, however there was no association (p-value = 0.99) and 95% CIs were too large to display thus smoking was excluded from this model
[d] Use for heating or cooking at least once a week

743 DIAGNOSTIC PERFORMANCE OF A SEMIQUANTITATIVE POINT-OF-CARE ASSAY FOR CRYPTOCOCCOSIS

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Background: Blood Cryptococcal Antigen (CrAg) titer is associated with risk of cryptococcal meningitis. We describe the diagnostic performance of a novel all-in-one CrAg semi-quantitative (SQ) lateral flow assay (LFA) compared to the FDA-approved Immy CrAg LFA in the rapid diagnosis of cryptococcosis. The CrAg SQ LFA provides a semi quantitative test result in a single test in contrast to traditional semi-quantitative testing which requires serial dilutions and multiple tests.

Methods: From February to September 2019, we compared the diagnostic performance of the CrAg SQ assay (Immy) with the CrAg LFA (Immy) on 100 CSF samples, 61 serum samples collected from HIV+ persons with meningitis and 50 serum samples from HIV+ persons with CD4<100 screened for cryptococcal antigenemia. The CrAg SQ levels (1+ to 4+) were compared with CrAg LFA titers to determine the corresponding cut off CrAg SQ titer. All specimens were prospectively tested.

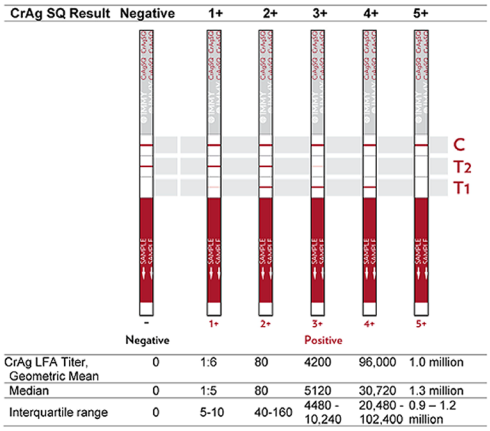
Results: Among meningitis patients, 69 had cryptococcal meningitis (68 CrAg+ by LFA and 1 false negative due to prozone with 1:1310720 CrAg LFA titer), and 31 had no cryptococcal meningitis by CrAg, culture, and India ink. The CrAg SQ on CSF had 100% (69/69) sensitivity and 100% specificity (31/31) when prospectively run on fresh specimens. CSF CrAg titers detected ranged from 1:2 to 1:209715520. In serum, sensitivity was 100% (46/46) and specificity 100% (15/15) among meningitis patients.

Using serum in asymptomatic patients, CrAg SQ had 100% sensitivity (13/13) and 97.4% (37/38) specificity with one CrAg SQ being trace 1+ positive. Among all specimen types, the overall CrAg SQ sensitivity was 100% (128/128) and specificity was 99% (83/84); (P=0.99 by McNemar).

Overall, CrAg SQ levels from 1+ to 5+ corresponded to increasing CrAg LFA titers (Figure). CSF CrAg SQ results of 3+ or higher were always CSF culture positive.

Conclusion: The CrAg SQ LFA appears to be an excellent semi-quantitative CrAg assay maintaining both sensitivity and specificity, with rapid stratification of patient risk. Training laboratory personnel on the usage and interpretation of the CrAg SQ is necessary.

Figure. Example CRAG SQ Test Results



CrAg LFA Titer, Geometric Mean	0	1:6	80	4200	96,000	1.0 million
Median	0	1:5	80	5120	30,720	1.3 million
Interquartile range	0	5-10	40-160	4480 - 10,240	20,480 - 102,400	0.9 – 1.2 million

744 EARLY FUNGICIDAL ACTIVITY AS SURROGATE ENDPOINT FOR CRYPTOCOCCAL MENINGITIS SURVIVAL

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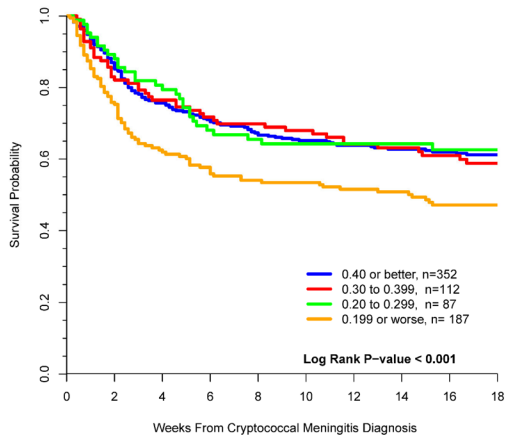
Background: In cryptococcal meningitis phase 2 clinical trials, early fungicidal activity (EFA) of Cryptococcus yeast clearance from cerebrospinal fluid (CSF) is used as a surrogate endpoint. The US FDA allows for surrogate endpoints for accelerated regulatory approval, but there are no accepted surrogate endpoints for this neglected disease. For tuberculosis, the FDA recognizes an official surrogate endpoint as "time to sputum culture conversion to negative." We examined the relationship between the rate of CSF Cryptococcus clearance (i.e. EFA) and mortality through 18 weeks.

Methods: We pooled individual-level CSF data from 3 sequential cryptococcal meningitis clinical trials conducted in Uganda during 2010-2013 (COAT trial, n=162; also in South Africa), 2013-2014 (ASTRO-CM pilot, n=179), and 2015-2019 (ASTRO-CM trial, n=397). All subjects received amphotericin B deoxycholate + fluconazole induction therapy and had serial quantitative CSF cultures performed. The $\log_{10}$ transformed colony forming units (CFUs) per mL CSF were analyzed by general linear regression vs day of CSF culture over the first 10 days. The slope of the fit line is the EFA or the rate of CSF fungal clearance in units of $\log_{10}$CFU/mL/day. We grouped subjects by EFA and compared mortality by Kaplan-Meier.

Results: 738 subjects had non-sterile initial cultures with a calculable EFA (median 0.38; IQR, 0.20-0.57 $\log_{10}$ CFU/mL). Risk of death through 18-weeks was higher with EFA <0.20 (50% mortality) versus EFA >=0.20 $\log_{10}$CFU/ml/day (37% mortality; Hazard Ratio 1.60; 95%CI, 1.25 to 2.04; P=0.002). Mortality through 18-weeks was 37% for EFA ≥0.60 (n=170), 36% for EFA 0.40-0.59 (n=182), 39% for EFA 0.30-0.39 (n=112), and 35% for EFA 0.2-0.29 (n=87). When adjusting for baseline Glasgow coma scale, hemoglobin, CSF quantitative culture, CSF WBC, biological sex, and cohort, EFA remained significant (adjusted Hazard Ratio 1.83, 95%CI, 1.40 to 2.40; P<0.0001).

Conclusion: EFA was associated with all-cause mortality using individual level data from 738 subjects receiving amphotericin-combination induction therapy. An EFA better than 0.20 $\log_{10}$ CFU/mL/day was associated with similar survival, and this threshold may be considered a target for a surrogate endpoint. Yet, 25% of patients receiving amphotericin had EFAs worse than 0.20 $\log_{10}$CFU/mL/day, with 50% mortality. This builds upon prior systematic reviews of smaller pooled studies from different sites to validate EFA as a surrogate endpoint.

Figure 1. Early Fungicidal Activity by 18-week Survival Time.



745 EVALUATING THE IMMY SEMI-QUANTITATIVE CrAg LFA IN HIV-POSITIVE PATIENTS IN BOTSWANA

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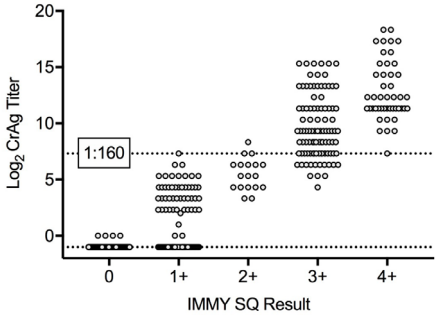
Background: Cryptococcal antigen (CrAg) titers are an important prognostic indicator in HIV-positive patients with cryptococcal infection and could potentially be used to stratify treatment. Current titration methods are expensive and labor intensive. A novel semi-quantitative (SQ) CrAg test has been developed that can provide an indication of CrAg titer using a simple dipstick lateral flow assay (LFA). We performed a study to evaluate the performance of the SQ-CrAg assay against the standard CrAg LFA in patients with HIV-associated cryptococcal infection in Gaborone.

Methods: Residual EDTA blood specimens from sequential HIV-positive patients undergoing routine CD4 testing with CD4 counts of ≤200 cells/ml were screened through the reflex CrAg-screening program in Botswana using both

the IMMY CrAg LFA and the novel SQ-CrAg LFA. The sensitivity and specificity of the SQ-CrAg in the reflex CrAg screening cohort were determined relative to the standard CrAg LFA. To further validate the SQ assay known CrAg+ EDTA blood samples from a prior CrAg-screening study and a CM treatment trial were also tested with both assays. Serial dilutions were performed for all CrAg+ samples and re-tested with the standard LFA to determine titres. SQ titers and conventional titers were compared. All testing was performed by two independent blinded investigators and inter-rater reliability assessed using the Kappa coefficient.

Results: 692 sequential samples were screened using both assays; 43 (6.2%) were IMMY CrAg LFA-positive. Using this standard CrAg LFA as a reference, the overall sensitivity and specificity of the novel SQ-CrAg LFA were 93.0% (95%CI 80.9 – 98.5%) and 93.8% (95%CI 91.7-95.6%) respectively. A further 180 known CrAg+ samples were tested and the combined results used to evaluate the SQ-CrAg quantification. Median (IQR) CrAg titers for SQ-CrAg 1+, 2+, 3+, and 4+ bands were 1:10 (1:5 – 1:20), 1:40 (1:20 – 1:80), 1:640 (1:160 – 1:2560), and 1:5120 (1:2560 – 1:20480) respectively (Figure 1). Inter-rater agreement in titer assessment was excellent at 98.2%, with a kappa coefficient of 0.96, p<0.001.

Conclusion: Overall sensitivity and specificity of the novel IMMY SQ-CrAg assay were high in a cohort of HIV-positive individuals with CD4 counts ≤200 cells/ml undergoing reflex CrAG screening. An SQ titre of 3+ or greater corresponded to a titer of >1:160 which has previously been shown to be associated with increased mortality.



746 HIGH RATES OF MENINGITIS OR MORTALITY AMONG CrAg+ PLHIV WITH CD4 100-200 CELLS/MM^3

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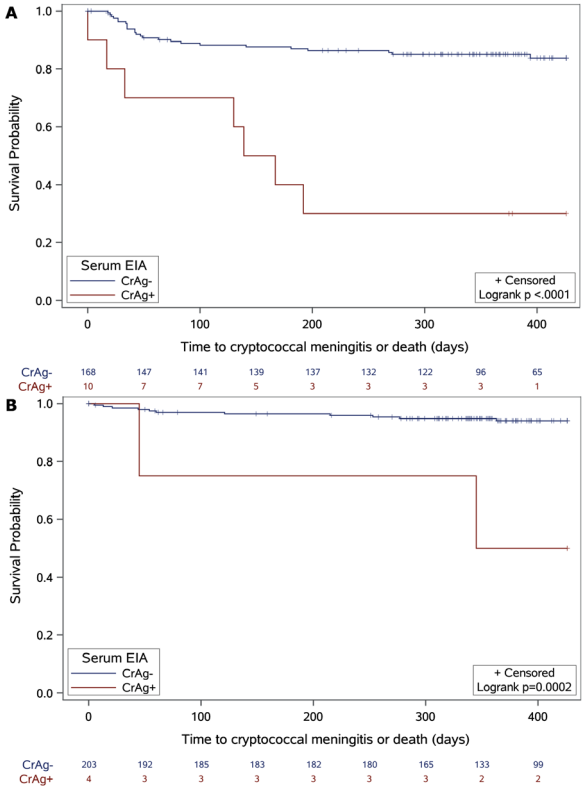
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Background: Cryptococcal antigen (CrAg) screening with fluconazole prophylaxis has been shown to prevent cryptococcal meningitis and mortality for people living with HIV (PLHIV) with CD4 <100 cells/mm$_3$. While cryptococcal meningitis occurs in individuals with CD4 100-200 cells/mm$_3$, there is limited evidence that CrAg screening predicts cryptococcal meningitis or mortality among this group with moderate immunosuppression. Current IDSA and WHO clinical guidelines recommend restricting CrAg screening to PLHIV with CD4 <100 cells/mm$_3$.

Methods: We conducted a prospective cohort study of PLHIV >=18 years who had not initiated ART in South Africa. We followed participants for 14 months to determine onset of cryptococcal meningitis or all-cause mortality. At study completion, we retrospectively tested stored serum samples for CrAg using an enzyme immunoassay (EIA). We calculated CD4-stratified incidence rates of outcomes and used Cox proportional hazards to measure associations between CrAg positivity and outcomes.

Results: We enrolled 2,383 PLHIV, and 1,309 participants and had serum samples tested by CrAg EIA. The median CD4 was 317 cells/mm$_3$ (interquartile range: 173-491 cells/mm$_3$. By CD4 count at baseline, there were 209 individuals with a CD4 count of 100-200 cells/mm$_3$ with available CD4 test results and four (1.9%) tested positive. Among this group, two of four (IR: 58.8 per 100 person-years) CrAg+ participants and 11 of 205 (IR: 5.6 per 100 person-years) CrAg- participants developed cryptococcal meningitis or died for an overall rate of death or cryptococcal meningitis that was 10.0-times higher for those who were CrAg+ (CI: 2.2-45.3) (figure). Among those with CD4 <100 cell/mm$_3$ and CrAG EIA test results (n=179), ten (5.6%) participants tested CrAg+. Among this group, seven of ten (IR: 137.6 per 100 person-years) CrAg+ participants and 26 of 169 (IR: 17.8 per 100 person-years) CrAg- participants developed cryptococcal meningitis or died for a rate of death or cryptococcal meningitis that was 6.3-times higher for those who were CrAg+ (CI: 2.7-14.6).

Conclusion: Although few PLHIV with moderate immunosuppression screened CrAg positive, a positive CrAg test was predictive of increased risk of cryptococcal meningitis or death. Systematic CrAg screening may reduce morbidity and mortality in PLHIV with CD4 100-200 cells/mm$_3$.



747 CSF CYTOKINES AND CHEMOKINES ASSOCIATED WITH MORTALITY IN CRYPTOCOCCAL MENINGITIS

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Background: Cryptococcal meningitis causes substantial mortality globally. Our understanding of the role of the host immune system in patient outcomes is limited. We investigated the cytokine and chemokine environment at the site of infection, the CNS, to better understand the impact of immune cell activation and tissue inflammation on mortality.

Methods: We prospectively enrolled Ugandans presenting with first episode cryptococcal meningitis from March 2015 to May 2017, as part of a larger study focused on drug treatment with amphotericin + fluconazole +/- sertraline to improve neurological outcomes. We analyzed the CSF of 321 subjects at diagnosis for soluble biomarkers of immune cell activation utilizing a luminex assay. Statistical analysis grouped each biomarker into quartiles (Q1, Q2+Q3, Q4) and compared each group for 14-day mortality via logistic regression, adjusted for Glasgow Coma Scale and CSF quantitative culture. We compared Q1 (low) and Q4 (high) to the reference Q2+Q3 group.

Results: Participants with Q1 (low) levels of markers indicative of cytotoxic cell function such as TRAIL (p=0.004),Granzyme-B (p=0.03), and IP-10 (p=0.007) had significantly increased risk of 14-day mortality compared to middle two quartiles (Q2+Q3) reference group levels. Participants with Q1 (low) levels of markers associated with naïve T cell activation and recruitment such as CXCL2 (p=0.003), PDL1 (p=0.013), and CCL19 (p=0.013) had increased risk of 14-day mortality while those with Q4 (high) levels of CCL19 (p=0.009) had decreased mortality , when compared to the Q2+Q3 ref group. Inflammatory mediators such as TNF-alpha, IFN-gamma, IL-6, and IL-1beta were not associated with

14-day mortality in either Q1 or Q4, but participants with Q1 (low) levels of cytokines involved in Th2 cell function IL-13 (p=0.004) and IL-33 (p=0.039) had increased risk of 14-day mortality.
Conclusion: These findings demonstrate a crucial role for cytotoxic cell populations and naive T-cell stimulation in human cryptococcal outcomes. Further research efforts should include characterizing the role and activating stimuli of cytotoxic cells in the clearance of Cryptococcus as well as T-cell function in activation of the adaptive immune response in humans with cryptococcosis.

748 TUBERCULOSIS IN HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS AND ITS IMPACT ON MORTALITY

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Background: Tuberculosis (TB) and cryptococcal meningitis are leading causes of morbidity and mortality in advanced HIV. Data on TB co-infection amongst people with cryptococcosis is scarce. We described the occurrence of TB in Ugandan adults with cryptococcal meningitis and determined the impact of co-infection on survival.
Methods: We performed a retrospective analysis of patients diagnosed with cryptococcal meningitis during 2010-2017. Baseline TB status was classified as: 1) 'prevalent TB' if TB diagnosed >14 days prior to cryptococcal diagnosis, 2) 'concurrent TB' if diagnosed with TB +/-14 days from cryptococcal diagnosis, or 3) 'No baseline TB'. Baseline demographics were compared. Among those with no baseline TB, 'TB incident' was defined as occurrence of TB >14 days after cryptococcal diagnosis. Time-updated proportional hazards regression models were used to assess TB diagnosis as a risk factor for death. Models were adjusted for age, antiretroviral therapy status, Glasgow Coma Scale <15, and initial CSF quantitative cryptococcal culture.
Results: Of 870 with cryptococcosis, 50 (6%) had prevalent TB, 67 (8%) had concurrent TB, and 753 (86%) had no baseline TB. Baseline demographics were similar between groups with exception of weight, duration on ART and CSF opening pressure. The 18-week mortality was 50% in prevalent TB, 46% in concurrent TB, and 45% in the no TB group. Among 753 participants without baseline TB, 67 (9%) were diagnosed with incident TB, with a median time to TB incidence of 41 [IQR, 22-69] days. TB diagnosis was associated with an increased risk of death (Hazard Ratio (HR)=1.62; 95%CI, 1.23, 2.14; p<0.01), which increased in models adjusted for age, ART use, GCS < 15 and CSF quantitative culture (HR=1.75; 95%CI, 1.33, 2.32; p<0.001) (table).
Conclusion: Nearly a quarter of adults with cryptococcosis received treatment for TB, giving rise to potential drug-drug interactions and overlapping toxicities. There is an increased risk of death in patients who begin TB treatment after cryptococcal diagnosis. Further studies are needed to better characterize the increased risk of mortality with Cryptococcus and TB co-infection, and to determine the benefit of systematic TB screening in patients with cryptococcal meningitis.

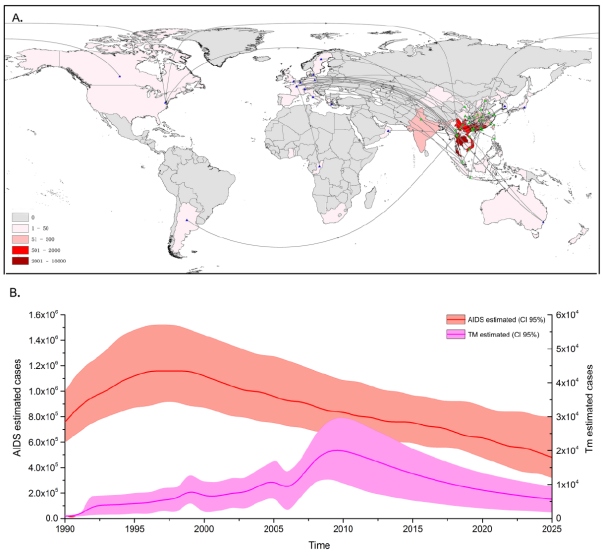
	Unadjusted Model		Adjusted Model*	
Event	HR (95% CI)	P-value	HR (95% CI)	P-value
Including TB prevalent† (N=870)				
Death by day 30	1.33 (0.90, 1.97)	0.15	1.47 (1.00, 2.17)	0.05
Any death	1.62 (1.23, 2.14)	<0.001	1.75 (1.33, 2.32)	<0.001
Excluding TB prevalent (N=805)				
Death by day 30	1.30 (0.80, 2.11)	0.29	1.34 (0.83, 2.19)	0.23
Any death	1.72 (1.25, 2.36)	<0.001	1.77 (1.28, 2.43)	<0.001

*Adjusted for age, antiretroviral use, GCS < 15 and CSF quantitative cryptococcal culture.
†Those who are prevalent have the time-updated indicator for TB active on study day 1.

749 THE GLOBAL DISTRIBUTION, DRIVERS, AND BURDEN OF TALAROMYCOSIS, 1964-2017

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Background: The disseminated talaromycosis (Tm) has emerged as a leading cause of opportunistic infections and mortality in patients with advanced HIV disease in Southeast Asia but remains largely neglected. Here, we presented the estimates of the global Tm burden and modeled Tm projection to inform treatment and prevention strategies.
Methods: First, we conducted a systematic review of all laboratory-confirmed, non-duplicating Tm cases published in the English and Chinese literature from the first case in 1964 to December 2017. We characterized the Tm global epidemiology, mapped Tm distribution, and used Maxent modeling to investigate ecological and meteroroligical drivers of Tm incidence. Second, we used numbers of known and unknown AIDS and treatment failure and treatment default from UNAIDS and national estimates to estimate the number of people at risk for Tm, and we estimated the cumulative and annual Tm cases and mortality based on reported regional Tm prevalence. Third, we used Bayesian regression modeling to predict the Tm epidemic to 2025 based on regional HIV/AIDS projection.
Results: 686 of 1086 screened studies were included after excluding duplicated reports. A total of 22, 537 Tm cases were reported in 33 countries to end of 2017. 89.9% of patients were infected with HIV; 74.4% were male; 0.5% were children; 99.7% were autochthonous cases from Asia. China (60.3%), Thailand (30.4%), and Vietnam (8.4%) were the highest burden countries. The AIDS incidence, distribution of the Rhizomys bamboo rat, precipitation of wettest month, mean temperature of warmest quarter, and mean temperature of driest quarter were independent predictors of Tm incidence. We estimated a mean Tm prevalence of 4.7% (95% CI 4.7–4.8) among individuals with AIDS in Southeast Asia, with a total of 181,900 (95% CI 107,900–251,600) accumulative Tm cases and 29,700 (95% CI: 16,600–45,700) Tm death globally. We estimated that 12,700 (95% CI: 7,900–14,400) Tm cases and 2,200 (95 CI: 1,200-2,800) Tm deaths occurred in 2015. Figure 1A showed the geographical distribution and travel routes of reported cases, and Figure 1B showed the Tm epidemic projection to 2025.
Conclusion: Despite substantial progress in HIV field, Tm remains a major neglected cause of HIV-associated morbidity and mortality in Southeast Asia. Our study highlights the need for improved Tm surveillance, diagnosis and treatment, and the need to improve HIV testing and treatment in this region.



750 SUPERIOR ACCURACY OF THE Mp1p ANTIGEN ASSAY OVER CULTURES IN DIAGNOSING TALAROMYCOSIS

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Background: Talaromyces marneffei infection (Tm) is a leading cause of HIV-associated morbidity and mortality in SE Asia. Diagnostic delays due to protracted culture methods is the most challenging clinical problem. We have demonstrated that the Mp1p antigen enzyme immunoassay (EIA) is more sensitive than blood culture in detecting Tm in a retrospective cohort. Here we

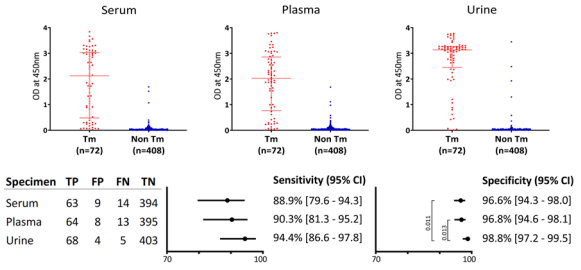
reported the accuracy and predictive values of the Mp1p EIA in a prospective study

Methods: We consecutively recruited HIV patients aged ≥18 who were hospitalized at the Hospital for Tropical Diseases in Ho Chi Minh city with any symptoms, had a CD4 count <100 cells/mL, were ART-naïve, or were on ART for <3 months or >12 months. Serum, plasma, and urine samples were collected for Mp1p testing alongside blood cultures. All patients were followed over 6 months. Diagnostic accuracy and predictive values were calculated based on the reference standard, defined as cumulative incidence of culture-positive Tm from any sterile sites over 6 months.

Results: 533 patients were recruited between January 2018 and July 2019. 78.4% were male; median age was 34 (IQR: 29-40) years; median CD4 count was 16 (IQR: 6-36) cells/mL. A total of 81 (15.2%) patients developed Tm: 69 during hospitalization, 12 during the follow up period, with sensitivity of cultures of 85.2%. The AUCs generated from the ROC curves in sera, plasma, and urine were 98.1%, 96.2%, 97.2%, respectively. Based on the OD cut off generated by the Youden indexes of 0.17, 0.23, and 0.39 for sera, plasma, and urine, respectively, the sensitivity was 88.9%, 90.3%, 94.4%; specificity was 96.6%, 96.8%, 98.8% (Psera-urine=0.011, Pplasma-urine=0.013, McNemar test); PPV 83.2%, 85.1%, 98.8%; NPV 98.2%, 98.4%, 99.0%. When testing all 3 specimens in combination, sensitivity=97.5%, specificity=96.5%, PPV=82.8%, NPV=99.1%. The sensitivity when testing all 3 specimens was higher than cultures (97.5% vs 85.2%, P<0.001, McNemar test). In 12 patients, Tm antigen was positive 1 to 16 weeks before cultures turned positive.

Conclusion: The Mp1p EIA offers superior sensitivity and excellent specificity (>95%) compared to cultures in diagnosing Tm. Urine is as sensitive and is more specific than plasma and sera for antigen testing. This test can detect Tm up to 4 months before cultures turn positive and could transform the current management of talaromycosis.

Figure: OD distribution between Tm and non Tm cases, and diagnostic accuracy of the Mp1p EIA performed in serum, plasma, and urine samples of 480 hospitalized patients with AIDS



751 IN VITRO ANTIFUNGAL SUSCEPTIBILITY AND ANTIFUNGAL TREATMENT OUTCOME IN TALAROMYCOSIS

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Background: The dimorphic fungus Talaromyces marneffei (Tm) causes an invasive mycosis which ranks 3rd as the most common HIV-associated infections in Southeast Asia with a mortality as high as 30%. We recently demonstrated in a randomized control trial (N=440 patients) that induction therapy with itraconazole was associated with higher mortality, persistent fungemia, incidence of relapse and IRIS when compared to amphotericin B over six months. We hypothesize that disease relapse and other complications in patients who received itraconazole are associated with a reduced susceptibility to itraconazole. Currently methods for antifungal susceptibility testing (AFST) and clinical breakpoints to define antifungal resistance have not been established for Tm.

Methods: To test our hypothesis, we developed a new AFST testing method for Tm. We followed the CLSI guidelines for broth microdilution of itraconazole and preparation of a standardized yeast inoculum of 10^6 cells/ml. We utilized alamarBlue, a dye which fluoresces as a result of cellular metabolic activity, allowing percent reduction in fluorescence intensity to be precisely calculated. We generated MIC_{50} and MIC_{90} values for 136 unique Tm strains isolated from patients treated with itraconazole, and we compared the MIC geometric means in patients who had a good treatment outcome and multiple groups of patients who had poor treatment outcomes.

Results: The assay performed consistently with intra-assay MICs of 0.008µg/mL for 6 sample replicates, and inter-assay MICs testing 6 runs on separate days were within the CLSI acceptable range of one 2-fold dilution. Among 136 isolates, 79% had MIC_{90}=0.008 µg/mL, 16% had MIC_{90}=0.016, and 4% had MIC_{90}=0.03. In multiple pairwise comparisons, the differences in MIC_{90} geometric means between patients who responded well to itraconazole (N=59) and patients who had any bad outcome (N=77), including death (N=23), relapse (N=9), prolonged fungemia (N=55), and IRIS (N=14) were not statistically significant, all P values from Wilcoxson rank sum tests were >0.05.

Conclusion: We developed a highly reliable and reproducible method for in-vitro AFST for Tm in the yeast form. The use of alamarBlue enables precise quantification of MIC without relying on visual perception and can be standardized across laboratories. The MICs against itraconazole in all isolates were low (≤0.03 µg/mL), and the MIC distribution did not correlate with the outcome of itraconazole therapy in HIV-associated talaromycosis.

Table 1. Comparison of MIC distribution between patients who had a good outcome and patients with poor outcomes

Comparisons	N	Geometric mean of MIC90 (µg/mL) (95% CI)	P value(*)
Good outcome	59	0.0094 (0.0073 - 0.0121)	Ref.
Composite poor outcomes (death, relapse, prolonged fungemia, or IRIS)	77	0.0096 (0.0076 - 0.0119)	0.91
Death	23	0.0089 (0.0061 - 0.0133)	0.48
Relapse	9	0.0086 (0.0048 - 0.0153)	0.51
Prolonged fungemia	55	0.0099 (0.0075 - 0.0129)	0.61
IRIS	14	0.0107 (0.0064 - 0.0181)	0.11

(*) By Wilcoxson rank sum test, *P* values from pairwise comparison to the reference group

752 PREVALENCE OF CMV VIREMIA AND ASSOCIATED RISK IN HIV-INFECTED PERSONS STARTING ART

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Background: Morbidity and mortality in advanced HIV-infection is still high despite ART use and prophylaxis for opportunistic infections. Data on prevalence of CMV viremia pre- and post- ART initiation at varying CD4 thresholds are limited. The impact of CMV viremia on morbidity and mortality is unclear.

Methods: Using plasma samples from participants initiating ART at study entry in 4 clinical trials (INSIGHT: FIRST, SMART, START, and ANRS: REFLATE), we measured CMV-specific IgG and CMV viremia at baseline and in year 1 visits. CMV DNA was measured centrally. Detectable (lower limit 88.5 IU/mL) CMV DNA was used for CMV+/CMV- classification. CMV+ during follow-up was defined as CMV DNA at any visit. Analyses for the association of CMV+/CMV- with clinical risk were limited to FIRST (longer follow-up and number of outcomes). Using all follow-up in FIRST, we estimated the hazard ratio (HR) for baseline CMV+ vs. CMV- for a composite outcome of AIDS, serious non-AIDS (SNA), or death. HRs were also computed for outcomes after 8 months of ART across 4 subgroups defined by baseline and follow-up CMV+/CMV- through month 8. Models were adjusted for CD4 counts and HIV RNA.

Results: There were 1169 participants from FIRST, 137 from REFLATE, 54 from SMART, and 1815 from START with median baseline CD4 counts of 153, 140, 429, and 648 cells/µL, respectively. CMV infection by IgG was ≥ 90% across trials. Baseline CMV+ prevalence was 17%, 26%, 1%, and 0% in FIRST, REFLATE, START, and SMART, respectively. Pooled across trials, baseline CMV+ prevalence by CD4 count was: ≤50 cells/µL: 39% of 382; 51-100: 29% of 148; 101-200: 12% of 221; 201-350: 4% of 289; 351-500: 1% of 195; > 500: 1% of 1941. FIRST participants were grouped using baseline and follow-up CMV+/CMV- at months 4 and 8 (n=1151): 2% were baseline CMV- but follow-up CMV+, 3% were baseline and follow-up CMV+, and 14% were baseline CMV+ and follow-up CMV-. Using baseline, months 4 and 6 in REFLATE (n=128), these percentages were 5%, 2%, and 21%. START and SMART percentages were <1. Table 1 presents HRs for the composite outcome across subgroups defined by baseline and/or follow-up CMV+/CMV- in FIRST.

Conclusion: Prevalence of CMV viremia at baseline was higher among ART-naïve HIV+ persons with lower CD4 counts. Persistent or development of CMV

viremia within 8 months of ART was associated with high risk of morbidity and mortality. Further exploration of reasons for the development/persistence of CMV viremia following ART is warranted.

Table 1: Hazard ratios[1] (HRs) for the risk of the composite outcome of AIDS, SNA, or death during follow-up in FIRST, by subgroups defined by baseline and follow-up CMV+/CMV- status.

Subgroup	N in Grp.	N. Evt.	Rate (100 PY)	Unadjusted HR (95% CI)	Adjusting for BL CD4 HR (95% CI)	Adjusting for BL CD4 and HIV RNA HR (95% CI)
Using all follow-up						
BL CMV+	201	71	9.4	2.0 (1.5, 2.6)*	1.2 (0.9, 1.6)	1.1 (0.8, 1.5)
BL CMV-	968	193	4.7	-- ref --	-- ref --	-- ref --
Subgroup	**N in Grp.**	**N. Evt.**	**Rate (100 PY)**	**Unadjusted**	**Adjusting for Month 8 CD4**	**Adjusting for Month 8 CD4 and HIV RNA**
Using follow-up after 8 months of ART						
BL CMV+, F/U CMV+	31	14	15.4	3.7 (2.1, 6.4)*	2.4 (1.4, 4.2)*	2.1 (1.2, 3.6)*
BL CMV-, F/U CMV+	24	10	14.7	3.5 (1.8, 6.7)*	3.4 (1.8, 6.4)*	3.0 (1.6, 5.7)*
BL CMV+, F/U CMV-	163	36	5.9	1.4 (1.0, 2.1)	0.9 (0.7, 1.4)	1.0 (0.7, 1.5)
BL CMV-, F/U CMV-	921	145	4.1	-- ref --	-- ref --	-- ref --

BL: baseline; CI: confidence interval; CMV+: detectable CMV DNA; CMV-: no CMV DNA; F/U: follow-up; SNA: serious non-AIDS (cancer, CVD, renal, liver)
* p-value < 0.05
[1] Time to first event, estimated using Cox proportional hazards models.

753 CMV VIREMIA IN PATIENTS WITH ADVANCED HIV INFECTION: A 48-WEEK FOLLOW-UP STUDY

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Background: Nowadays, the incidence of CMV end-organ disease (EOD) is very low even though the prevalence of CMV viremia is around 30% in patients with HIV infection and ≤100 CD4 T-lymphocytes (TL). We hypothesize that immune reconstitution after initiation of antiretroviral therapy (ART), rather than anti-CMV specific treatment, is the best strategy to clear CMV viremia in patients without EOD. We aim to study the dynamics of CMV viral replication and the recovery of specific immune response against CMV after the initiation of ART. A pre-planned interim analysis of this study was presented at CROI 2017. Here we present the final results of a 48-week prospective study.

Methods: A prospective observational study including patients with HIV infection and <100 CD4 TL was performed between September 2015 and July 2018. We determined HIV viral load (VL), CD4-TL and CMV VL by quantitative PCR at baseline, 4, 12, 24 and 48 weeks. We determined specific immune response against CMV (QuantiFERON-CMV®) at baseline and at 48 weeks. ART was started for all patients but only patients with CMV EOD received anti-CMV treatment. Statistical analysis: Friedman's (quantitative) and chi-square (qualitative) tests were used to assess the evolution over time.

Results: Fifty-two patients were included, 19 (36.5%) were women, median age (IQR) was 43.8 (36.5-53.1) years. At baseline median (IQR) CD4-TL count was 30/µL (20-60) and median (IQR) HIV VL was 451,500 copies/mL (179,750-1,285,000). Sixteen (30.8%) patients had detectable CMV viremia at baseline, 3 (7.7%) at 12 weeks and none at 48 weeks. Only 1 patient developed EOD (stomatitis) during follow-up. Six (11.5%) patients were lost to follow-up and 7 (13.4%) died, none of them related to CMV infection. Thirty-seven (71.2%) patients had specific CMV immune response at baseline compared to 27 (69.2%) at 48 weeks. The specific CMV IFN-γ response increased from baseline (median: 1.25, IQR: 0.12-5.24) to 48 weeks (median: 2.5, IQR: 0.1-7.425) in the 39 patients that completed the follow-up (p=0.07).

Conclusion: The prevalence of CMV viremia in patients with advanced HIV infection is high but the incidence of CMV-EOD is low nonetheless. CMV viremia gets suppressed after starting ART without specific anti-CMV treatment.

Table 1

	Baseline (n=52)	Week 4 (n=49)	Week 12 (n=39)	Week 24 (n=41)	Week 48 (n=39)
HIV infection					
CD4 TL (cells/µL), median [IQR]	30 [20-60]	120 [60-190]	140 [82.5-197.5]	145 [100-240]	190 [130-305]
HIV VL (copies/mL), median [IQR]	451500 [179750-1285000]	394 [123.8-2665]	180 [24-667]	41 [24-159]	24 [24-101]
Undetectable HIV VL (<50 copies/mL), n (%)	2 (3.8)	7 (14.3)	12 (30.7)	21 (51.2)	26 (66.7)
CMV infection					
Positive CMV PCR, n (%)	16 (30.8)	18 (36.7)	3 (7.7)	1 (2.4)	0 (0)
PCR CMV+ (copies/mL), media [IQR]	28074 [3708-82324]	4312 [857-43315]	2178 [1542-51008]	2490	-
CMV specific immune response (QuantiFERON-CMV®)					
Reactive, n (%)	37 (71.2)				27 (69.2)
CMV-specific IFN-γ (UI/mL), median [IQR]	1.44 [0.15-5.582]				2.5 [0.1-7.425]

754 RISKS OF OPPORTUNISTIC INFECTIONS FOR HIV +/- VETERANS UNDERGOING CANCER CHEMOTHERAPY

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Background: Persons living with HIV (PLHIV) treated for cancer may be at increased risk of opportunistic infections (OIs) compared with uninfected patients.

Methods: Using the Veterans Aging Cohort Study we evaluated OI incidence in 5,289 patients with malignancies diagnosed 1996-2018, and treated with chemotherapy. We identified zoster, cytomegalovirus (CMV), tuberculosis, Candida esophagitis, pneumocystis pneumonia (PCP), toxoplasmosis, Cryptococcus, atypical Mycobacterium, Salmonella bacteremia, histoplasmosis, coccidiomycosis or Progressive Multifocal leukopathy using ICD diagnosis codes, chart review confirmed, within 6 months of chemotherapy initiation. We fitted Poisson models to evaluate the association between HIV and OI risk overall, stratified by hematological and non-hematological cancers. We used inverse probability weighting (IPW) of HIV status to control for differences between groups and adjusted for prophylaxis use. Models including only PLHIV were fitted to evaluate risk factors for OI incidence.

Results: Amongst 2,237 PLHIV, a greater proportion of malignancies were hematologic (29%) than in uninfected Veterans (16%). Median age was 58 years, 98% were males, 81% were current/ever smokers, 49% were African-American. PCP prophylaxis was used more frequently in PLHIV (42% vs. 5%; p<0.001). We confirmed 107 OIs in 101 subjects: Candida esophagitis (n=43), zoster (n=31), CMV (n=11), PCP (n=11), Cryptococcus (n=3), atypical Mycobacterium (n=6), Salmonella bacteremia (n=1), histoplasmosis (n=1). HIV was an independent risk factor for OIs (incidence rate ratio [IRR] 4.3; 95% CI: 2.3-8.1) after accounting for IPW and prophylaxis use. 83% of OIs in PLHIV occurred in the setting of a viral load >500 copies/mL and/or CD4 count <200/mm$_3$. There were no definitive cases of PCP in non-hematologic tumors among PLHIV with CD4>200/mm$_3$. In multivariable analyses of PLHIV only, HIV viremia (IRR 9.9; 95% CI: 5.9-16.5) and comorbidity burden (IRR 1.1; 95% CI: 1.05-1.3 for 1 point Charlson increase) were independently associated with OI risk.

Conclusion: OIs were significantly increased in PLHIV with malignancies undergoing chemotherapy. However, our study does not support systematic PCP prophylaxis in PLHIV with non-hematological malignancies and controlled HIV-disease.

	Number of events (persons with first OI)		OI Incidence rate/1000 p-y (95%CI)		HIV incidence rate ratio and 95% CI*	
All cancers (n=5,289)	**PLHIV (n=2,237)**	**HIV-negative (n=3,052)**	**PLHIV**	**HIV-negative**		
	78 (1.47%)	23 (0.75%)	88.2 (71.2-109.2)	17.0 (11.3-25.6)	4.3	2.3-8.1
Hematological (n=1,131)	**PLHIV (n=647)**	**HIV-negative (n=484)**	**OI Incidence rate/1000 p-y (95%CI)**		**HIV incidence rate ratio and 95% CI***	
	37 (5.72%)	4 (0.83%)	138.6 (100.4-191.3)	18.1 (6.8-48.2)	9.8	3.1-31.3
Non-Hematological (n= 4,158)	**PLHIV (n=1,590)**	**HIV-negative (n=2568)**	**OI Incidence rate/1000 p-y (95%CI)**		**HIV incidence rate ratio and 95% CI***	
	41 (2.58%)	20 (0.74%)	60.0 (44.0-81.2)	17.7 (11.-27.5)	3.12	1.4-7.0

*Inverse probability weighted and adjusted by PCP prophylaxis use; OI: opportunistic infection; CI: confidence interval

Table. Opportunistic infection incidence after cancer chemotherapy by HIV status.

755 CHARACTERISATION OF SOUTH AFRICA'S XPERT MTB/RIF ULTRA "TRACE" LABORATORY RESULTS

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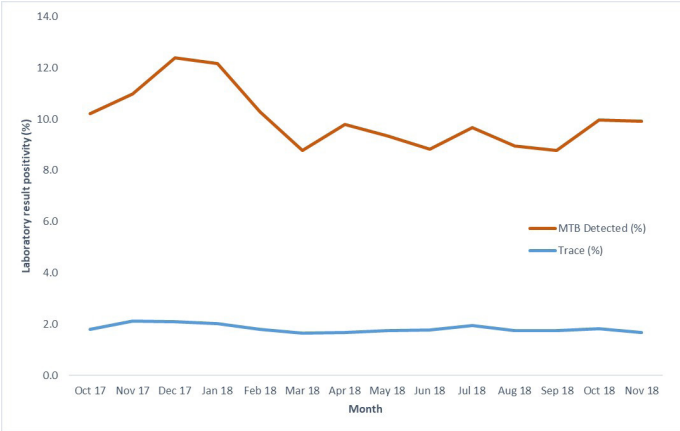
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Background: South Africa introduced Xpert-MTB/RIF Ultra (Ultra) assay into their national TB program in October 2017. Increased sensitivity of the Ultra over the previous Xpert MTB/RIF assay is attributed to the inclusion of IS6110/IS1081, improved chemistry, and larger PCR reaction volume. The lower limit of detection of Ultra is 15.6cfu/ml, and a new semi-quantitative category "trace" identifies paucibacillary specimens that are IS6110/IS1081 positive but rpoB negative. The complexities of "trace" was explored.

Methods: Exact demographic matching was applied to NHLS's centralised laboratory test result data between Oct17-Nov18. This generated a cohort of uniquely identified patients (UIDs) with an initial "trace" result and at least one subsequent laboratory follow-up test (Ultra, smear, culture).

Results: Overall, Ultra "trace" test results contributed an additional ~2% over the national ~10% positivity rate during the review period (see Figure). A total of 35623 "trace" UIDs were identified with 48.7% (n=17342) reflecting ≥1 additional laboratory follow-up test within the cohort time. Ultra was requested in 49.9% (n=8648/17342); culture 57.5% (n=9964/17342) and smear 64.2% (n=11133/17342) of cases. Follow-up occurred within 14 days of the first ultra "trace" result for 81.9% (n=14208/17342) of the cohort. Cases with a positive follow-up test were reported in 40.0% (n=6934) of cases: 52.9% (n=4575/8648) Ultra; 33.8% (n=3364/9964) culture [with rifampicin resistance confirmation]; 6.7% (n=750/11133) smear. 60.0% of (n=10408/17342) UIDs generated negative follow-up results: 47.1% (n=4073/8648) by Ultra; 66.2% (n=6600/9964) culture; 93.3% (n=10383/11133) smear. Follow-up Ultra generated the highest proportion of positive test results.

Conclusion: Ultra's "trace" category likely indicated TB disease in 40.0% of cases, which would have been undiagnosed by Xpert MTB/RIF testing, and at least 33.8% available for confirmation of rifampicin susceptibility by culture. Laboratory diagnostic algorithms can be refined to reduce testing costs and suggests clinical cohort studies are required to further explore "trace" for patient management.



756 URINE-BASED TB SCREENING WITH TB-LAM AND ULTRA IN HIV+ UGANDANS WITH MENINGITIS

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Background: Tuberculosis (TB) is a common cause of HIV-related death, yet diagnosis is often missed, particularly with concurrent illness such as meningitis. In one study, use of urine TB-lipoarabinomannan lateral flow assay (LAM) reduced missed TB diagnoses and mortality in HIV+ inpatients with CD4 <100 or suspected TB. The utility of the novel Xpert MTB/Rif Ultra (Ultra) assay on urine has not been evaluated. We sought to determine the prevalence of disseminated TB by testing urine with LAM and Ultra in hospitalized adults with meningitis in Uganda.

Methods: We prospectively enrolled HIV+ adults with meningitis in Kampala or Mbarara, Uganda. Participants were tested for meningitis etiologies using a stepwise algorithm. In parallel, participants underwent systematic urine-based screening for TB using the LAM (Alere) and Ultra (Cepheid). 60 µL of urine was tested with the LAM. All remaining urine was centrifuged and the cell pellet resuspended in 2mL of urine for Ultra testing. Results were reported to clinicians in real-time.

Results: From Jan 2018 to Sept 2019, we enrolled 251 HIV+ inpatients. Table 1 shows baseline characteristics (median CD4 = 37 cells/mcL; IQR 12-85). The majority had cryptococcal meningitis (59%, 148/251), and 15% (38/251) had definite/probable TB meningitis (Table 1). Overall, 25% (63/251) had evidence of disseminated TB by either urine assay. In cryptococcal subjects, 20% (29/145) had evidence of disseminated TB by LAM and 5% (5/96) by Ultra. In definite/probable TB meningitis, 32% (12/37) had a positive urine LAM and 33% (12/36) had a positive Ultra (Table 1). 178 participants had both urine LAM and Ultra results: 18% (32/178) were LAM positive, 11% (20/178) by Ultra, and 4% (8/178) positive by both assays. Mortality was higher in patients with evidence of disseminated TB by either urine assay (table 1).

Conclusion: In hospitalized Ugandans with advanced HIV disease and suspected meningitis, systematic screening with urine LAM and Ultra found a high prevalence of disseminated TB (25%). Cryptococcosis and TB co-infection was common (20%). Given the overlap in symptoms, TB may be missed in this setting without systematic testing. In those with TB meningitis, urine tests were positive in one-third; these tests may represent rapid, non-invasive adjunctive tests for TBM diagnoses. There was little concordance of Ultra and LAM, the reason for which warrants further investigation.

	Cryptococcal Meningitis	TBM (definite)	TBM (probable)	Unknown Other[1]	total
Number participants	148	28	10	65	251
Demographics	**Median [IQR] or N (%)**	**Median [IQR] or N (%)**	**Median [IQR] or N (%)**	**Median [IQR] or N (%)**	**p-value[2]**
Women, n (%)	59 (39.9%)	12 (44.4%)	6 (60.0%)	27 (42.9%)	0.64
CD4+ cell count, cells/mcL	19 [6, 66]	74 [46, 122]	133 [47, 336]	125 [30, 325]	<0.01
Weight, kg	52 [46, 58]	55 [50, 60]	56 [55, 60]	51 [50, 59]	0.11
Currently on antiretroviral therapy	73 (49.3%)	15 (53.6%)	3 (33.3%)	42 (64.6%)	0.13
Clinical					
Fever	56 (37.8%)	22 (78.6%)	9 (90.0%)	30 (46.2%)	<0.001
Focal neurologic deficit	6 (4.1%)	12 (42.9%)	3 (30.0%)	12 (18.5%)	<0.001
Glasgow coma scale < 15	49 (33.1%)	24 (88.9%)	10 (100.0%)	30 (46.9%)	<0.001
Seizure	33 (22.3%)	9 (32.1%)	2 (20.0%)	15 (23.1%)	0.89
Diagnostic Results					
Urine LAM positive	29 (20.0%)	9 (33.3%)	3 (30.0%)	10 (15.4%)	0.23
Urine Ultra positive	5 (5.2%)	12 (44.4%)	0 (0.0%)	3 (6.0%)	<0.001
In-hospital Mortality					**Overall**
Urine TB-LAM positive	10/28 (35.7%)	5/9 (55.6%)	1/2 (50.0%)	1/8 (12.5%)	17/47 (36.2%)
Urine TB-LAM negative	34/106 (32.1%)	4/16 (25.0%)	2/7 (28.6%)	7/46 (15.2%)	47/175 (26.9%)
Urine TB-LAM p-value[3]	0.72	0.13	0.67	0.84	0.21
Urine Ultra positive	2/5 (40.0%)	6/11 (54.5%)	3/8 (37.5%)	0/3 (0.0%)	8/19 (42.1%)
Urine Ultra negative	23/86 (26.7%)	2/14 (14.3%)	0/0	8/41 (19.5%)	30/149 (24.2%)
Urine Ultra p-value[3]	0.52	0.03		0.40	0.09

[1] Includes possible TBM cases. [2] Kruskal-Wallis test for medians, chi square test or Fisher's exact test for proportions. [3] P-values from chi square test

757 APPLICABILITY OF URINE LAM TEST IN ADVANCED HIV-INFECTED ADULTS IN UKRAINE

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Background: Tuberculosis (TB) remains the leading cause of death among HIV-infected adults in Ukraine. Urine lipoarabinomannan (LAM) antigen testing is a new rapid TB diagnostic that recently was implemented by Ukrainian National Public Health Center. We evaluated the utility of urine LAM in high TB prevalence and resource constrained settings.

Methods:
Between March-August 2019, 1770 consecutive HIV-infected patients presenting for routine follow-up visits had LAM testing performed in Kyiv (North), Odessa (South), Dnipro (East) and Lviv (West) regions of Ukraine. The inclusion criteria were: HIV+, ≥18, CD4 < 200 cells/mm$_3$ and/or clinically advanced HIV disease, regardless of TB symptoms. TB was confirmed by chest radiography, CT and/or bacteriological methods The project was funded by All-Ukrainian Network of People Living with HIV/AIDS.

Results: In total 918 patients with both TB assessment and LAM performed were included in preliminary analyses. Mean age of participants was 41.0 years, 56.9% were male, and the mean baseline CD4 count was 157 cells/mm$_3$.Of 586 confirmed TB cases, 400 (43,6%) had positive LAM test failed to detect 186 (26,3%) TB cases. TB prevalence in the sample was 63.83%. Sensitivity of LAM tests - 68.26%, Specificity – 87.35%. Positive predictive value - 90.5%. Negative predictive value – 60.92% (Table). Kappa statistics provided an estimate of moderate agreement (kappa 0.51,p-value <.0001, 95% CI=0.46, 0.56).

Conclusion: LAM urine test is useful as an add-on rapid diagnostic method in Ukraine for HIV patients with a CD4 of <200. Sensitivity was satisfying, however for accurate and quick diagnosis LAM should be used in combination with other TB diagnostics

Table. LAM test results by TB confirmation.

LAM		TB confirmation		
		0	1	Total
Frequency	0	290	186	**476**
Percent		31.59	20.26	**51.85**
Row %		60.92	39.08	
Column %		87.35	31.74	
Frequency	1	42	400	**442**
Percent		4.58	43.57	**48.15**
Row %		9.5	90.5	
Column %		12.65	68.26	
Total		**332**	**586**	**918**
		36.17	**63.83**	**100**

758 EVALUATION OF A BLOOD-BASED ANTIGEN TEST FOR TUBERCULOSIS IN INFANTS

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Background: Improved methods are urgently needed for pediatric tuberculosis (TB) diagnosis. We evaluated the performance of a blood-based assay (NanoDisk-MS), which utilizes immunoenrichment and mass spectrometry to quantify a TB-specific CFP-10 peptide, for TB diagnosis in HIV-exposed South African infants enrolled in an isoniazid TB prevention trial (IMPAACT P1041).

Methods: Cryopreserved sera from 519 infants (284 HIV-exposed infected [HEI], 235 HIV-exposed uninfected [HEU]) were evaluated for CFP-10 peptide expression by NanoDisk-MS. At entry, all subjects were BCG-immunized, 90-120 days of age, and TB-disease-negative. They were randomized 1:1 to isoniazid or placebo and followed for up to 192 weeks for TB disease or infection. For this analysis, all children were classified as Confirmed, Unconfirmed or Unlikely TB cases using 2015 NIH TB diagnostic criteria and clinical, laboratory, histopathological, and radiological data.

Results: NanoDisk-MS exhibited sensitivity for Confirmed (5/5, 100%; 95% CI: 47.8–100) and Unconfirmed (36/43, 83.7%; 69.3–93.2) TB cases in HEI, with 93.1% (203/218, 88.9–96.1) specificity. In the HEU group, NanoDisk-MS detected the single Confirmed TB case and most of the Unconfirmed TB cases (15/20, 75.0%; 50.9–91.3), and had 96.2% (177/184, 92.3–98.5) specificity. Most (72.7%) CFP-10-positive subjects with Unlikely TB diagnoses also exhibited at least one criterion for TB diagnosis (11/15; 73.3% HEI and 5/7; 71.4% HEU). For TB cases, CFP-10 peptide could be detected in serum drawn ≤ 60 weeks before TB diagnosis, and its diagnostic sensitivity reached 83.3% (5/6, 35.9–99.6) at ≤ 12 weeks before diagnosis. CFP-10 peptide positivity and expression levels declined following anti-TB therapy initiation.

Conclusion: NanoDisk-MS detection of a TB-specific CFP-10 peptide in sera revealed sensitivity and specificity for TB diagnosis in HEI and HEU infants and displayed results suggesting its potential for early TB detection and the monitoring of anti-TB treatment responses.

759 PROMISING COMBINED IMMUNOLOGICAL ASSAYS TO DIAGNOSE CHILDHOOD TUBERCULOSIS

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Background: Children account for a substantial part of the tuberculosis (TB) burden. However, the real burden of the disease is imprecise because the diagnosis of active tuberculosis remains a challenge in children. The development of non-sputum-based diagnostics assays and triage assays to rule-out TB are considered as especially critical to improve TB diagnosis in children. We aimed at constructing an algorithm aimed to improve the diagnostic of TB in children using a combination of immunoassays based on the T cells and serologic response against cytokine and Interferon-γ release assays.

Methods: We designed an early proof-of-principle evaluation phase including children with confirmed TB and healthy controls in Zambia. The confirmed TB group consisted of children with positive clinical signs (prolonged cough, unexplained weight loss or fever, lethargy) and tested positive for MTB culture or GeneXpert® MTB/RIF assays. The control group consisted of healthy children without any clinical signs and no history of direct exposure to TB. Blood specimens were tested using the QuantiFERON Gold-IT®assay, (QFT®) and cytokines released in supernatants were quantified using a 25-plex cytokine multiplex test and ELISA assays. Serological response directed against Ag85A, B and D were tested by ELISA. A Random Forest classification analysis using values of all biomarkers was used in order to identify the most discriminant biological factors. Thresholds for each values were fixed with ROC curves. A simplified score was constructed out of these values.

Results: The TB confirmed group consisted of 37 children with 51% being HIV coinfected, for the control group, 70 children were enrolled, 44% being HIV coinfected. We identified anti-Ag85B Abs, IL2/IFNg ratio, MIG and IP10 as the most sensitive biomarkers for TB diagnosis. Because MIG and IP10 responses were strongly correlated, we kept only MIG in further analysis. Using ROC curves and the Youden index, the threshold of 151 pg/mL, 0.76 and 48.6, discriminated best confirmed TB children from controls, for MIG, Ag85B Ab and IL2 Elisa/IFNg ratio respectively. According to our combined tests, a child was declared with TB if (i) IL2/IFNg <48.6 or (ii) both MIG (from QTF® supernatant) >151 pg/mL and Ag85B Ab > 0.76. The ROC curve derived from our score showed an AUC of 0.94 (0.90-0.99), giving 86% sensitivity and 87% specificity.

Conclusion: The encouraging diagnostic performance of this score is the highest so far using immunological tests. In addition, the score is independent of the HIV status of the child.

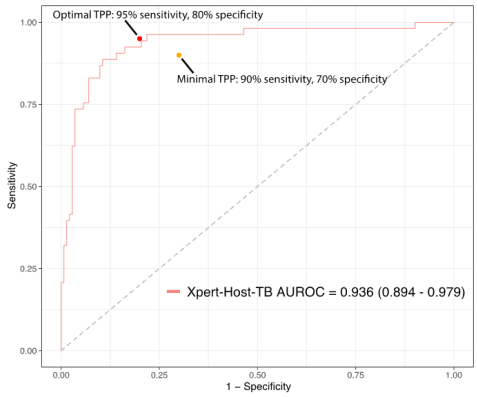
760 WITHDRAWN

761LB ACCURACY OF NOVEL BLOOD ASSAY FOR IDENTIFICATION OF TB DISEASE IN PEOPLE WITH HIV

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Background: A non-sputum triage test to rule out tuberculosis disease has been identified as a high-priority need for diagnostic development to reach the End-TB targets of the World Health Organization (WHO). The target product profile defines a minimum of 90% sensitivity and 70% specificity for the test to be used by first-contact providers to identify patients who need further confirmatory testing. A combinatory score based on a novel 3-gene host-signature has shown promise in discriminating TB disease from other respiratory illnesses and healthy controls. Cepheid (Sunnyvale, CA, USA) has developed an early prototype GeneXpert PCR test ('Xpert Prototype'), that quantifies relative mRNA-levels of the 3-gene signature in a patient whole blood sample.

Methods: Whole blood from symptomatic people living with HIV (PLHIV) in South Africa were collected from February 2016 to August 2017 and biobanked in PAXgene tubes. The accuracy of the Xpert Prototype on these biobanked samples was compared against a comprehensive microbiological reference standard (culture and Xpert® MTB/RIF). The performance was also compared against Xpert® MTB/RIF alone, as Xpert will be the most likely confirmatory assay used in programmatic settings in high-burden countries. We depict results in ROC curves and for pre-set cut-points based on performance targets set for a triage test by the World Health Organization.
Results: Of the 201 patients included, 67 were culture-positive. At a cut-point chosen to maximize the Youden index, sensitivity was 77.6% (95% Confidence Interval [CI] 66.3–85.9), specificity was 92.2% (CI 86.3–95.7) and the AUC was 0.89 (CI 0.83-0.94) against the comprehensive reference standard. Considering the Xpert-Prototype as a triage test (fixed sensitivity value closest to 90%), the corresponding specificity was 55.8% (CI 47.2-64.1). Comparing to Xpert® MTB/RIF alone as a confirmatory test at fixed value of sensitivity closest to 90% (90.6%), the Xpert Prototype specificity was 85.9% (CI 79.3-90.7). Considering the Xpert Prototype as a stand-alone diagnostic test, at a specificity of 95%, the test achieves a sensitivity of 65.7% (CI 53.7-75.9).
Conclusion: In this first accuracy study of a novel blood-based host-marker assay on a commercial platform, we show the possible value of the assay for triage and potentially also for diagnosis, when a sputum sample is difficult to obtain, as often the case in PLHIV.



762LB PROSPECTIVE VALIDATION OF A BLOOD RNA TB BIOMARKER IN AMBULANT HIV-INFECTED ADULTS

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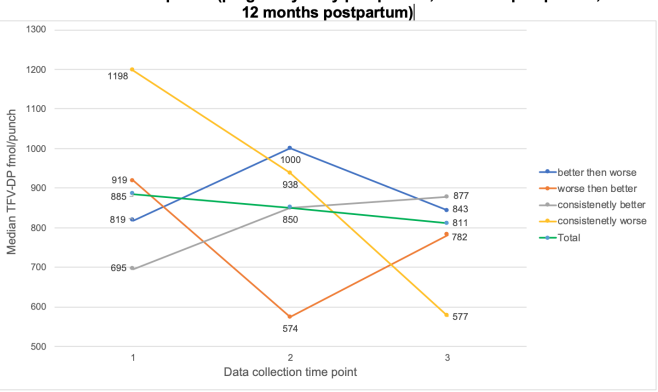
Background: New non-sputum tuberculosis (TB) biomarkers for predicting progression to active TB disease are needed to achieve the goals of the WHO End TB Strategy. We previously developed and validated a blood transcriptomic correlate of risk, RISK11, that identified individuals with active TB or high risk of progression to active TB in case-control studies. This study aimed to test diagnostic and predictive RISK11 performance for prospective community-based TB screening in HIV+ individuals, and to compare predictive performance with QuantiFERON-TB Gold Plus (QFT).
Methods: Ambulant HIV+ adults were enrolled across 5 sites in South Africa. ART naïve participants were referred for ART and isoniazid preventive therapy per country guidelines. RISK11 status was assessed at baseline and was double-blinded; RISK11 positivity was pre-defined at 60% score threshold. Participants were assessed at enrollment and underwent active surveillance for microbiologically-confirmed TB for up to 15 months. Here we report preliminary results.
Results: Among 861 participants (median age 35; 72% female; 11% symptom+; 78% ART experienced with median ART duration 3 years; median CD4 count 529 [IQR 350-725]), 33.1% were RISK11+ and 45.6% QFT+.
Ten cases of TB were identified at baseline; prevalence was 2.5% in RISK11+ vs 0.2% in RISK11- participants (diagnostic risk ratio 13.1, 95%CI 2.1-81.6; AUC 88.2%, 95%CI 77.6-96.7; sensitivity 87.5%, 95%CI 57.1-95.8; specificity 65.8%, 95%CI 62.4-69).
Nine cases of incident TB were identified through median 15 months follow-up; incidence was 2.5% in RISK11+ vs 0.2% in RISK11- participants (RISK11 cumulative incidence ratio, CIR 16.6, 95%CI 2.1-133.9; AUC 80.1%, 95%CI 70.7-87.1; sensitivity 88.9%, 95%CI 44.5-98.8; specificity 69.1%, 95%CI 65.3-72.5).
TB incidence was 1.6% in QFT+ vs 0.7% in QFT- participants (QFT CIR 2.3, 95%CI 0.6-9.3; AUC 72.6%, 95%CI 57.8-83.7; sensitivity 65.8%, 95%CI 30.5-89.5; specificity 56.1%, 95%CI 52.3-59.9).
Conclusion: RISK11 screening identified ambulant HIV+ adults with prevalent TB and predicted risk of progressing to active TB within 15 months. RISK11 performance approaches the WHO screening (sensitivity 90%; specificity 70%) and predictive (sensitivity and specificity 75%) test target product profiles (TPP) among HIV+ adults at the pre-specified score threshold. QFT performance falls short of the predictive TPP. RISK11 translation to a point-of-care assay may allow early identification of HIV+ adults that would benefit from further TB testing, therapy, or intensified follow-up.

763 A NOVEL PHARMACOLOGICAL ADHERENCE MEASURE IN PREGNANT AND POSTPARTUM KENYAN WOMEN

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Background: Antiretroviral therapy (ART) adherence among pregnant and postpartum women with HIV (PWHIV) is critical to promote maternal health and prevent HIV transmission. Tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) is an objective assessment of long-term drug exposure and adherence that is associated with viral suppression. Tenovofir disoproxil fumarate (TDF) is part of the first-line regimen for PWHIV in Kenya, providing the opportunity to quantify ART adherence with this novel biomarker.
Methods: 150 PWHIV receiving TDF-based ART regimens for a minimum of 10 weeks recruited from 24 health facilities in southwestern Kenya provided DBS samples at three time points (pregnancy/early postpartum (PP), 6 months PP, and 9-12 months PP). DBS were analyzed using validated laboratory testing.
Results: 419 DBS samples were collected. Median (IQR) TFV-DP at baseline (pregnancy/early PP), 6 months PP, and 9-12 months PP was: 885 (635, 1172), 851 (608, 1132), and 811 (519,1012) fmol/punch, respectively. TFV-DP ≥1250 fmol/punch (threshold for daily adherence in healthy US volunteers) was detected in only 11% at baseline and decreased to <6% in both the PP time periods. Using a more conservative estimate of adherence, TFV-DP ≥700 fmol/punch (threshold for ≥4 doses/week in healthy US volunteers), adequate adherence was detected in 68%, 65% and 60% of PWHIV at baseline, 6 months PP and 9-12 months PP, respectively. We identified four discrete adherence trajectories in PWHIV (Figure): those whose TFV-DP level consistently decreased across the PP period (19%); those whose TFV-DP level consistently increased across PP (15%); those who improved initially but then worsened (35%); and those who worsened initially but then improved (30%). Those with consistently decreasing TFV-DP had the lowest median late PP adherence results (577 fmol/punch).
Conclusion: Cumulative ART exposure in PWHIV, quantified by TFV-DP in DBS, demonstrated a trend towards decreased concentrations (i.e., adherence) over time from pregnancy into the PP period. Over half of PWHIV show decreasing adherence postpartum. This raises concern for higher likelihood of poor adherence and viremia in the critical PP period during breastfeeding. The use of TFV-DP in DBS as a measure of ART adherence in PWHIV in sub-Saharan Africa could be an important tool to optimize health outcomes.

Trajectories of median TFV-DP fmol/punch among 150 pregnant and postpartum women with HIV at three time points (pregnancy/early postpartum, 6 months postpartum, and 9-12 months postpartum)



764 DETECTABLE HIV RNA IN LATE PREGNANCY ASSOCIATED WITH LOW TFV HAIR LEVELS AT BIRTH

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Background: Adherence to antiretroviral therapy (ART) is vital to prevention of mother-to-child transmission of HIV (PMTCT) and maternal health, although peripartum life events can disrupt adherence. Hair levels measure cumulative ART exposure and are associated with viral suppression in nonpregnant and postnatal populations. We evaluated correlates of peripartum tenofovir (TFV) exposure via hair measures among women living with HIV (WLHIV) in the United States.
Methods: Hair samples were collected at or shortly after childbirth among WLHIV enrolled in the Surveillance Monitoring for ART Toxicities Study of the Pediatric HIV/AIDS Cohort Study between 6/2014-7/2016. Among WLHIV on TFV-based regimens during pregnancy, TFV hair levels were analyzed using validated liquid chromatography/tandem mass spectrometry methods. Weight-normalized TFV hair concentrations were log transformed. Correlates of TFV hair concentrations were identified using multivariable linear regression. Covariates with p<0.25 in univariable models were included in multivariable models.
Results: Among 370 WLHIV with TFV-based ART use during pregnancy, hair collection acceptability was high (only 65/370 [18%] of all WLHIV using TFV declined); 111 women had TFV hair levels and were included in the final analysis. Median age at delivery among the 111 WLHIV was 31 years (IQR 26-36); 70% self-identified as non-Hispanic black, 71% had achieved high school graduation, 13% reported recreational drug use during pregnancy, and 9% had unsuppressed viral loads (VL) in late pregnancy, defined as HIV-RNA ≥400 copies/mL. The median time from birth to hair collection was 4 days (IQR 1-14) and 31% of samples had TFV hair levels ≥0.038 ng/mg (equivalent to 7 doses/week). In multivariable models (Table 1), an unsuppressed VL in late pregnancy was most strongly associated with lower peripartum TFV hair levels. Attainment of high school education and not using TFV-based ART after the 1st trimester were also independently associated with lower peripartum TFV levels.
Conclusion: Unsuppressed VL among WLHIV in the U.S. during late pregnancy, a critical period for PMTCT, was strongly associated with low maternal TFV hair levels at birth. Over two-thirds of WLHIV had hair levels suggestive of imperfect adherence although viremia in late pregnancy was rare (9%). Efforts to improve PMTCT outcomes could incorporate drug exposure monitoring using hair or other metrics and include adherence promotion strategies that address issues unique to the peripartum period.

Table 1: Adjusted associations of covariates with TFV concentration (N=111)

Covariate	N (%) or Median (IQR)	% of Change (95% CI) [1]	P-value
ART regimen containing 3 or more classes	10 (9%)	-11.7 (-58.8, 89.7)	0.75
Gestational age (weeks): per one week increase	38 (37-39)	-8.4 (-21.1, 6.3)	0.25
INSTI use during pregnancy	42 (38%)	41.2 (-8.9, 118.9)	0.12
Latest HIV RNA (copies/mL) during pregnancy ≥400	9 (9%)	-73.1 (-86.8, -44.9)	< 0.001
Achieved at least high school graduation	79 (71%)	-39.9 (-61.5, -6.0)	0.03
TDF use in 1st trimester only	2 (2%)	-85.6 (-96.6, -39.0)	0.01

TFV=tenofovir; ART=antiretroviral therapy; INSTI=Integrase Strand Transfer Inhibitor; RNA=ribonucleic acid; TDF=tenofovir disoproxil fumarate

1 Estimated percent of change in TFV concentration: 1) per one unit increase in continuous covariate measures; or 2) between pregnancies with a specific characteristic vs the reference group for categorical covariate measures.
Covariates with p-value < 0.25 in univariable analysis were included in the multivariable model.

765 EARLY POSTPARTUM VIREMIA PREDICTS LONG-TERM NONSUPPRESSION AND INFANT TRANSMISSION

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Background: Long-term viral load (VL) suppression among HIV-positive reproductive-aged women on antiretroviral therapy (ART) is key to eliminating infant HIV transmission. We report trends in postpartum (PP) VL for Malawian women on ART, factors associated with detectable VL, and associations with cumulative infant HIV transmission and/or death.
Methods: From 2014-2016, 4-26 week PP HIV-positive mothers were screened and enrolled with their infants in Malawi clinics. At enrollment, 12 and 24 months PP, socio-demographic and prevention of mother to child transmission of HIV (PMTCT) indicators were collected and infants had HIV-1 DNA testing. Venous samples determined maternal plasma VL (<40 copies/ml = 'undetectable'); standard national VL monitoring guidelines were in early implementation across Malawi.
Results: 585 women were retained to 24 months (N=1281,45.7%), and were more likely to be >30 years (51.6 vs 41.4%, p<0.01), parity =>4 (41.0 vs 33.5%, p=0.02) and have undetectable VL at enrollment (79.7 vs 70.8%, p<0.01) than those lost to follow-up (LTFU). Of 573 women on ART (median 29.7 mos.(IQR 26.8-61.3)), 424 (74.0%) with VL data at all 3 visits were included in analysis. Table 1 shows 341 (80.4%) women had durable undetectable VL, 83 (19.5%) had >= 1 detectable VL and 32 (7.5%) had persistent detectable VL. Cumulative incidence of detectable VLs over 24 months was higher among women with detectable VL at enrollment than with undetectable VL (74 detectable VL measures/67 women vs 19/357; p<0.01). In multivariable analysis, adjusted odds ratios for detectable VL at 24 months were 10.1 among women with 1 prior detectable VL (95%CI 3.7-28.1, p<0.001) and 240.4 for women with 2 prior detectable VLs (95%CI 68.0-849.8, p<0.001) (adjusted for age, parity, education, partner disclosure, time on ART and adherence). Women with durable undetectable VL (N=341) had no infant transmissions and 2 infant deaths (0.6% combined outcome). Women with persistent detectable VL (N=32) had 4 infant transmissions and 1 infant death (15.6%; p<0.01).
Conclusion: Detectable VL in early PP signals a risk of ongoing PP viremia with major implications for infant HIV transmission, in a setting with limited high VL management. These findings suggest differentiated VL monitoring and targeted adherence support may be required during pregnancy and breastfeeding.

Table 1. Detectable VL measures over 24 months, stratified by enrollment VL (N=424)

	Enrollment	12 months		24 months	
VL<40 copies/ml	357	VL <40	351	VL <40	341
				VL >40	10
		VL >40	6	VL <40	3
				VL >40	3
VL >40 copies/ml	67	VL <40	31	VL <40	25
				VL >40	6
		VL >40	36	VL <40	4
				VL >40	32

766 VIRAL LOAD MONITORING IN PREGNANCY TO PREDICT PERIPARTUM VIRAEMIA IN SOUTH AFRICA

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Background: WHO guidance recommends VL monitoring in pregnant women on ART to help identify high-risk infants for enhanced prophylaxis but there are few data evaluating this approach in routine care.
Methods: Data come from the screening procedures of a RCT of postpartum HIV care strategies at a large primary care clinic in Cape Town. In this setting VL monitoring takes place at the earlier of 12 weeks on ART, or 34 weeks' gestation. In this context we identified consecutive HIV+ women initiating ART (TDF+FTC+EFV) who underwent VL testing during pregnancy, and for women with VL<400 copies/mL documented during pregnancy, repeated a VL within 4 weeks postpartum. All VL testing was done by the National Health Laboratory Services using the Abbott Realtime HIV-1 assay (Abbott Laboratories, Waltham, MA). We calculated sensitivity (SE), specificity (SP) and positive and negative likelihood ratios (LR+ and LR-) for antenatal VL<100 copies/ml in predicting peripartum VL<100 and <400 copies/mL, with sensitivity analyses examining subgroups of gestation at antenatal VL and prior ART exposure.
Results: In 323 women (median age 28y, 40% with a history of previous ART), antenatal VL was taken at a median gestation of 33w (IQR 30-36), and at that time, 89.2% of women had a VL<100 copies/mL and 10.9% had a VL 100-400 copies/mL. Peripartum VL was taken at a median of 9 days (IQR 6-17) postpartum, at which point women were on ART for a median duration of 23w (IQR 18-28), and at that time 91.6%, 6.8% and 1.6% had VL<100, 100-400 and >400 copies/mL, respectively. The SE of antenatal VL<100 copies/mL in predicting peripartum VL<100 copies/mL was 0.95 (95% CI 0.92-0.97) and the corresponding SP was 0.74 (95% CI 0.54-0.89; LR+3.7, LR- 0.07). The ability of antenatal VL to predict peripartum VL was similar across strata of gestation at VL testing and history of ART use. Predictive performance was slightly weaker at thresholds of <400 copies/mL (LR+ 2.25, LR- 0.17).
Conclusion: These novel data suggest that antenatal VL<100 copies/mL is a useful predictor of peripartum viraemia and may be used to target enhanced PMTCT interventions in this setting. The high SE and low LR- suggest few women who are virologically suppressed during antenatal care subsequently become viraemic peripartum.

Table: Performance characteristics of antenatal VL testing to predict peripartum viraemia in a routine care setting in Cape Town, South Africa

	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio	Negative likelihood ratio
	To detect peripartum VL<100 copies/ml			
All women (n=323)	0.95 (0.92-0.97)	0.74 (0.54-0.89)	3.66	0.07
Antenatal VL≤32 weeks (n=129)	0.94 (0.88-0.98)	0.7 (0.35-0.93)	3.14	0.08
Antenatal VL >32 weeks (n=194)	0.95 (0.91-0.98)	0.76 (0.50-0.93)	4.06	0.06
Women with history of previous ART use (n=141)	0.98 (0.93-0.10)	0.80 (0.44-0.97)	4.89	0.03
Women without history of previous ART use (n=182)	0.93 (0.88-0.96)	0.71 (0.44-0.90)	3.15	0.1
	To detect peripartum VL<400 copies/ml			
All women (n=323)	0.90 (0.86-0.93)	0.60 (0.15-0.95)	2.25	0.17
Antenatal VL≤32 weeks (n=129)	0.90 (0.83-0.94)	0.33 (0.01-0.91)	1.35	0.31
Antenatal VL >32 weeks (n=194)	0.90 (0.85-0.94)	1 (0.16-1)	-	0.1
Women with history of previous ART use (n=141)	0.93 (0.88-0.97)	0.5 (0.07-0.93)	1.87	0.13
Women without history of previous ART use (n=182)	0.87 (0.82-0.92)	1 (0.03-1)	-	0.13

ART: antiretroviral therapy, CI: confidence interval, VL: viral load.

767 HIGH VIRAL SUPPRESSION AMONG HIV-POSITIVE POSTPARTUM WOMEN: CLUSTER RANDOMIZED TRIAL

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Background: HIV-positive women are particularly vulnerable to poor retention and ART adherence in the postpartum period with low viral suppression that poses risks to maternal health and to transmission of HIV to their infants. We assessed the effect of a multidisciplinary integrated management team intervention on viral suppression in a cohort of HIV-positive pregnant women in Lesotho.
Methods: The IMPROVE cluster randomized study evaluated an intervention that included a multidisciplinary management team with maternal child health staff, village health workers, and peer mentor mothers to work together to support HIV-positive and negative women in uptake and retention in HIV and MCH services. Training together, using job aids, and adding early home based follow-up of new ANC attendees were included in the intervention. Twelve facilities were randomized to intervention or control arms. HIV-positive pregnant women were enrolled at their first ANC visit with prospective follow-up for at least 12 months postpartum. Study nurses conducted interviews with participants, extracted medical record information and collected dried (whole) blood spots from HIV-positive women for viral load testing. We compared viral load (VL) results at 12 months postpartum using Chi-square tests to test for differences between study arms.
Results: 613 HIV-positive women were enrolled in the study, 308 in the interventional arm and 305 in the control arm. 570 women had delivery information, all of whom were on ART at the time of delivery. VL results from 11-15 months postpartum were available for 351 (57%) women. There was no difference in follow-up (pregnancy losses/stillbirths, transfer to facilities outside the district, and loss to follow-up) by study arm. Overall 325 (93%) women were suppressed with a VL <1000 copies/ml. A greater proportion of women in the intervention group had a suppressed VL (166/175, 95%) compared to women in the control arm (159/176, 90%) but the difference was not statistically significant (p=0.106). Significantly more women in the intervention group had an undetectable viral load (83% intervention vs. 72% control, p=0.016).
Conclusion: The multi-component IMPROVE intervention led to a small but not significant increase in viral suppression in HIV positive women one year after delivery, with high rates of suppression in both arms.

768 CHANGES IN BONE MINERAL DURING AND AFTER LACTATION IN UGANDAN WOMEN ON OPTION B+ ART

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Background: Antiretroviral therapy (ART) in persons living with HIV (PWH) is associated with bone loss and increased risk of fracture, but data are limited in pregnant and lactating women when physiological bone mobilisation is also occurring. This research investigated changes in areal bone mineral density (aBMD) in breastfeeding HIV+ve Ugandan women initiated on lifelong ART in pregnancy compared to HIV-negative (HIV-ve) counterparts.

Methods: Two groups of pregnant Ugandan mothers planning to breastfeed, 95 HIV+ve (on Option B+ tripple ART [TDF-3TC-EFV], previously ART naïve) and 96 HIV-ve took part. Measurements were made postpartum at 2 (L02), 14 (L14), and 26 (L26) weeks of lactation, and at 14 weeks post-lactation when neither pregnant nor lactating (NPNL). Lumbar spine (LS), total hip (TH), femoral neck (FN) and whole body-less-head (WBLH) areal bone mineral density (aBMD) was measured by DXA.

Results: Median age was 24.5 (IQR 21.1, 26.9) yrs. HIV+ve women had lower body weight and a shorter duration of breast feeding (47.8±13.4 vs 65.6±18.1 weeks, p<0.05). Both groups experienced lactational bone mobilisation but HIV+ve women had greater decreases in TH, FN and WBLH aBMD during lactation, and a trend towards a smaller reduction in LS aBMD at L14. Both groups had recovered LS aBMD by NPNL. Hip and WBLH aBMD had returned to L02 values in HIV-ve women but not in HIV+ve (Figure 1). Adjusting for parity, age, body size, breastfeeding practices, duration of breastfeeding, use of depo-provera, resumption of menses, and other potential confounders did not attenuate the results.

Conclusion: These data show accentuated mobilisation of hip and WBLH bone mineral during lactation, and slower skeletal recovery post-lactation in HIV+ve Ugandan women initiated on lifelong ART (TDF-based) in pregnancy, compared to HIV-ve women. Studies are ongoing to understand the mechanisms and long term consequences for bone health and growth of the child, to inform interventions aimed at reducing bone loss in pregnant and lactating HIV+ve women on ART.

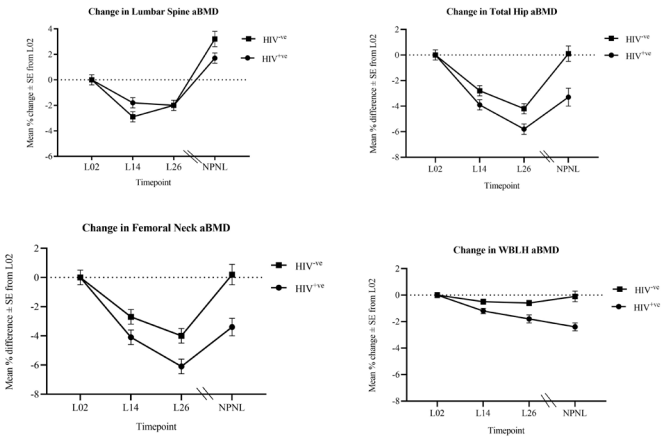


Figure 1: Change in aBMD during and after lactation in HIV^{+ve} and HIV^{-ve} Ugandan women

HIV^{-ve}= HIV-negative women (ART naïve), HIV^{+ve}= HIV-positive women initiated on lifelong ART during pregnancy (Option B+ ART, TDF-3TC-EFV, previously ART naïve), aBMD= areal Bone mineral density (g/cm^2), WBLH= whole body-less-head, SE=standard error, L02= 2 weeks of lactation, L14= 14 weeks of lactation, L26=26 weeks of lactation, NPNL= neither pregnant nor lactating. NPNL measurement was scheduled at 14 weeks post-lactation. Data were analysed using DataDesk 6.3.1 software (Data Description Inc, Ithaca, NY, USA). Results were obtained from Scheffés post hoc tests for group*visit (time point) interaction terms in hierarchical repeated measures ANOVA models that included subject (nested by group), group, visit, and group*visit interaction. Variables were transformed into natural logarithms (loge) before data analysis. Bars and error bars represent the mean±SE sympercent changes within groups.

769 HIGH BLOOD PRESSURE AND ADVERSE BIRTH OUTCOMES IN HIV+ AND HIV– SOUTH AFRICAN WOMEN

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Background: HIV+ women on ART are at increased risk of some adverse birth outcomes. Both HIV and ART may increase the risk of high blood pressure (BP) outside of pregnancy, but little is known about the prevalence and impact of high BP in pregnancy among HIV+ women.

Methods: We followed a cohort of HIV- and HIV+ pregnant women initiating TDF+XTC+EFV from first antenatal care visit (ANC) through delivery in Cape Town. Gestational age (GA) was estimated from ultrasound and BP from automated monitors. BP was categorized as normal (<120/80mmHg), elevated (120–129/ <80), stage 1 (>130–139 /or 80–89) or stage 2 hypertension (>140 / or >90). Multivariable modified Poisson regression was used to estimate associations between high (elevated or higher) versus normal BP and HIV status, as well as birth outcomes. We explored modification by HIV status for associations between BP and adverse birth outcomes. We addressed missing data with multiple imputation (n=50 imputations).

Results: In 1116 women (HIV+ 53%) with singleton live births (median gestation at 1st ANC, 20 weeks), 48% presented with high BP (53% HIV+ vs. 43% HIV-) at 1st ANC. HIV+ women were more likely to have high BP (RR 1.24; 95%CI 1.04-1.49), controlling for estimated pre-pregnancy body mass index (BMI), maternal age, gravidity, socioeconomic status, alcohol use and education. Overall 12% of infants were preterm (<37 weeks' gestation), 12% were low birthweight (LBW, <2500g), and 11% were small-for-GA (SGA, <10th percentile for GA). Compared to HIV- women, HIV+ women had more SGA (12% vs. 9%) and LBW (14% vs. 10%) infants, and a similar proportion of preterm births (13% vs. 12%). In multivariable analyses, there was no evidence that high BP increased the risk of preterm birth (RR 1.17, 95% CI 0.83-1.66), LBW (RR 1.14, 95% CI 0.82-1.57) or SGA (RR 1.00, 0.70-1.41), overall or when stratified by HIV status (Table). There was a trend towards high BP increasing the risk of preterm birth (RR 1.43 95% CI 0.85-2.38) and LBW (RR 1.30, 95% CI 0.83-2.04) in HIV- women, but not HIV+ women.

Conclusion: In this setting nearly half of all women had high BP at 1st ANC. HIV+ women initiating ART were more likely to have high BP, compared with HIV- women. There was no strong evidence that high BP increased the risk of LBW, SGA or preterm birth overall, but results differed somewhat by HIV status. The high prevalence of high BP in pregnancy, particularly in HIV+ women, requires further investigation.

Table. The relationship between high (elevated or higher) blood pressure (BP) versus normal BP at entry into antenatal care and adverse birth outcomes among 1,116 pregnant women in Cape Town, South Africa, overall and by HIV-infection status.

	Overall		HIV-uninfected		HIV-infected	
	N (%)	Adjusted[1] RR (95% CI)	N (%)	Adjusted[1] RR (95% CI)	N (%)	Adjusted[1] RR (95% CI)
Preterm birth	118 (12.1)		56 (11.5)		62 (12.6)	
Normal BP	58 (11.5)	1.00	29 (10.5)	1.00	29 (12.7)	1.00
High BP	66 (11.5)	1.17 (0.83, 1.66)	27 (12.8)	1.43 (0.85, 2.38)	33 (12.6)	1.05 (0.66, 1.69)
LBW	113 (11.9)		46 (10.0)		67 (13.7)	
Normal BP	58 (11.8)	1.00	27 (10.3)	1.00	31 (13.6)	1.00
High BP	55 (12.0)	1.14 (0.82, 1.57)	19 (9.6)	1.30 (0.83, 2.04)	36 (13.7)	1.09 (0.71, 1.67)
SGA	101 (10.6)		41 (8.9)		60 (12.2)	
Normal BP	58 (11.8)	1.00	30 (11.5)	1.00	28 (12.3)	1.00
High BP	43 (9.4)	1.00 (0.70, 1.41)	11 (5.6)	0.98 (0.60, 1.61)	32 (12.2)	1.05 (0.64, 1.72)

N (%) based on observed data. Effect estimates based on multiply imputed data (n=50 imputations) to address missing data in blood pressure at entry into antenatal care (12%), body mass index (12%), gestational age at enrollment (2.0%), alcohol use (11%), CD4 cell count (2.4%), LBW (3.2%), SGA (3.2%), LGA (3.2%), infant birthweight (3.2%). Preterm birth: <37 weeks gestation, LBW: low birthweight (<2500 grams); SGA: small for gestational age (<10th percentile birthweight for gestational age), LGA: large for gestational age (>90th percentile birthweight for gestational age). [1]Adjusted for gestational-age adjusted BMI category at entry into antenatal care, SES category, maternal age (linear spline), gravidity (linear spline), alcohol use, and educational attainment. Non-stratified models are additionally adjusted for HIV status. Stratified models among HIV-infected women are additionally adjusted for CD4 count at entry into antenatal care.

770 BLOOD PRESSURE TRAJECTORIES AND ASSOCIATED FACTORS IN PREGNANT HIV– AND HIV+ WOMEN

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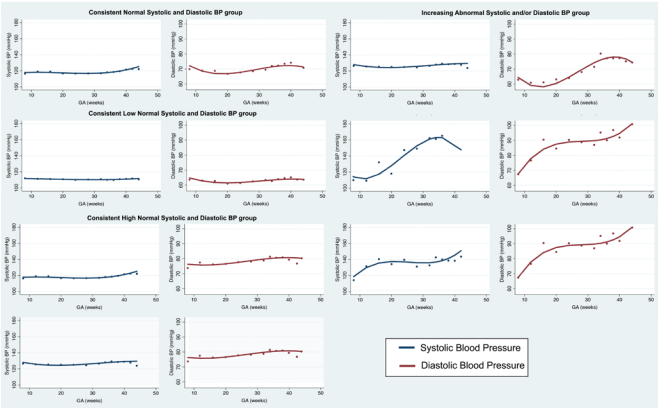
Background: Blood pressure (BP) levels are associated with maternal and fetal outcomes. While associations between HIV/ART and BP have been suggested, little is known about BP trajectories across gestation and their association with pregnancy outcome.

Methods: We recruited HIV+ and HIV- women at first antenatal visit at a large primary care facility in Cape Town, South Africa. HIV+ women, predominately on TDF+XTC+EFV regimen, initiated either pre-conception or during pregnancy. Automated BP measurements were used and a combination of ultrasound, last menstrual period and clinical exam for pregnancy dating. Group-based trajectory analysis identified distinct joint systolic and diastolic BP trajectory groups among women with ≥3 antenatal BP measurements. Multinomial regression assessed BP trajectory group associations with HIV/ART status and modified Poisson regression to determine preterm delivery (PTD) and low birthweight (LBW).

Results: Of 1583 women (median age 28y; median gestation at 1st ANC 18w), 37% were HIV+, of whom 54% initiated ART pre-conception (n=306) and 46% during pregnancy (n=265). We identified 7 systolic and diastolic joint trajectory groups combinations based on Bayesian information criterion, then classified as consistent normal (50%), low normal (25%), high normal (20%), and increasing abnormal 5%) (Figure 1). The proportion of women in the low normal group was higher among HIV+ than among HIV- women (28% vs. 23%), but differences

were not statistically significant in multivariate analysis (RR 1.27, 95% CI 0.98-1.63, reference category: consistent normal). Among HIV+ women, more women initiating ART in pregnancy were in the abnormal trajectory group than those initiating ART preconception (5% vs 2%), however association was observed (RR2.40, 0.94-6.15). Older (RR1.52, 1.11-2.10) and obese (RR2.06, 1.31-3.25) women were at increased risk of being in the high normal group. In multivariable analyses, low normal trajectory (RR0.59, 0.41-0.85) was associated with decreased risk of PTD, while high normal (RR1.47, 1.11-1.94) and abnormal trajectories (RR3.18, 2.32-4.47) were associated with increased risk of PTD, and abnormal with increased risk of LBW infants (RR3.25, 2.18-4.87).
Conclusion: We identified pregnant women with distinct antenatal BP trajectories, which were not associated with HIV/ART status. Further work is required to inform understanding of different BP trajectories in pregnancy, particularly in high HIV prevalent settings.

Figure 1: Joint systolic and diastolic group trajectory membership

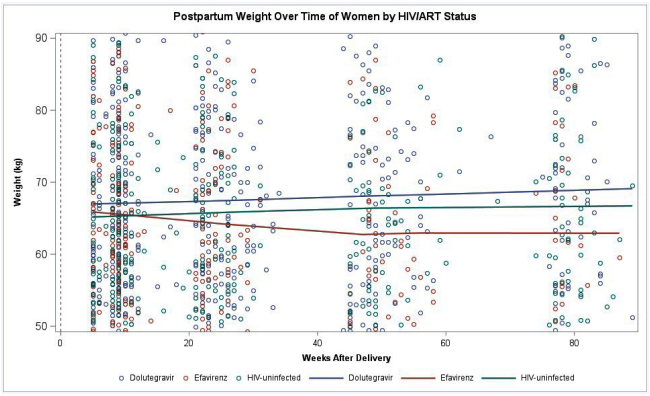


771 POSTPARTUM WEIGHT CHANGES IN WOMEN INITIATING DTG VS EFV IN PREGNANCY: DOLPHIN-2

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Background: There are growing concerns about weight gain with dolutegravir (DTG) use, with some suggestion of heterogeneity of effects across populations especially among women. However there are no data from pregnancy and the postpartum (PP) period.
Methods: DolPHIN-2 (NCT03249181) is an open label trial randomising (1:1) pregnant women from Uganda and South Africa (SA) initiating ART from 28w gestation to DTG vs efavirenz (EFV) plus 2 NRTIs. Maternal weights were measured using standardized procedures at enrolment, <14 days of delivery and at 6, 12, 24 and 48 weeks PP. For this secondary analysis we examined changes in PP weight and body mass index (BMI) between study arms.
Results: Enrolment took place between Jan and Aug 2018, and follow-up data were censored Sept 2019; 230 women (mean age, 28y) were included with median follow-up of 60 months. At enrolment (median gestation, 31w) the mean weight and BMI was 74 kg and 28 kg/m_2, respectively, with no differences between trial arms but higher third trimester weight in SA (mean, 81 kg) versus Ugandan (mean, 68 kg) sites. 73%, 61% and 3% of women reported breastfeeding the infant at 12, 24 and 48w PP, respectively, with no differences by arm. Across both arms and sites, mean change in weight from enrolment to 6w PP was -5.9 kg, with mean weight approximately constant from 6 to 48w PP. However this masked notable inter-site differences. In Uganda, there was a small non-significant decrease in mean weight from 6 to 48w PP that was more marked in the EFV arm (DTG: 63.6 to 63.2 kg; EFV: 60.6 to 59.8 kg; p=0.28). In SA, there was a notable but non-significant increase in mean weight over the same period that was more marked in the DTG arm (DTG: 76.1 to 78.3 kg; EFV: 73.0 to 73.7 kg; p=0.33). After adjusting for site and enrolment weight, the overall mean difference in weight change, 48w-6w PP for DTG-EFV, was 1.00 kg (95% CI -0.98 to 2.97; p=0.32). This difference was larger in SA (1.30 kg; 95% CI -2.21 to 4.80) than in Uganda (0.75 kg; 95% CI -1.48 to 2.97; p for interaction=0.82). Similar findings were observed for BMI throughout.
Conclusion: These randomised data show no differences in PP weight changes between DTG and EFV in women initiating ART late in pregnancy. Substantial PP weight gain among SA women points to potential heterogeneity across populations that requires further investigation.

772 DOLUTEGRAVIR USE IS ASSOCIATED WITH HIGHER POSTPARTUM WEIGHT COMPARED TO EFAVIRENZ

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Background: Postpartum weight retention impacts cardiometabolic risk. Recent studies show higher weight gain with dolutegravir (DTG)-based antiretroviral therapy (ART) compared to other ART. We assessed the association of DTG with postpartum weight over time in women with HIV (WHIV) in Botswana using comparator groups of women on efavirenz (EFV) and HIV-negative (HIV-) women.
Methods: The Tshilo Dikotla study enrolled pregnant HIV- women and WHIV on either tenofovir (TDF)/emtricitabine or lamivudine (XTC)/DTG or TDF/XTC/EFV initiated during or before pregnancy. This analysis included women with weight measurements 1 to 18 months postpartum. Mixed models were fit to assess the association between HIV/ART status and postpartum weight over time, adjusting for confounders. Interaction terms between time and HIV/ART group were evaluated to assess for differences in weight trajectories. Subgroup analysis was performed among WHIV to further assess the association of DTG vs EFV and postpartum weight, adjusting for HIV specific factors.
Results: Of 406 women, 170 received DTG and 114 EFV. Women on DTG or EFV were older than HIV- women (median age 28 vs 33 vs 25 years respectively, p<0.01), and fewer had a college education (13.5% vs 4.4% vs 29.5% respectively, p<0.01). Average weight gain per week (wk) between 2nd and 3rd trimester was highest in HIV- women (0.3 vs 0.2 for DTG vs 0.1 kg/wk for EFV, p<0.01) as was breastfeeding duration (35.7 vs. 19.0 for DTG vs. 22.6 wks for EFV, p<0.01). No differences in income, gestational diabetes (GDM), gestational age at delivery, or BMI at 1 month postpartum were noted across groups. Among WHIV, no differences in CD4 or log viral load at enrollment were noted between ART group; more women on EFV were on their ART at conception (86% vs. 35.3%, p<0.01). Compared to HIV- women, WHIV on DTG had similar postpartum weight through 18 months but were on average 5 kg heavier postpartum than WHIV on EFV (β=5.0, p<0.01) after adjusting for age, GDM, breastfeeding duration, and weight gain between 2nd and 3rd trimester. (Fig) No differences in slope trajectories were noted between groups. This association persisted in subgroup analysis of WHIV even after further adjusting for CD4, viral load, and ART at conception (β=2.4 for DTG vs. EFV, p=0.04).
Conclusion: WHIV on DTG have persistently higher weight through 18 months postpartum than those on EFV in Botswana but similar weight to HIV- women. Further studies to assess mechanisms of postpartum weight retention are needed.



773 OBESITY, GESTATIONAL WEIGHT GAIN, AND ADVERSE BIRTH OUTCOMES IN SOUTH AFRICAN WOMEN

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Background: HIV and/or ART may increase adverse birth outcomes including low birthweight (LBW) and small for gestational age (SGA) infants. In parallel, there are increasing concerns regarding obesity (BMI ≥30kg/m_2) in HIV+ individuals on ART; in pregnancy obesity is known to contribute to high birthweight (HBW) and large for gestational age (LGA) infants. However, there are few data on obesity and gestational weight gain (GWG) in HIV+ pregnant women on ART.

Methods: We examined obesity and high GWG (>75thpercentile), and associations with birth outcomes in HIV+ (predominantly using TDF+XTC+EFC) and HIV- women in Cape Town. We consecutively enrolled 2828 pregnant women ages ≥18y at 1stantenatal visit. Follow-up was through routine medical records, with repeated GWG assessments available for the subset of 471 HIV+ women enrolled <=24 weeks gestation in an intensive study. Associations between obesity, high GWG and birth outcomes (birthweight and size for GA) were assessed via multinomial logistic regression adjusting for age, ART status, GA at enrolment and parity.

Results: At 1st antenatal visit (median gestation, 19w), median BMI was 30 kg/m_2 (IQR, 26-35) in both HIV+ (36% of all participants) and HIV- women, with obesity prevalence of 49% and 50%, respectively. In the HIV+ subset, median GWG was 0.25 kg/week (IQR, 0.11-0.42); high GWG prevalence was 25%. In adjusted models, obesity in HIV- women was significantly associated with reduced risk of LBW (aOR 0.47, 95% CI 0.26-0.84) and SGA (aOR 0.51, 95% CI 0.32-0.82), and with increased risk of HBW (aOR 3.00, 95% CI 1.13-7.99) and LGA (aOR 2.13, 95% CI 1.28-3.55). In HIV+ women, obesity was also significantly associated with reduced risk of LBW (aOR 0.43, 95% CI 0.23-0.80) and SGA (aOR 0.59, 95% CI 0.35-0.99), and non-significantly with increased risk of HBW (aOR 1.30, 95% CI 0.46-3.65) and LGA (aOR 1.34, 95% CI 0.73-2.48). In the HIV+ subset, high GWG was associated with increased risk of HBW (aOR 4.51, 95% CI 1.67-12.15) and LGA (aOR 2.52, 95% CI 1.13-5.59).

Conclusion: Obesity in pregnancy and high GWG are prevalent in this setting in both HIV+ and HIV- women. High GWG in HIV+ women was associated with increased risk of HBW and LGA, while obesity was associated with reduced risk of LBW and SGA. Outcomes of HIV+ women may now parallel those of HIV- women.

Table 1. Association between obesity, high GWG and adverse birth outcomes among HIV+ women with live singleton births in the overall and subset cohorts in Cape Town, South Africa

	BMI (kg/m²)			GWG (kg/week)		
	Normal n = 228	Obese n = 519		Normal n = 351	High n = 120	
		aOR (95% CI)	p-value		aOR (95% CI)	p-value
Birth weight (g)						
Low (<2500)	1.00 (Ref)	0.43 (0.23-0.80)	0.008	1.00 (Ref)	1.18 (0.58-2.42)	0.650
High (≥4000)	1.00 (Ref)	1.30 (0.46-3.65)	0.621	1.00 (Ref)	4.51 (1.67-12.15)	0.003
Size for GA (centile)						
Small (<10th)	1.00 (Ref)	0.59 (0.35-0.99)	0.047	1.00 (Ref)	1.17 (0.65-2.08)	0.601
Large (>90th)	1.00 (Ref)	1.34 (0.73-2.48)	0.344	1.00 (Ref)	2.52 (1.13-5.59)	0.023

774 FACTORS ASSOCIATED WITH GESTATIONAL DIABETES IN HIV+ AND HIV– WOMEN IN PUNE, INDIA

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Background: HIV is associated with an increased risk of diabetes, but its association with gestational diabetes (GDM) is still debated. We undertook this study to investigate the prevalence of GDM among HIV+ and HIV- pregnant women and its associated risk factors in each group.

Methods: From 2016 to 2019, we conducted a prospective, longitudinal cohort study designed to characterize the effects of pregnancy on the immune response to M. tuberculosis (PRACHITi) in Pune, India. The study enrolled HIV+ and HIV- pregnant women in their 2nd trimester and followed them through 1 year postpartum. All women were screened with the WHO-recommended oral glucose tolerance test (OGTT), to diagnose GDM. We identified the prevalence of GDM in HIV+ and HIV- women among the whole cohort. A case-control study was then done to identify risk factors. Women with a positive OGTT were matched to controls based on HIV status and age in a 1:4 ratio.
Prevalence of GDM was compared by HIV status with Fisher's exact test. Demographics were compared between cases and matched controls via chi-square or Mann-Whitney U test. Univariate and multivariate logistic regression was used to determine factors associated with GDM.

Results: Among enrollees, 11 (13.9%) of 79 HIV+ and 10 (6.5%) of 155 HIV- had GDM (p=0.06). In the case control study of the 21 GDM and 74 matched non-GDM controls, median pre-pregnancy BMI was 21.7 kg/m_2 (IQR 19-24.2). Median CD4 in HIV was 420 cells/mm_3, 5 (1.1%) were on protease-inhibitor (PI)-based antiretroviral therapy (ART), and 37 (82%) were on NNRTI-based ART. Weight (54.3 vs 48.9 kg, p=0.02) at study entry, MUAC (26.4 vs 23.7 cm, p=0.04) at study entry, and pre-pregnancy BMI (24.1 vs 21.2 kg/m_2, p=0.00) was significantly higher among cases than controls. Among HIV+, weight at study entry and 3rdtrimester, MUAC at study entry and 3rdtrimester, and pre-pregnancy BMI were significantly higher among cases than controls. Among HIV-, only pre-pregnancy BMI was significantly higher. Use of PIs showed a trend toward significant association.

Conclusion: In our study of pregnant women in India, HIV+ women had a higher prevalence of GDM than HIV- women, which was incompletely explained by PI use. Higher MUAC, weight, and BMI were associated with increased risk of GDM among HIV+ but not HIV-participants. Ongoing studies are identifying the pathogenesis behind this increased risk.

775 CABOTEGRAVIR PHARMACOKINETIC TAIL IN PREGNANCY AND NEONATAL OUTCOMES

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Background: Cabotegravir (CAB) is a long-acting (LA) HIV integrase inhibitor in Phase 3 development for HIV treatment in combination with rilpivirine LA, and as monotherapy for HIV prevention. Injectable CAB LA, given monthly or every 2 months, maintains plasma concentrations that may persist for a year or longer following discontinuation. Nonclinical reproductive toxicology studies of CAB have not identified a birth defect risk at supratherapeutic exposures. We evaluated CAB pharmacokinetics (PK) in HIV-infected women becoming pregnant and neonatal outcomes to date in ViiV-Sponsored trials.

Methods: As of December 7, 2018, ≥ 594 HIV-infected or un-infected females of reproductive potential have been exposed to ≥1 dose of CAB (oral/LA) through Phase 3 in ViiV-sponsored clinical trials. Per protocol, CAB troughs were obtained pre-injection with dosing discontinued upon pregnancy detection, however PK sampling continued quarterly for 52 weeks after last injection. Available CAB PK collected pre-pregnancy and during long term follow-up to evaluate the PK tail during pregnancy, delivery, and post-partum were summarized with birth outcomes.

Results: Thirteen pregnancies were reported during CAB dosing (4 oral CAB; 9 CAB LA), 4 resulting in live births (1 in DAIDS HPTN077 study; conception post CAB LA discontinuation), 5 terminated electively, and 4 with miscarriage in first 9 weeks of gestation. No cases of birth defects have been reported. Three HIV-infected women receiving CAB LA 400mg IM monthly injections (range: 16-176 weeks on therapy) became pregnant with subsequent live birth outcomes. All were virologically suppressed with pre-dose CAB concentrations of 2.41-4.63 µg/mL just prior to pregnancy and 2.10-5.04 µg/mL at time of pregnancy confirmation. Following CAB LA discontinuation, residual CAB concentrations remained measurable throughout pregnancy with a predicted concentration of ~0.5 µg/mL(3x PA-IC_{90} [0.166 µg/mL]) at delivery and remaining detectable post-partum (range: 2-23 weeks) in 2/3 women.These data are consistent with absorption-rate limited PK.

Conclusion: Pre-pregnancy CAB trough concentrations were consistent with population estimates for monthly dosing and declined slowly following drug discontinuation in pregnancy with predicted concentration 3x PA-IC_{90} at time of delivery in 2 of 3 HIV-infected women with live birth outcomes. CAB PK tail in pregnancy was within the expected range for non-pregnant women. Pregnancy surveillance in the treatment and prevention program continues.

Maternal CAB Concentration (µg/mL) Profile Pre-Pregnancy and During PK Tail in Pregnancy and Post-Partum			
Event	Subject No. (# weeks relative to gestational week or delivery date)		
	Subject #1	Subject #2	Subject #3
Duration of CAB LA exposure prior to pregnancy (weeks)	16	176	32
Last available pre-pregnancy CAB trough concentration	4.63	2.41	2.95
PK at pregnancy confirmation visit	4.83 (7 weeks)	2.10 (5 weeks)	5.04 (4 weeks)
Residual PK 1	2.7 (15 weeks)	1.13 (14 weeks)	0.295 (13 weeks)
Residual PK 2	1.13 (28 weeks)	0.439 (30 weeks)	Non-quantifiable (NQ) (28 weeks)
Predicted PK at delivery*	0.5 (39 weeks, healthy infant, birth weight 2800g)	0.5 (37 weeks, healthy infant, birth weight 2666g)	NQ (measured value) (38 weeks, healthy infant, birth weight unknown)
Residual PK 3	0.82 (5 weeks post-partum)	0.578 (2 weeks post-partum)	NQ (6 weeks post-partum)
Residual PK 4	0.054 (23 weeks post-partum)	0.353 (15 weeks post-partum)	NA
*Prediction based on median half-life derived from population PK model			

776 RILPIVIRINE IN HIV-1–INFECTED WOMEN INITIATING PREGNANCY: TO SWITCH OR NOT TO SWITCH?

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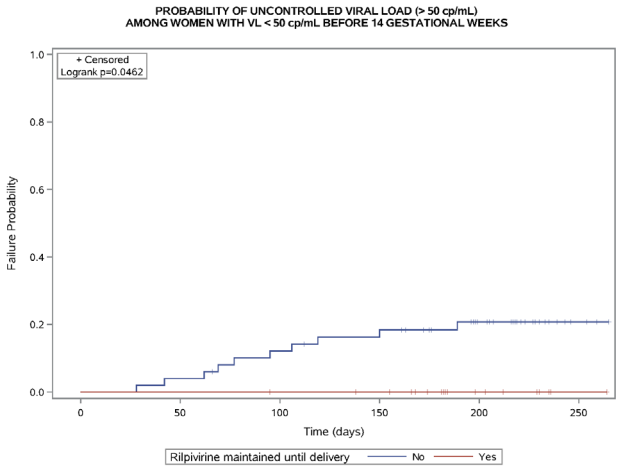
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Background: Data about safety and efficacy of rilpivirine (RPV) during pregnancy remain scarce. Because RPV plasma concentrations are reduced during 2nd and 3rd trimesters of pregnancy and viral breakthroughs were observed, French guidelines recommend switching to RPV-free cART during pregnancy. This study aimed to describe the characteristics of women initiating pregnancy while on RPV and to compare the outcome of virologically-suppressed subjects continuing RPV until delivery or switching to RPV-free cART.

Methods: We included all women in the French Perinatal HIV cohort receiving RPV at the time of conception in 2010-2018, with prospective, monthly follow-up of pregnant women and pediatric follow-up from birth to 18–24 months. We compared maternal and infant characteristics in case of maintain of RPV throughout pregnancy or switch to RPV-free cART. In women with available results of HIV-1 viral load (VL) before 14 weeks of gestation (WG) and viral suppression (VL<50 copies/mL) while on RPV, we compared the probability of viral rebound (≥50 copies/mL) during pregnancy between those continuing RPV versus those switching to RPV-free cART.

Results: Overall, 248 women were receiving RPV, mostly combined with TDF/FTC in single-tablet regimens (93.5%). At the beginning of pregnancy, most women were virologically suppressed (88.2%) and median CD4 count was 564/µL (IQR: 431-716). During pregnancy, 185 women (74.6%) switched to RPV-free cART (mostly IP/r + NRTI(s)), at a median gestational age of 8.0 WG (IQR: 6.0 – 12.0). The VL nearest delivery was <50 copies/mL in 95.7% of women. Few adverse events occurred during pregnancy (birth defects: 3.8%; ectopic pregnancies: 0.4%; stillbirths: 1.6%; preterm deliveries: 8.9%; very preterm deliveries; 2.8%) with similar proportions in patients continuing RPV and in those switching to RPV-free cART. The characteristics of newborns were similar between groups. No child was infected with HIV. Among 69 women with documented viral suppression before 14 WG, the risk of viral rebound during pregnancy was significantly higher when switching to a RPV-free cART than when continuing RPV until delivery (21.0% versus 0.0%, p = 0.046) (Figure).

Conclusion: Continuing RPV in virologically-suppressed women initiating pregnancy may be associated with better virological outcome than changing cART. Larger studies are required to confirm these results and establish the safety of fetal exposure to RPV in the long term.



777 COST-EFFECTIVENESS OF BROADLY NEUTRALIZING ANTIBODIES FOR INFANT HIV PROPHYLAXIS

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Background: Injectable infant prophylaxis with a broadly neutralizing antibody (bNAb) could help overcome gaps in the prevention of vertical HIV transmission cascade by providing long-acting protection from postnatal transmission, but there are few insights into the potential cost-effectiveness of this strategy.

Methods: Using the Cost-effectiveness of Preventing AIDS Complications (CEPAC)-Pediatric model, we simulated children known to be HIV-exposed from birth through death in South Africa. We compared four strategies: standard of care oral prophylaxis for 6-12 weeks per WHO guidelines (SOC), and oral prophylaxis plus a bNAb given at birth (bNAb birth), birth and 3 months (bNAb birth+3 m), or every 3 months throughout breastfeeding (bNAb extended). Base-case model inputs, varied in sensitivity analyses, included: prophylaxis uptake (oral: 50-86%, bNAb: 54-96%, each by month postpartum), preventive efficacy (oral: 90%, bNAb: 80%), duration of effect (bNAb: 3m), costs (oral: $7-11/m, bNAb: $60/dose), and mean breastfeeding duration (both: 6m). Simulated transmission risks were based on maternal ART use, viral load, and breastfeeding status. Model outcomes included total pediatric HIV incidence, pediatric life-expectancy (LE), lifetime HIV-related per-person costs (2019 USD), and incremental cost-effectiveness ratios (ICERs) calculated from discounted (3%/y) LE and costs. We defined cost-effective as an ICER <$900/YLS.

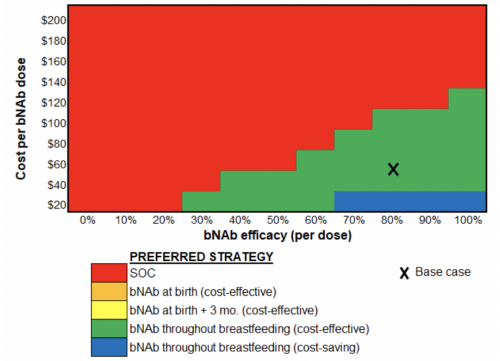
Results: All bNAb strategies led to lower total pediatric HIV incidence and greater LE, but greater lifetime HIV-related costs than SOC (Fig 1). bNAb extended was the preferred strategy and was cost-effective: ICER $420/YLS vs. SOC. bNAb extended remained the preferred strategy unless bNAb efficacy was <60% or costs exceeded $100/dose. When the analysis was restricted to only high-risk infants, as defined by WHO infant prophylaxis guidelines, bNAb extended remained the preferred strategy and was cost-effective at base case bNAb costs and efficacy.

Conclusion: At current estimates of efficacy and costs as high as $100/dose, bNAb prophylaxis for children who are HIV-exposed throughout breastfeeding would be a cost-effective strategy to prevent vertical HIV transmission in South Africa. More data on the efficacy of bNAb prophylaxis for infants and its implementation costs in sub-Saharan Africa are needed.

Fig 1. Preferred strategy for infant prophylaxis at a cost-effectiveness threshold of ICER <$900/YLS

	Pediatric HIV incidence (%)	LE from birth (life-years)	HIV-related costs[a] (2019 USD)	ICER[b] ($/YLS)
Base case (bNab efficacy: 80%, costs: $60/dose)				
SOC	3.7	61.27	300	*Ref*
bNAb birth	3.4	61.37	330	Ext. dominance[c]
bNAb birth+3 m	3.2	61.50	340	Ext. dominance[c]
bNAb extended	3.0	61.60	350	420

USD: United States dollars, **ICER**: incremental cost-effectiveness ratio, **YLS**: years of life saved.
[a]Costs discounted at 3%/year. [b]Calculated from discounted life expectancy (not shown) and costs, rounded to the nearest $10. [c] Less cost-effective than another more effective strategy.



778 RISK OF VERTICAL TRANSMISSION FROM MOTHERS WITH PERINATAL HIV INFECTION IN ZIMBABWE

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Background: Data from all PHIV women 18 years and above active in care by April 2019 in Mpilo ART Clinic (Zimbabwe) with at least one pregnancy in the last five years were included in the study and compared with a sample of HIV+ women not perinatally infected meeting the same criteria. Demographic and clinical data was extracted from databases and complemented with individual interviews to get information on pregnancy outcomes and HIV status of exposed infants. For data analysis, proportions were compared using Chi square. Logistic regression was used to identify predictors of MTCT.
Methods: Data from all PHIV women 18 years and above active in care by April 2019 in Mpilo ART Clinic (Zimbabwe) with at least one pregnancy in the last five years were included in the study and compared with a sample of HIV+ women not perinatally infected meeting the same criteria. Demographic and clinical data was extracted from databases and complemented with individual interviews to get information on pregnancy outcomes and HIV status of exposed infants. For data analysis, proportions were compared using Chi square. Logistic regression was used to identify predictors of MTCT.
Results: Out of 564 PHIV women in the ART clinic database, 148 accepted to be interviewed and provided complete information on 166 pregnancies. Similarly, 152 non-Perinatally infected HIV positive (non-PHIV) women were interviewed yielding 174 pregnancies. Women in the PHIV group were younger (median age 20 years old versus 34 in non-PHIV) and have been longer in HIV care at the time of pregnancy (median 9 years versus 6 in non-PHIV). 81% of all participants have a VL test in the previous 12 months, with 66.4 % of PHIV women and 87.2% of non-PHIV women achieving a VL < 1,000 copies/ml. On pregnancy outcomes, risk of abortion/stillbirth was double in the PHIV group (24.1% [40/166] vs (13.8% [24/174], OR: 2.0 p: 0.01). MTCT rate was slightly higher in PHIV women (8.7% [11/126] vs 7.3%% [11/150]) but the difference was not statistically significant. When adjusting for age, education, last VL and time in HIV care at the time of pregnancy, mode of acquisition of HIV of the mother was not independently associated with the risk of MTCT.
Conclusion: Our results from a large ART clinic in Zimbabwe do not confirm findings from a US-based cohort where MTCT rate was more than double in PHIV mothers compared with those with horizontally acquired HIV. We identified, however, an increased risk of abortion/stillbirth in PHIV women, as well as, a high prevalence of unsuppressed VL what highlights the importance of intensive VL monitoring to optimize ART in that group.

779 HIV SEROCONVERSION DURING PREGNANCY AT ROUTINE ANTENATAL CARE CLINICS IN BOTSWANA

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Background: Risk of HIV acquisition during pregnancy and postpartum is high in sub-Saharan Africa. While current prevention of mother-to-child HIV transmission (PMTCT) programs are designed to detect and treat women with chronic HIV infections, women who are newly infected or acquire HIV after initial antenatal testing may have infections that go undetected. Botswana was the first African country to routinize HIV testing for pregnant women attending antenatal care (ANC) and ANC attendance in Botswana is high at 97%. Repeat HIV testing during ANC is both time and cost intensive. We evaluated the frequency of detecting previously undiagnosed HIV infections among routine ANC attendees in Botswana.
Methods: From January 2018 to September 2019, a national HIV testing program was implemented at 139 ANC clinics in 15 districts in Botswana. Electronic data captured information on demographics (age, sex, citizenship), HIV testing (date, location, result) and linkage to antiretroviral treatment (ART). For this analysis, individuals who previously tested HIV-positive prior to their first identified ANC visit were excluded, enabling an evaluation of frequency of detecting previously undiagnosed HIV. Among HIV-negative individuals who had a repeat HIV test at a subsequent ANC visit, we measured time to re-testing and frequency of HIV seroconversion during ANC follow-up.
Results: In total, 29,583 women (median age 26 years, IQR 22-31) were tested for HIV at ANC clinics and 97% tested HIV-negative (28,735). Of those, 28% (8,005) had a repeat HIV test at a subsequent ANC visit; median time to HIV re-testing was 92 days (IQR 70-112) and frequency of HIV seroconversion was 0.3% (23). ART initiation among all women who tested HIV-positive at ANC (854) was 88% (686/782). Women who tested HIV-negative were similar in age, citizenship, and urban testing location to those who tested HIV-positive; women who initiated ART were similar in age and urban testing location, but not citizenship status (99% citizens vs 52% non-citizens, p<0.001), to those that did not initiate ART, Fig. 1.
Conclusion: In this large evaluation, we detected previously undiagnosed HIV infection and seroconversion among ANC attendees in Botswana, despite high ANC testing and PMTCT coverage. To reach elimination of MTCT, repeat HIV testing and primary prevention during ANC remain key components of PMTCT programs.

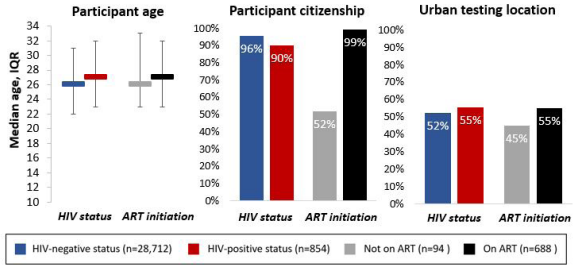


Fig. 1. Characteristics of HIV-negative and HIV-positive women (newly diagnosed during pregnancy) who HIV tested within routine ANC clinics in Botswana

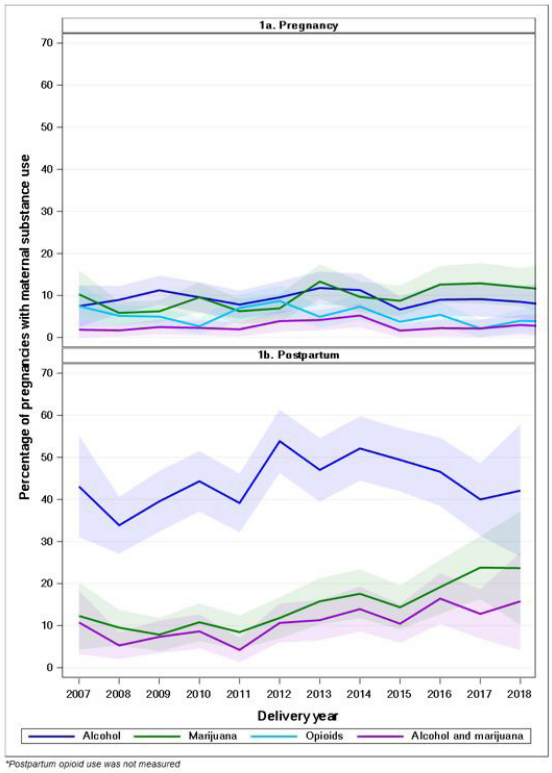
780 TRENDS IN MARIJUANA, ALCOHOL, AND OPIOID USE IN PREGNANT AND POSTPARTUM HIV+ WOMEN

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Background: Concurrent with the opioid epidemic in the United States (US), rates of marijuana use have risen among pregnant and non-pregnant women of reproductive age. Amid evolving legal and social changes, little is known about substance use among pregnant and postpartum women living with HIV (WLHIV).

Our objective was to evaluate trends over time in marijuana, alcohol, and opioid use during pregnancy and the first year postpartum among US WLHIV.
Methods: We analyzed data on marijuana, alcohol, and/or opioid use from the Surveillance Monitoring for ART Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study. SMARTT has been enrolling pregnant WLHIV at 22 US sites since 2007. SMARTT-enrolled pregnant WLHIV from 2007-2019 with self-reported substance use data available in pregnancy, 1 year postpartum, or both were included (postpartum opioid use not collected). Prevalence of any marijuana, alcohol, opioid, and concomitant alcohol and marijuana use was calculated by calendar year, separately for pregnancy and postpartum periods. We fit log binomial general estimating equation models to evaluate linear trend in use over time, accounting for repeat pregnancies.
Results: Substance use data were available for 2,926 pregnancies from 2,310 WLHIV. Women were primarily non-Hispanic black (63.5%) or Hispanic (28.1%) and aged 25-39 years (67.6%). Between 2007 and 2019, marijuana use during pregnancy increased from 7.1% to 11.7% (Figure 1a). Alcohol and opioid use in pregnancy were unchanged over this period (mean prevalence 9.4% and 5.2% respectively). Alcohol and marijuana use were more prevalent in the 1st trimester compared to the 2nd or 3rd, while opioid use was similar across trimesters. In the postpartum period, alcohol and marijuana use were common (mean prevalence 44.4% and 13.6% respectively), with marijuana increasing over time (Figure 1b). On average, risk of marijuana use increased each year by 6% and 11% for pregnancy and postpartum, respectively (Relative Risk [RR] 1.06, 95% Confidence Interval [CI] 1.03-1.10; RR 1.11, 95% CI 1.06-1.16). Postpartum combined alcohol and marijuana use increased from 6.7% to 16.4%, a 10% per year increase (RR 1.10, 95% CI 1.05-1.15).
Conclusion: Opioid use among pregnant and postpartum WLHIV in SMARTT remained low and stable despite the US opioid epidemic, whereas the prevalence of marijuana use increased between 2007 and 2019, as did postpartum concomitant alcohol use. Increasing marijuana use in pregnant and postpartum WLHIV warrants further attention.

Figure. Maternal Alcohol and Substance Use in Pregnancy and the Postpartum Period by Delivery Year among Women Living with HIV in the United States



*Postpartum opioid use was not measured

781 TRANSMISSION, VARIATION, AND EVOLUTION OF IN UTERO TRANSMITTED HIV-1

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Background: HIV-1 can be transmitted from infected mothers to their fetuses during pregnancy. However, the transmission timing, viral diversity, and selection pressure on fetal viruses during pregnancy is poorly understood. A better understanding of transmission mechanisms will be key to further reduce the mother-to-child-transmission (MTCT) rate.
Methods: Viral RNA was extracted from plasma of 12 mothers (at birth) and their in utero infected infants (from birth to 3 months after delivery). All infants were HIV-1 positive by detecting HIV-1 DNA genome in infant or cord blood at birth. Multiple env gene sequences were obtained from each sample using single genome amplification (SGA). Genetic diversity, phylogenetic trees, highlighter plots were used to infer transmitted/founder (T/F) viruses in the infants and to study the viral populations in both mothers and infants. Infection time was estimated using the Poisson-Fitter tool. Selection signatures in paired maternal viruses were analyzed using SNAP and amino acid sequence alignments.
Results: A total of 846 env gene sequences (317 from mothers and 529 from infants) were obtained. Homogenous viral populations were found in 6 infants and 2 were infected with 2 to 3 T/F viruses. The estimated time of infection for these infants is within 2 months (37-3 days) before delivery. High genetic diversity was found in 4 other infants. The time of infection for these 4 infants could not be reliably estimated by current computational analysis tools, possibly due to extensive recombination in the samples. The high genetic diversities strongly suggest that the fetuses were infected in early pregnancy. SNAP and amino acid sequence analysis showed that C1, V1 and V5 regions in the infant Env sequences were highly variable. Some of these signatures in infant viruses were distinct from mother, indicating that placentally-transmitted viruses were under strong selection pressure in fetuses. Higher IgG-mediated neutralization potency was found in some placental plasma compared to that of peripheral plasma from the same mother, suggesting possible selection of HIV-neutralizing IgG subpopulations for placental transfer.
Conclusion: The majority of in uterus transmissions occur in the late third trimester during pregnancy, possibly due to the thinning placenta membrane. The variable regions in the infant env sequences suggest that immune system in fetuses is able to exert strong selection pressure on fetal viral population.

782 MATERNAL RISK STRATIFICATION TO IDENTIFY HIGH-RISK INFANTS FOR HIV BIRTH TESTING

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Background: In 2017, Zimbabwe adopted a modified version of the World Health Organization 2016 recommendation on HIV birth testing by offering HIV testing at birth only to infants at "high risk" of HIV transmission (criteria based on timing of maternal diagnosis, viral load, and ART adherence). However, there is paucity of evidence on sensitivity, specificity and predictive value for this approach. This study focuses on assessing the sensitivity and specificity of birth testing "high risk" infants only compared to birth testing of all HIV-exposed infants.
Methods: This was an analytic cross-sectional study. A five-question maternal risk screening tool based on the national guidelines definition of risk was administered to mothers of all HIV-exposed infants identified within 48 hours of birth at 10 study sites from November 2018 to July 2019. At these sites, a nucleic acid HIV test was performed on all HIV-exposed infants irrespective of risk status. Univariate and bivariate analysis were used to estimate the performance of the risk screening tool.
Results: A total of 2,080 infants were enrolled. A nucleic acid test for HIV was successfully performed on 1,970 infants (95%) of whom 266 (13.5%) were classified as high risk infants. HIV prevalence for all infants tested was 1.5% (95% CI: 1%—2%) while prevalence among high risk infants and low risk infants was 6.8% (95%CI: 3.7%—9.8%) and 0.6% (95%CI: 0.3%—1%) respectively. There was a significant association between maternal HIV transmission risk status and HIV infection (p-value <0.001). Sensitivity and specificity of the maternal risk screening tool was at 62.1% (95%CI: 44.4%—79.7%) and 87.2% (95%CI: 85.7%—88.7%), respectively; positive and negative predictive values were 6.8% (95%CI: 3.7%—9.8%) and 99.4% (95%CI: 99.0%—99.7%) respectively Sensitivity and specificity in detecting HIV status

varied for different individual screening questions. A 'yes' response to starting ART after 32 weeks' gestation had the highest sensitivity in predicting HIV infection 58.6%, (95%CI: 40.7—76.5) and a 'yes' to non-adherence to ART had the lowest sensitivity 7.1% (95%CI: -2.4%—16.7%).

Conclusion: Although there was a significant association of maternal risk stratification with risk of infant infection and the negative predictive value of the risk screening tool was relatively high, the sensitivity was relatively low, and 38% of infants infected at birth would be missed if birth testing was based solely on a positive risk screen.

Risk-Strata Result	Infant HIV Infection Status		Total	Predictive value (PV)
	Positive	Negative		
High risk	18	248	266	Positive PV = 6.8%
Average risk	11	1693	1704	Negative PV = 99.4%
Total	29	1941	1970	
	Sensitivity 62.1%	Specificity 87.2%		

783 POINT-OF-CARE TESTING IMPROVES EARLY INFANT DIAGNOSIS IN THE PUBLIC HEALTH SECTOR

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Background: Despite progress in the scale-up of early infant diagnosis (EID) programs in the last decade, in 2018 only 51% of HIV-exposed infants received a diagnostic nucleic-acid test within the recommended two months of birth. Point-of-care (POC) testing has been shown to dramatically increase rates of early diagnosis and initiation of ART for HIV-positive infants. As national programs in sub-Saharan Africa incorporate POC EID technologies, it is critical to document the impact of POC EID within routine public sector programs and understand implications for national scale-up.

Methods: A 6-month pre-/post-evaluation comparing conventional laboratory (pre) to POC (post) EID testing using either Cepheid GeneXpert or Abbott mPima devices was conducted in 36 facilities across three countries, Cameroon, Ethiopia and Zimbabwe, between 2018-2019. On-site trainings for POC devices were held for facility and laboratory staff prior to implementation. Data were retrospectively extracted from routine records at health facilities for all infants (aged 0-2 years) tested. The primary outcome was the proportion of infants tested in which the infant's caregiver received the test results within 28 days of sample collection (WHO recommendation, 2010). ART initiation within 28 days of sample collection was also analyzed for HIV-positive infants.

Results: Before POC introduction, 2465 EID tests were conducted, of which 123 (5.0%) were HIV-positive. After POC implementation, 4288 tests were conducted, 189 (4.4%) of which were HIV-positive. POC EID resulted in faster turnaround times [median of 0 days (POC) vs. 40 days (conventional)] and POC EID results were more than four times as likely to be received by a caregiver within 28 days of sample collection (19.5% for conventional vs. 86.1% for POC; RR: 4.67; 95% CI: 1.51-7.83). The proportion of caregivers receiving results within 28 days of POC sample collection varied from 76.0% in Cameroon to 96.2% in Ethiopia (Table 1). Infants tested on POC had a much greater probabilty of initiating ART within 28 days (9.8% for conventional vs. 67.2% for POC; RR: 6.72; 95% CI 2.13-11.32).

Conclusion: POC EID significantly improved rates of test result returned to caregiver and ART initiation within routine care at public health facilities. However, in some settings gaps remained in timely results return and treatment initiation. To maximize the impact of faster testing through POC, programs must focus on ensuring test results are used and follow-on care is provided.

Table 1: Multi-country comparison of Conventional and Point-of-care early infant diagnosis on caregiver result received and ART initiation

	Conventional (pre)			POC (post)				
	N	%	(95% CI)	N	%	(95% CI)	RR	(95% CI)
Caregiver result received within 28 days								
Cameroon	318	12.9%	(3.1%-40.3%)	512	76.0%	(27.0%-96.4%)	5.89	(1.56-22.34)
Ethiopia	117	4.3%	(1.9%-9.4%)	131	96.2%	(87.6%-98.9%)	22.50	(9.91-51.10)
Zimbabwe	2030	21.4%	(8.8%-43.4%)	3645	87.2%	(77.1%-93.2%)	4.07	(1.92-8.64)
Pooled	2465	19.5%	(8.8%-38.0%)	4288	86.1%	(76.6%-92.2%)	4.67	(1.51-7.83)
Initiated on ART within 28 days								
Cameroon	12	16.7%	(3.1%-55.4%)	28	78.6%	(30.2%-96.9%)	4.71	(0.93-23.83)
Ethiopia	3	0.0%	--	3	33.3%	(0.3%-98.9%)	1.00	--
Zimbabwe	108	9.3%	(5.4%-15.4%)	158	65.8%	(46.2%-81.2%)	7.11	(3.68-13.72)
Pooled	123	9.8%	(6.1%-15.2%)	189	67.2%	(50.2%-80.7%)	6.72	(2.13-11.32)

784 EVALUATION OF PERFORMANCE AND USABILITY OF CEPHEID XPERT HIV -1 QUAL ASSAY IN MALAWI

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Background: As countries work towards attaining UNAIDS 90-90-90 targets, challenges related to Early Infant Diagnosis (EID) of HIV should be addressed. In Malawi, EID programmes use dried blood spot (DBS) and HIV PCR with turn-around-times (TAT) of 2-3 months with 33% of exposed infants lost to follow-up. There is an urgent need for point-of-care tests (POCTs) which can improve TAT and reduce loss to follow-up. We evaluated the feasibility, sensitivity and specificity, turn-around-time, acceptability and usability of Cepheid Xpert HIV-1 Qual assay (Xpert HIV) whole blood protocol in a rural district hospital compared to HIV PCR.

Methods: This prospective diagnostic study consecutively recruited children aged 0-14 years attending Mulanje District Hospital (MDH) in Malawi between July-September 2018. All POCT were done on site using Xpert HIV. DBS were prepared for HIV PCR testing at a central facility, Queen Elizabeth Central Hospital (QECH). As a standard procedure for EID testing DBS were also sent to Thyolo District Hospital (TDH) for testing by PCR. We compared the sensitivity and specificity between Xpert HIV and PCR. We also compared the median TAT between Xpert HIV from MDH and PCR from QECH and TDH. Acceptability of Xpert HIV was evaluated among caregivers and nurses.

Results: Of 600 participants, 324 (54%) were female. 272 (45.3%) were aged over 5 years, 227 (37.83) between 1-5 years and 101 (16.83%) <1 year. Most of the participants 585 (97.5%) were HIV non-infected. A total of 15 participants were diagnosed with HIV. Most HIV positives aged >1 year (11/13 (85%)) started antiretroviral therapy in 1 day and 4/15 (26%) of all HIV positives were lost to follow up. Sensitivity and specificity of Xpert HIV versus PCR at QECH were 100% (95% CI: 78.2 - 100%) and 100% (95% CI: 99.4 - 100%), respectively. Xpert HIV had the shortest median TAT from time of blood test (median = 5.34 hours (interquartile range: 2.45–10.19) compared to PCR performed at QECH (median = 3 days (IQR: 1.05–4.19)), p<0.001 and PCR performed at TDH (median = 24 days (IQR: 20–28)), p<0.001. Results for only 17 of the 32 samples sent to TDH were received. Xpert HIV was well accepted by caregivers and nurses; and was deemed easy to use by laboratory technicians in comparison to PCR.

Conclusion: These results suggest that implementing Xpert HIV may improve EID and linkage into HIV care.

785 EARLY INFANT DIAGNOSIS: STRENGTHEN EXISTING SYSTEMS OR INVEST IN POINT-OF-CARE?

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Background: To improve early infant HIV diagnosis (EID) programs, options include replacing lab-based tests with point-of-care (POC) assays or investing in strengthened systems for sample transport and return of results. We projected the clinical benefits and cost-effectiveness of these approaches.

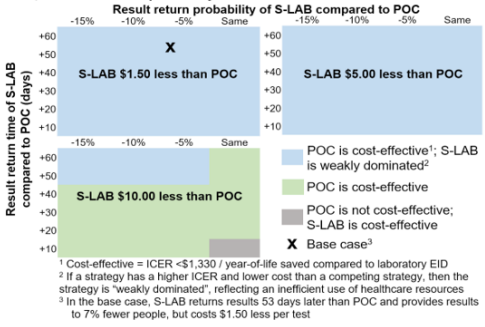
Methods: We used the Cost-Effectiveness of Preventing AIDS Complications-Pediatric model, with programmatic and published data, to examine

clinical benefits and costs of three strategies for EID in Zimbabwe for infants 6 weeks of age: 1) lab-based EID (LAB), 2) strengthened lab-based EID (S-LAB), defined as improved sample transport, two additional lab staff, and increased lab maintenance, and 3) POC EID. Assays differed in sensitivity (LAB and S-LAB 100%, POC 96.9%) and specificity (LAB and S-LAB 99.6%, POC 100%). LAB/S-LAB/POC algorithms also differed in: probability of result return (79/91/98%), time until result return (61/53/0 days), probability of linking to ART after confirmed positive result (52/71/86%), and total cost/test ($17.09/$29.80/$31.26), which included transport, salary, training, and maintenance costs derived from a resource utilization analysis in Zimbabwe. Monthly cost of HIV care and ART varied by age, CD4 count, regimen, and weight. We projected life expectancy (LE) and average lifetime per-person cost for all HIV-exposed infants, including those who did and did not acquire HIV. We calculated incremental cost-effectiveness ratios (ICERs) from discounted (3%/year) LE and cost results in $/year-of-life saved (YLS), defining cost-effective as an ICER <$1,330/YLS (Zimbabwe per-capita GDP). In multi-way sensitivity analyses, we varied differences between S-LAB and POC in: result return probability, result return time, and cost.

Results: For infants who acquired HIV, LAB/S-LAB/POC led to projected one-year survival of 67/70/76% and undiscounted LE of 21.77/22.75/24.51 years. For all HIV-exposed infants, undiscounted LE was 63.34/63.38/63.42 years, at undiscounted costs of $330/$360/$390 per infant. S-LAB was dominated in cost-effectiveness analysis; the ICER of POC vs. LAB was $870/ YLS. In multi-way sensitivity analyses, S-LAB was only cost-effective if it cost $10 less than POC, had the same result return probability as POC, and had 10-day result return time (Figure).

Conclusion: Current EID programs will attain greater benefit for additional investments by integrating POC EID rather than strengthening lab-based systems; decreases in POC test cost will amplify the benefits of POC EID.

Figure. Cost-effectiveness of POC EID: effect of S-LAB cost, result return time, and result return probability



[1] Cost-effective = ICER <$1,330 / year-of-life saved compared to laboratory EID
[2] If a strategy has a higher ICER and lower cost than a competing strategy, then the strategy is "weakly dominated", reflecting an inefficient use of healthcare resources
[3] In the base case, S-LAB returns results 53 days later than POC and provides results to 7% fewer people, but costs $1.50 less per test

786 MOTIVATIONAL INTERVIEWING RETENTION COUNSELING AND CHILD HIV TESTING IN SOUTH AFRICA

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Background: The improvement of health outcomes of vertically infected infants requires earlier HIV diagnosis through greater adherence to the HIV testing schedules for HIV-exposed children.

Methods: This is a randomised controlled trial among HIV positive postpartum mother-baby dyads enrolled immediately after the postnatal consultation at four midwife obstetric units in Gauteng (South Africa) and randomised into (A) Motivational Interviewing (MI) retention counselling by lay counsellors at baseline and telephonically at six and 12-month, (B) bi-annual tracing calls, (C) standard care. Mother-baby pairs were followed up to 18 months postpartum telephonically and via paper files (25 primary care clinics) and electronic medical records (a search of the National Health Laboratory Services database). Log-binomial regression was used to assess the timing of the ten-weeks infant polymerase chain reaction (PCR) test, the uptake of the child 18-months antibody test, maternal retention and viral load (VL) suppression at six, 12 and 18-month postpartum.

Results: Overall, 710 mother-baby pairs were recruited with a median age of 30 years (interquartile range: 25-34). While, 70.1% of HIV-exposed babies received a second HIV PCR test by six-month (70.0% in the MI intervention group, 70.5% in the control groups B and 70.0% in group C), among those tested (n=501), 85.0% of the intervention (A) children were tested at 7-90 days of age, 69.0% in group B and 75.3% of group C (adjusted Risk Ratio (aRR)=1.13 for the MI intervention vs. group C (95% Confidence Interval (CI): 1.0-1.3) and aRR 1.2 vs. group B (95%CI: 1.1-1.4)). Overall only 58 (8.2%) children were tested at 18-months (10.7% group A, vs 5.5% in group C, RR 2.0, 95% CI: 1.0-3.7) with a final vertical transmission rate of 0.7%. Maternal retention and VL suppression rates were similar across randomisation groups at 349 (49%) retained at six months (180/226 VL suppressed), 151 (21%) at 12 months (93/114 VL suppressed), 130 (18%) at 18-months (99/111 suppressed).

Conclusion: MI retention counselling by unskilled lay personnel is feasible and can reduce delays in the uptake early infant diagnostic tests for HIV-exposed infants. However, greater efforts are needed to improve adherence to the 18-months child antibody test, postpartum maternal retention in HIV care and viral monitoring.

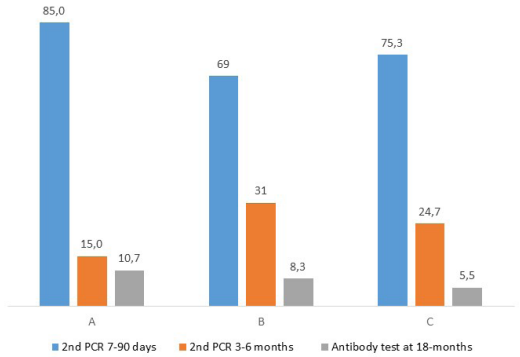


Figure 1. Uptake and timing of the second (ten-weeks) infant HIV PCR and 18-month antibody test among HIV-exposed children in the Gauteng Province of South Africa

787 MOTHERS' ADHERENCE HELPS IN IDENTIFYING MORE INFANTS IN NEED OF EXTENDED PROPHYLAXIS

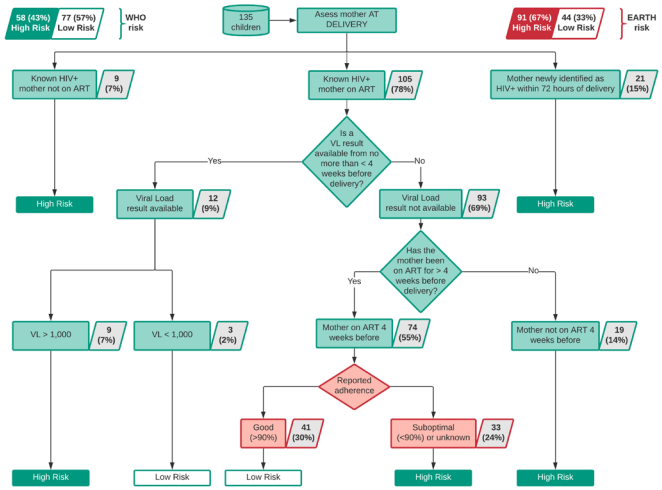
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Background: The WHO recommends extended HIV prophylaxis (ePCP) for infants at high-risk of PMTCT. High risk is defined by maternal factors: a mother first identified as HIV-infected at delivery or postpartum, a known HIV+ mother not on ART, viral load (VL)>1000 copies/mL <1 month before birth, or unavailable VL but ART for <4 weeks by delivery. Well controlled cohorts of pregnant women show that 10% of pregnancies are high risk and contribute to 57% of vertical infections. 90% of pregnancies are low risk and result in 43% of infections. In practice, some of the high-risk infants are miscategorized and treated with standard prophylaxis instead of ePCP. The aim is to evaluate the sensitivity of WHO algorithm to correctly identify high risk infants, based on the given outcome which is HIV infected infant, and to assess the improvement of adding extra information to the algorithm

Methods: EARTH is a multicenter prospective cohort, part of the EPIICAL consortium, enrolling HIV-perinatally infected infants,diagnosed in the first 3 months of life and treated in the first 3 months after diagnosis, in Mozambique and South Africa. We categorized infants as high risk or low risk, based on WHO criteria and then re-categorized infants after including mother self-reported adherence

Results: 135 children were analyzed. Median age at enrolment was 38 days (31-75), and median age at ART was 33 days (19-66). Prophylaxis after birth was prescribed to 80%. Only 26% of high-risk infants received extended ePCP with NVP and AZT. Median mother's age at enrollment was 28 years and only 68% had detectable VL. Of those, their last median VL was $\log_{10}$ 4.21. To date, no mothers died. Only 58 (43%) mothers were classified as high risk and 77 (57%) as low risk. Of these, 74/77 (96%) had not a recent VL prior to delivery but were on ART for >4 weeks. Maternal self-reported adherence was good in 52% and 56%,

respectively. After adding maternal self-reported adherence to risk definition, 67% of perinatally infected infants became high risk, increasing a 24% of high-risk patients the WHO classification, while low risk reduced to 33% (Figure 1)
Conclusion: In our cohort, 24% HIV infants were miscategorized as low risk using the current WHO algorithm. Including self-reported adherence information can help to provide ePCP to all eligible infants



788 IMPROVED HEMATOLOGICAL OUTCOMES WITH NEVIRAPINE FOR INFANT HIV POSTNATAL PROPHYLAXIS

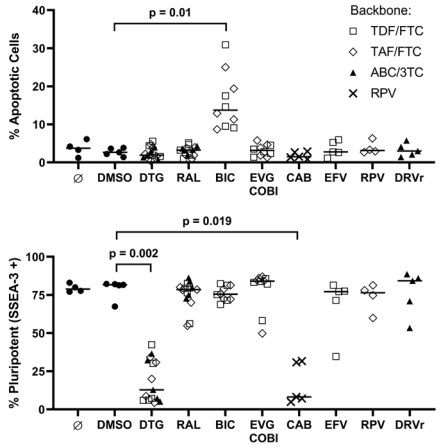
Catherine Dollfus[1], Jérôme Le Chenadec[2], Laurent Mandelbrot[1], Roland Tubiana[1], Albert Faye[3], Stephane Blanche[1], Pierre Frange[1], Josiane Warszawski[2], for the ANRS CO1 et CO11
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Background: With combination antiretroviral therapy (cART) in HIV-infected women, mother-to-child transmission rates declined to less than 1%. For post-natal infant prophylaxis, in situations of low risk of perinatal HIV transmission, high income countries use zidovudine (ZDV), whereas low income countries use either nevirapine (NVP) or ZDV. Given the low transmission risk and the concerns about the toxicities of ZDV in newborns, French national guidelines recommend since 2015 the use of NVP as an alternative to ZDV for post-natal prophylaxis in full term babies born to HIV1-infected mothers with suppressed viral load and no history of NVP resistance. We compared hematological outcomes between ZDV-exposed and NVP-exposed infants.
Methods: In the French prospective national Perinatal Cohort Study, we compared hematological outcomes (blood cell counts and differentials) at birth, 1 and 3 months among the infants born in 2016-2017 , at >=37weeks gestation. We included only mothers treated with cART without ZDV, to exclude a potential impact of maternal treatment on infant outcomes. ZDV was prescribed for 4 weeks, NVP for 2 weeks; mothers did not breastfeed.
Results: 137 infants were exposed to NVP and 251 to ZDV. None became infected.68% of mothers were born in sub-Saharan Africa (79.4% in NVP group, 62.9% in ZDV group) .Median hemoglobin levels were respectively 17.4 g/dL vs 17.0 at birth (p=0.49),11.7 vs 11 g/dL at 1month (p=0.003) and 11.4 vs 11.2 g/dL at 3 months(p=0.02).Anemia grade >=2 was observed in 0.8% vs 1.7 % of infants at birth (p=0.66), 1.2% vs 9.4% at 1 month (p=0.014), 3.6% vs 7.3% at 3 months(p=0.40). Median neutrophil counts were similar, grade >=2 neutropenia was found in 4.2% vs 2.7% infants at birth(p=0.53),15.9% vs 13.1% at 1 month(p=0.56), and 12.2 vs 13.4% at 3 months(p=0.84). No difference was found in platelets counts.
Conclusion: In this population of HIV-exposed uninfected infants, post-natal prophylaxis with NVP, compared to ZDV was associated with higher hemoglobin levels at 1 and 3 months and a 9-fold lower incidence of anemia at 1 month of age. These findings support the use of nevirapine as a first choice for single drug post-natal prophylaxis in low risk situations.

789 TOXICITY OF INTEGRASE INHIBITORS IN A HUMAN EMBRYONIC STEM-CELL MODEL

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Background: Women living with HIV give birth to ~1.5M infants each year, 80% of them exposed to ARVs in utero. Most ARVs can cross the placenta, but their safety has not been fully elucidated in the context of pregnancy. The Tsepamo study reported a signal for risk of neural tube defects in infants exposed to the InSTI dolutegravir (DTG) from conception. Many ARVs affect mitochondria, which could impact embryonic development. Our objective was to characterize and compare the effects of 14 ARV regimens on cultured human embryonic stem cells (hESCs), with respect to pluripotency, and cellular and mitochondrial health.
Methods: CA1S hESCs were cultured (n=5 independent experiments) in the presence of 0.1% DMSO or 1X C_{max} of the following regimens: DTG, raltegravir (RAL), bictegravir (BIC), cobicistat-boosted elvitegravir (EVG/COBI), or efavirenz (EFV) on a TDF/FTC backbone; DTG, RAL, BIC, EVG/COBI, or rilpivirine (RPV) on a TAF/FTC backbone; DTG, RAL, or ritonavir-boosted darunavir (DRVr) on an ABC/3TC backbone; cabotegravir (CAB)/RPV. After 3 days, cells were assessed via flow cytometry using markers for mitochondrial mass, intermembrane potential, reactive oxygen species (ROS), cell viability, and apoptosis. Two markers of pluripotency, specifically SSEA-3 (lost early in differentiation) and TRA-1-60 (a later marker), were also assessed. Regimens were grouped according to base ARV and compared to DMSO control using Kruskal-Wallis with Dunn's correction.
Results: HESCs exposed to DTG or BIC had a 3-fold reduction in cell counts ($p \leq 0.005$) compared to controls. BIC exposure resulted in a 5-fold decrease in viability (p=0.026) and a 6-fold increase in apoptosis (p=0.01). In regards to pluripotency, exposure to regimens containing DTG or CAB resulted in a >80% loss of SSEA-3 expression compared to controls ($p \leq 0.02$). There were no significant differences between regimens with respect to mitochondrial mass, intermembrane potential, ROS, or loss of TRA-1-60 expression. No effects were detected for the backbones, RAL, EVG/COBI, EFV, RPV, or DRVr.
Conclusion: These data indicate that exposure to some ARV regimens at pharmacological concentrations, especially DTG or BIC, appear toxic to cultured hESCs. Our results further suggest that exposure to the InSTIs DTG and CAB can induce hESC differentiation. Given the increasing use of DTG and other InSTIs, it is imperative to investigate their long-term safety in the context of pregnancy and embryonic development.



790 ESTIMATES OF PERICONCEPTIONAL EXPOSURES TO INTEGRASE INHIBITORS UNITED STATES

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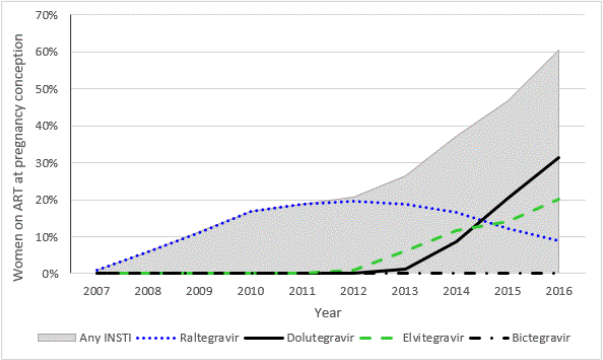
Background: In 2018, an increased risk of neural tube defects among infants with periconceptional dolutegravir (DTG) exposure was reported from Botswana, triggering changes to global treatment guidelines for women and limiting access to DTG. Estimates of periconceptional integrase inhibitor (INSTI) exposures are needed to understand the potential to study the impact of INSTI use on pregnancy and birth outcomes in the United States.
Methods: We estimated U.S. periconceptional INSTI exposures as follows. We used hospital discharge data from the Healthcare Cost and Utilization Project from 2007-2014 to predict the number of deliveries in 2015-2017 to women with diagnosed HIV using Poisson regression. We used National Vital Statistics Report estimates of proportions of all pregnancies resulting in live births (65%) and the

proportions of pregnant women with HIV diagnosed prior to pregnancy (80%) (Nesheim, et al, PIDJ, 2019) and on antiretroviral treatment (ART) (58%-74%) (CDC) to estimate annual pregnancies to women on ART at conception. We then utilized data from the North American AIDS Cohort Collaboration on Research and Design from 2007-2016, the most current years available, (Jennifer Lee, personal communication, February 4, 2019) and factored the proportion of women aged 15-45 years with ≥ 1 month exposure to each INSTI to estimate periconceptional INSTI exposures by year.

Results: In 2007-2016, women with diagnosed HIV in the United States had an estimated 63,085 pregnancies and 41,005 live births. Among 29,272-37,346 pregnancies conceived by women on ART, an estimated 6,727-8,583 (23%) had periconceptional INSTI exposure, of which 3,694-4,713 (55%) were exposed to raltegravir (RAL), 1,610-2,055 (24%) to DTG, 1,413-1,801 (21%) to elvitegravir (ELV) and none to bictegravir. Periconceptional INSTI use among women on ART increased steadily with 1% exposed in 2007 and 61% in 2016. In 2016, among 1,535-1,959 periconceptional INSTI exposures, 15% were exposed to RAL, 52% to DTG and 33% to ELV. An additional 5,314 pregnancies among women with HIV occurred in 2017; assuming same proportion on INSTIs as in 2016, there would have been an additional 1,492-1903 periconceptional INSTI exposures (746-801 DTG exposures).

Conclusion: INSTI use by U.S. women on ART at pregnancy conception has increased. This is the first U.S. national estimate, and ascertainment of exposures will be an important component of monitoring safety of new pharmacologic agents used in pregnancy.

Estimated percentage of INSTI exposures among women on antiretroviral therapy at pregnancy conception, United States, 2007-2016



791 OUTCOMES FOLLOWING PRENATAL EXPOSURE TO DOLUTEGRAVIR: THE DOLOMITE-EPPICC STUDY

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Background: Dolutegravir (DTG) was approved for treating HIV in adults and adolescents in 2013. In 2018, the Tsepamo Study reported a significantly increased neural tube defect (NTD) risk in women conceiving on DTG (0.94%), leading to a safety alert. In July 2019, additional data showed NTD prevalence with periconception DTG to be lower than in the initial analysis, but still greater than seen for other antiretroviral exposures (0.3% vs 0.1%). We aimed to assess birth outcomes following prenatal DTG use using real-world data

Methods: Dolomite-EPPICC is a multi-cohort European observational study of DTG use in pregnant women living with HIV and their infants. Analysis of prospectively collected individual patient data on all pregnancies with any prenatal DTG exposure and with birth outcomes reported by Feb 2019 was conducted. Periconception exposure was defined as being within the first 6 weeks of gestation (WG).

Results: A total of 453 pregnancies in 428 women from 6 cohorts were included. Women were mainly of black African (229, 54%) and white (129, 30%) ethnicity. Most (326/428, 76%) women had heterosexual HIV acquisition, 42 women were vertically infected and 11 had injecting drug use history. Of 443 singleton pregnancies, 16 were terminated (1 for birth defects at 29WG for neuronal migration disorder and severe microcephaly, with periconception DTG exposure) and 22 ended in spontaneous abortion; of 10 twin pregnancies, 1 was terminated and in 1, a fetus miscarried. There were 417 live-born infants (229 male, 185 female, 3 missing), born at median 39WG (IQR 38, 40). Five infants were stillborn, all exposed to periconception DTG, none with birth defects. The Table shows birth outcomes for the 400 live-born singleton infants (no twins had birth defects); 266 (67%) had periconception DTG exposure. One neonate died at 2 days (born at 23 GW) with periconception DTG exposure. Among the 417 live-born infants there were 17 with reported birth defects (4.1%, 95% CI 2.4, 6.5); 1 infant had 2 defects. The 18 defects were in the following systems: genitourinary (7), heart (3), limb addition (polydactyly, 3), gastrointestinal (2), other (3); no CNS defects were reported. There were no vertical transmissions (106 infants still indeterminate)

Conclusion: The birth defect rate and pattern add further support to current evidence on safety of periconception DTG use. This study is ongoing, in order to provide robust pharmacovigilance data in Europe.

	Earliest Dolutegravir exposure (400 live-born singleton infants)		
	Periconception* (n=266)	**Later T1*** (n=30)	**T2 / T3*** (n=104)
Preterm delivery (<37 weeks)	32/254 (12.6%)	3/29 (10.3%)	16/102 (15.7%)
Very PTD (<34 weeks)	*8/254 (3.1%)*	*1/29 (3.4%)*	*3/102 (2.9%)*
Low birth weight (<2500g)	31/261 (11.9%)	3/29 (10.3%)	14/100 (14.0%)
Very LBW (<1500g)	*8/261 (3.1%)*	*1/29 (3.4%)*	*3/100 (3.0%)*
Infant with birth defect	13/265 (4.9%)	0/30	4/104 (3.8%)
*Periconception: up to 6 completed gestational weeks; Later T1: 7-12 weeks; T2/T3: from 13 weeks			

792 CHANGES IN DTG USE FOLLOWING THE NTD SAFETY SIGNAL IN BOTSWANA

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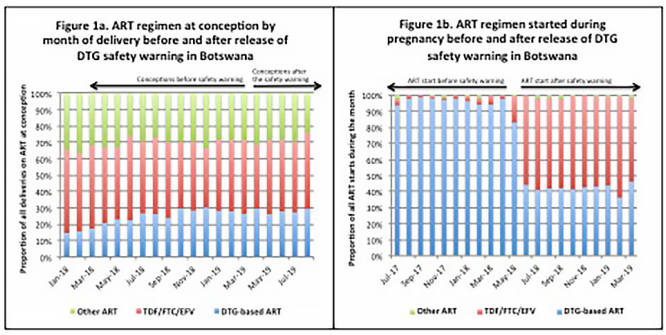
Background: In May 2018 a preliminary safety signal for neural tube defects among women on dolutegravir (DTG) at conception led to in-country guidance for individualized counseling for pregnant women who had already conceived on DTG and women on DTG or starting antiretroviral treatment (ART) who desired pregnancy; DTG-based ART otherwise remained the recommended regimen for new ART starts. We evaluated patterns of DTG use before and after this guidance.

Methods: This is a secondary analysis of data abstracted from Aug 2016-Sept 2019 in the Tsepamo birth outcomes surveillance study. HIV diagnosis date, ART regimens taken before or during pregnancy and dates of ART initiation and discontinuation were collected from all women living with HIV who delivered at study sites. Botswana national HIV treatment guidelines recommended DTG-based ART from May 2016 onward, with updated guidance related to pregnancy intention issued in May 2018.

Results: Among 20,254 women living with HIV who delivered from Aug 15, 2016-Aug31, 2019, 13,205 (65.2%) were on ART prior to conception, 5,718 (28.2%) started ART during pregnancy, 904 (4.5%) received no ART and 427 (2.1%) had unknown timing of ART start. The proportion of deliveries with DTG conception exposure increased steadily during the study period to a maximum of 30% in 10/2018 (Figure 1a). Among women who likely conceived in the 5 months after the May 2018 guidance, 27% of conceptions were on DTG-based ART, which was unchanged from 28% in the 5 months prior to the guidance. Before May 2018, 97% of women initiating ART in pregnancy started DTG-based ART (1.7% <6 weeks gestational age)(Figure 1b). After May 2018, only 43% of starts in pregnancy were DTG-based ART (1.6% <6 weeks gestational age), and 56% started EFV-based ART. Among 441 who changed ARVs during pregnancy, 177 (40%) switched from DTG-based ART to EFV-based ART (99% after May 2018). Only 71 (0.4%) women completely discontinued ART during pregnancy, including 35 women on DTG and 24 on EFV.

Conclusion: Program guidance based on individual counselling regarding pregnancy intention had no apparent impact on the number of women who conceived on DTG-based ART in 2018-2019 in Botswana. However, pregnant women frequently initiated non-DTG-based ART, or switched off DTG-based ART, despite being beyond the NTD risk period. Evaluation of clinician and patient perceptions of the NTD risk, and improvement in understanding

pregnancy intention and barriers to pregnancy planning, will be critical for developing treatment guidelines within DTG-based ART programs.



793 METABOLITES, PRETERM LABOR, AND ANTIRETROVIRAL THERAPY

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Background: Antiretroviral treatment (ART) has significantly reduced AIDS-related deaths, however, ART, including protease inhibitors, has been associated with an increased risk of preterm birth (PTB). In PROMISE, PTB (<37 weeks) occurred in 20.5% of pregnancies where mothers received zidovudine, lamivudine, lopinavir-ritonavir (PI) versus 13.1% where mothers received zidovudine alone (ZDV), p<0.001. To date the mechanisms involved in ART-associated PTB remain elusive.

Methods: Untargeted metabolomics was performed on maternal plasma and dried blood spots (DBS), and infant DBS from 100 mother-infant pairs enrolled in PROMISE; 50 preterm and 50 term deliveries, divided evenly between ZDV or PI. Maternal samples were obtained at the timepoint closest but prior to preterm delivery with controls matched for gestational age (GA) at sampling. Infant DBS were earliest available. Linear regression and random forests (RF) models were used to identify metabolic predictors of PTB.

Results: The mean GA at delivery was 33.1 weeks (Preterm) and 40.0 weeks (Term) and at sample collection 30.4, 30.5, 31.0 and 31.0 weeks for Preterm ZDV, Term ZDV, Preterm PI, and Term PI, respectively. DBS from one collection site separated from all others and were dropped because they were deemed unreliable (N=21 pairs, 9 preterm and 12 term). RF models for PTB using maternal plasma metabolite levels achieved out-of-bag accuracies of 86.1% and 79.1% for the ZDV and PI groups, respectively. Similar results were achieved with maternal DBS profiles (83.3% and 83.7% accuracy). Key predictors of PTB in the ZDV group identified by both RF and linear regression analyses included increased levels of 17a-hydroxypregnanolone glucuronide, methionine sulfone, pantothenate, and urate. PTB in the PI group was associated with increased nucleotide and amino acid metabolism (7-methylguanine, N2,N2-dimethylguanosine, N-acetylputrescine, methionine sulfone). RF models using infant metabolite profiles from the first 3 days of life (N=61) achieved 79.2% and 83.8% accuracy for PTB classification showing decreases in infant steroid metabolism in both the ZDV and PI groups.

Conclusion: In this exploratory study of HIV infected gravidas receiving ART, untargeted metabolomics identified perturbations in both steroid hormone metabolism and nucleotide/ amino acid metabolism that predict PTB. Untargeted metabolomics may be an effective strategy for identifying potential mechanisms of PTB associated with ART, and warrants further investigation.

794 GENITAL TRACT & PLASMA CYTOKINES & SYSTEMIC T-CELL ACTIVATION IN HIV+ PREGNANT WOMEN

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Background: Term and preterm labour are inflammatory events. Early data indicate that PBMCs migrate to the genital tract to influence inflammation. The genital mucosa-systemic cytokine gradient has been proposed as a surrogate for the migration of PBMCs to the genital mucosa. No data in HIV infected pregnancy are available. We characterized the gradient of cervicovaginal (CVF) cytokines to plasma cytokines in HIV infected and uninfected pregnant women.

Methods:
CVF, plasma and PBMCs were isolated from HIV uninfected (n=27) and cART treated, infected (n=48) pregnant women in the 2nd trimester. Concentrations of 10 cytokines in CVF and plasma were measured using multiplex immunoassays. Flow cytometry was performed for T cell surface markers: CD4, CD8, HLA-DR and CD25. Maternal characteristics, immunovirologic parameters and pregnancy outcome were recorded. Gradients were compared by HIV status, cART exposure, prematurity and correlations with T cell subsets and gestational age at delivery were explored.

Results: All measured genital-plasma cytokine gradients were greater in HIV infected than uninfected pregnant women p<0.0001, largely driven by high CVF cytokine concentrations (Table). In HIV infected women: the greatest gradients observed were for pro-inflammatory cytokine IL-1β and chemokine IL-8, followed by IL-2; CD4 cell % correlated positively with inflammatory IL-2 gradient (rho=0.28, p=0.01) and immune-regulatory IL-13 (rho=0.23, p=0.04); CD25+ T cell subsets associated inversely with IL-1β gradient (CD4+CD25+%; rho=-0.30, p=0.003; CD8+CD25+%; rho=-0.26, p=0.03); CD4:CD8 ratios correlated positively with IL-2 gradient (rho=0.25, p=0.02) and CD4+HLA-DR+% correlated inversely with IL-2 gradient (rho=-0.28, p<0.01). In this small sample no association between genital-plasma cytokine gradient with cART exposure or gestational age at delivery was observed.

Conclusion: HIV infected women have elevated genital mucosal cytokine gradients compared to uninfected women during the 2nd trimester pregnancy notably IL-1b and IL-8; both known for their role in preterm labour initiation. Activated CD25+T cell subsets were inversely correlated with IL-1b suggesting a regulatory role in genital inflammation. The role of genital inflammation and its regulation warrants further investigation in adverse pregnancy outcomes in HIV infected women.

Table: Median genital-plasma cytokine gradients during second trimester by HIV status

Cytokine gradient Median (IQR)	HIV infected pregnant	Uninfected pregnant	p value
IFN-γ	63 (9-468)	1 (0-4)	<0.0001
IL-1β	17294 (5076-115968)	5675 (663-14654)	<0.0001
IL-2	1068 (325-2304)	5 (3-29)	<0.0001
IL-8	15788 (4347-64995)	1812 (219-7160)	<0.0001
IL-12	464 (86-949)	4 (1-28)	<0.0001
TNF-α	99 (11-316)	1 (0-8)	<0.0001
IL-4	353 (97-9790	2 (1-6)	<0.0001
IL-6	262 (50-742)	49 (9-143)	<0.0001
IL-10	152 (61-467)	2 (0-20)	<0.0001
IL-13	579 (226-1328)	6 (1-34)	<0.0001

795 MATERNAL BIOMARKERS OF ENDOTHELIAL DYSFUNCTION BY HIV/ART STATUS AND BIRTH OUTCOMES

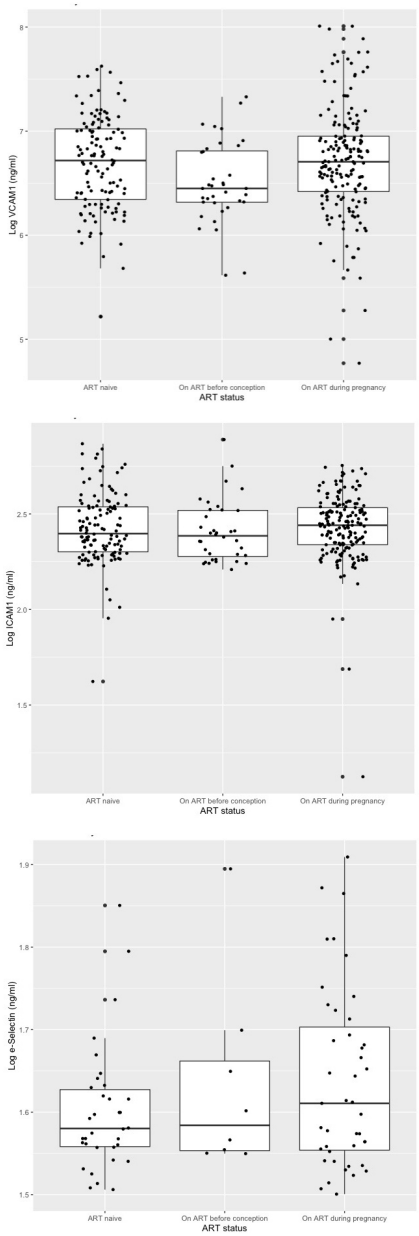
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Background: Women living with HIV (WLHIV) are at higher risk of having an adverse birth outcomes, with underlying mechanism(s) unknown. We hypothesized that HIV-associated endothelial activation could adversely impact placental function and lead to impaired fetal growth or stillbirth.

Methods: We used previously-collected data and samples from WLHIV and HIV-negative women enrolled during pregnancy in the observational Botswana Tshipidi cohort. We measured plasma levels of markers endothelial activation [soluble vascular adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1) and E-selectin] from samples taken during pregnancy. We compared log biomarker levels by maternal HIV status and by timing of ART initiation (prior

to conception vs. during pregnancy/prior to sample collection vs. no ART prior to sampling) using t-tests and Kruskal-Wallis rank test. We also evaluated the association between these biomarkers and adverse birth outcomes (composite of stillbirth or SGA <10th percentile weight-for-GA) using univariate and multivariate log-binomial regression controlling for age and timing of ART start.
Results: Specimens were available for 414 women (372 WLHIV and 42 HIV-negative), with median age 28 years and median gestational age at sample collection 30 weeks (Q1,Q3: 26,35). WLHIV had statistically significantly higher median VCAM1 (p=0.002) than HIV-negative women. HIV-negative women higher median ICAM1 (p=0.01); there was no statistically significant difference in e-Selectin levels. ICAM1 and e-Selectin were not statistically different by ART status or timing. Women starting ART during pregnancy had higher $\log_{10}$ VCAM1 levels than those on ART before conception, regardless of whether the sample was collected before (p=0.02) or after (p=0.03) ART initiation. Ninety-eight women (91 WLHIV and 7 HIV-negative) had stillbirth (total 9 mothers) or baby with SGA (total 89 babies). Univariate and adjusted analyses did not show significant associations between levels of any of these biomarkers and adverse birth outcomes (stillbirth or SGA).
Conclusion: Maternal HIV infection, and lack of ART or recently starting ART, were associated with one marker of greater endothelial activation (VCAM-1), but not with other markers (ICAM-1 nor E-selectin) in pregnancy. Markers of endothelial activation were not associated with SGA or stillbirth



796 MATERNAL AND CORD PLASMA BIOACTIVE EICOSANOID PROFILES DIFFER IN HIV+ AND HIV– WOMEN

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Background: Pregnant women with HIV (WHIV) are more likely to experience adverse birth outcomes, through mechanisms not fully understood. Eicosanoids play important roles in pregnancy and fetal growth and development, but data are lacking in the context of pregnancy, HIV, and antiretroviral therapy (ART). We examined bioactive eicosanoids (cell-signaling molecules derived from polyunsaturated fatty acids) in maternal and cord plasma from a Canadian cohort of WHIV and HIV negative (HIV-) pregnant women.
Methods: 76 maternal samples at gestational week 33-38 (39 WHIV, 37 HIV-) and 55 cord samples (31 WHIV, 24 HIV-) were included. All WHIV received protease inhibitor (PI)-based ART. Levels of 139 eicosanoids were measured using liquid chromatography-mass spec and quantified against standard curves with a lower limit of 0.025ng. Differences between groups for each eicosanoid were assessed using Mann-Whitney test corrected for multiple comparisons using a false discovery rate of 0.05. Orthogonal partial least squares discriminant analysis (OPLS-DA) was used to differentiate groups by maternal HIV status. Correlations between eicosanoids in maternal and cord plasma were examined by Spearman r.
Results: A total of 53 eicosanoids were detected in maternal and 58 in cord plasma. Cord and maternal eicosanoid profiles differed, with only 3 correlating between compartments among HIV- women and none among WHIV. Compared to the HIV- group, maternal plasma in WHIV had higher levels of circulating arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), and elevated levels of lipoxygenase pathway metabolites including several hydroxyeicosatetraenoic acids (HETEs), which have been associated with inflammatory and vasoconstrictive properties. In cord plasma, only 3 eicosanoids differed significantly between groups. All were vasodilating and pro-angiogenic dihydroxyeicosatrienoic acids (DHETs) (CYP/epoxygenase/soluble epoxide hydrolase metabolites of AA), and were lower in WHIV. OPLS-DA analysis indicated group separation by eicosanoids with maternal (see figure) and cord specimens.
Conclusion: Bioactive eicosanoid profiles differ in maternal and cord plasma, and are altered in pregnant WHIV. Elevated maternal levels of inflammatory lipoxygenase metabolites and lower cord levels of DHETs in the context of HIV/PI exposure may indicate or contribute to poor placenta function. Our findings also suggest an altered in utero environment that could contribute to fetal programming.

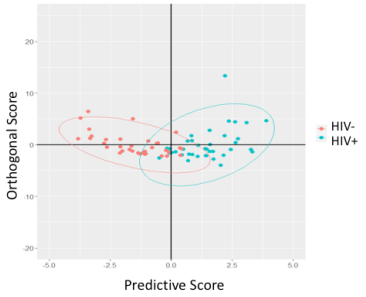


Figure: Bioactive eicosanoids in maternal plasma collected at gestational week 33-38 separates groups by HIV status using orthogonal partial least squares discriminant analysis. HIV-negative (HIV-) shown in red and HIV-positive (HIV+) shown in blue. Each dot represents a study participant.

797 BREASTMILK MICROBIOME/VIROME OF HIV+ KENYAN WOMEN IS NOT ALTERED BY IMMUNOSUPPRESSION

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Background: Breast milk (BM) harbors a diverse community of bacteria (microbiome) and viruses (virome) that are transmitted from mother-to-infant during breastfeeding and are important for establishing a healthy infant gut flora. Whether the BM microbiome and virome of women living with HIV are

altered by immunosuppression and influence morbidity in HIV-exposed infants are unknown. We hypothesized that immunosuppression, as measured by low maternal CD4 count, alters BM virome and microbiome.

Methods: We performed next-generation sequencing (NGS) to comprehensively define the virome and microbiome in BM samples collected during the pre-ART era in Kenya (2003-2005) from 53 HIV-infected women at 1 month postpartum: 30 women with CD4 <250 and 23 women with CD4 >500. Illumina sequencing was performed on Phi29-amplified nucleic acid (virome) and the 16S rRNA gene V4 region (bacterial microbiome). Quantitative real-time PCR (qPCR) was used to quantify select viral species.

Results: Among 53 HIV+ women, BM bacterial microbiomes were highly diverse and shared a core bacterial microbiome composed of Streptococcaceae (18.1%), Staphylococcaceae (10.1%), Moraxellaceae (4.1%) and Eubacteriaceae (3.6%) families. There was no significant difference in the diversity of BM bacterial microbiome between women with CD4>500 compared to CD4<250 in terms of ecological measurements of richness (p>0.65), alpha-diversity (p>0.14) and beta-diversity (p>0.17).

The BM virome was dominated by cytomegalovirus (CMV). The average proportion of CMV virome sequences did not differ between women with CD4 >500 and <250, with an average of 55.6% vs 69.4%, respectively (p>0.21). These NGS results were corroborated by qPCR measurements of CMV viral loads in BM (p>0.09). All women had a high abundance of bacteriophage families: Myovirdae (20.7%), Siphoviridae (11.6%) and Podoviridae (3.4%). Other eukaryotic viruses detected include papillomaviruses and anelloviruses. There was no significant difference in the BM virome richness (p>0.68), alpha-diversity (p>0.15) or beta-diversity (p>0.30) between women with CD4>500 compared to CD4<250.

Conclusion: In this cohort of HIV+ Kenyan women from the pre-ART era, BM harbors a core bacterial microbiome and a diverse virome that is dominated by CMV. Diversity and richness of the BM microbiome and virome were not significantly influenced by immunosuppression at 1 month postpartum.

798 REDUCED BASAL GANGLIA AND TOTAL GREY MATTER VOLUME IN HIV-EXPOSED UNINFECTED NEONATES

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Background: Evidence suggests HIV-exposed uninfected (HEU) children have impaired early growth and development compared to HIV-unexposed (HU) children. However, little is known about the neurobiological mechanisms underlying adverse developmental outcomes in this population. We examined the effects of in utero exposure to HIV and ART on the neuroanatomy of uninfected neonates in a South African birth cohort.

Methods: A subgroup of neonates in the Drakenstein Child Health Study (DCHS), born after 36 weeks' gestation, without medical comorbidities or neonatal intensive care admission, had magnetic resonance imaging (MRI) at the Cape Universities Brain Imaging Centre, South Africa. Mother-child pairs received antenatal and postnatal HIV testing and ART per local guidelines. Acquired structural T2-weighted images were processed using statistical parametric mapping software. Subcortical regions-of-interest were defined using the automated anatomical labeling atlas and volumes were extracted from grey matter segmented images bilaterally. Subcortical and total grey matter volumes were compared between groups using multivariable linear regression adjusting for intracranial volume, infant age and sex.

Results: 183 neonates in the DCHS had multimodal MRI between October 2012 and September 2015. Following quality control, 143 structural images were included (HEU n=39; HU n=104) (mean age 3.2 weeks, 51% male). All HEU infants were exposed to ART (87% to maternal triple ART). HEU infants had smaller caudate volumes bilaterally compared to HU (left hemisphere p=0.006, adjusted Cohen's d effect size -0.50 [95% CI -0.87 to -0.13]; right hemisphere p<0.001, adjusted Cohen's d -0.68 [-1.06 to -0.31]). There were no group differences in other subcortical volumes (all p>0.2). Total grey matter volume was also reduced in HEU infants (p=0.039, adjusted Cohen's d -0.33 [-0.70 to 0.04]). The associations remained significant after further adjusting for maternal age and education, household income, and prenatal alcohol exposure.

Conclusion: In utero exposure to HIV and ART without infection was associated with reduced basal ganglia and total grey matter volume in early infancy. To our knowledge this is the first cohort study to examine the neuroanatomy of HEU neonates. These findings are consistent with brain regions reported to be affected in HIV-infected children and suggest that HIV/ART exposure may impact brain structural development during pregnancy.

799 POSTNATAL LPV/R EXPOSURE, GROWTH, AND NEUROPSYCHOLOGICAL OUTCOMES AT SCHOOL AGE

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Background: In the ANRS 12174 randomized controlled trial, HIV-exposed uninfected African neonates who received lopinavir-ritonavir (LPV/r) prophylaxis for one year exhibited slower growth from birth to week 50 compared with those receiving lamivudine (3TC). We assessed whether this difference in growth persisted over time, and was accompanied by differences in neuropsychological and clinical outcomes.

Methods: Between February 2017 and February 2018, we conducted a cross-sectional clinical evaluation among former trial participants who completed the 50-week follow-up and who were not HIV-infected. In addition to HIV testing and clinical examination, neuropsychological outcomes were assessed using the Kaufman Assessment Battery for Children, 2nd edition (KABC-II), Tests of Variables of Attention (TOVA), the Movement Assessment Battery for Children, second edition (MABC-2), and the caregiver-reported Strengths and Difficulties questionnaire (SDQ).

Results: Of 1101 eligible children, aged 5 to 7 years, 553 could be traced and analysed (274 in the LPV/r and 279 in the 3TC groups). Changes from baseline value in height-for-age, body mass index and weight-for-age Z-scores, were greater in the LPV/r group compared to the 3TC group (estimated differences ranging from 0.19 to 0.30), but Z-scores did not differ between groups at follow-up.

No differences in the KABC-II and MABC-2 tests and SDQ questionnaire were found. A marginally better performance was observed for the 3TC group on the TOVA test. Clinical outcomes were similar between groups.

Conclusion: The impact of LPV/r on growth did not persist over time after drug discontinuation. At school age, children exposed to LPV/r and 3TC at birth for one year had comparable growth and neuropsychological outcomes without evidence of long-term side-effects of LPV/r. It provides reassuring data on clinical outcomes for all HIV-infected children treated with this antiretroviral in early life.

800 MALNUTRITION IN HIV-EXPOSED UNINFECTED CHILDREN IN LONG-TERM OBSERVATIONAL FOLLOW-UP

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Background: For unclear reasons, HIV exposed uninfected children (HEUs) are at risk of malnutrition, which increases childhood infections and mortality. Stunting, particularly in the first 2 years of life, potentially affects cognitive functioning and educational achievement, adult height and future risk of metabolic disease. Stunting in girls may be passed on to their future offspring. We set out to establish the rate of severe growth faltering and correlates of stunting in a cohort of HEUs aged 2-5 years in follow-up since birth in four African countries.

Methods: Child anthropometric parameters were measured six-monthly using standardized procedures in the ongoing PROMOTE observational study of women with HIV and their children. Enrolment occurred between December 2016 and June 2017. The WHO child-growth standards (2006) were used to calculate age-and-sex appropriate Z-scores for weight (WAZ), height (HAZ), and weight-for-height (WHZ). Severe growth-faltering (stunting, underweight and wasting) was defined as more than two standard deviations below the WHO population median, respectively. Generalised estimating equations (GEE) were used to assess correlates of stunting including maternal factors (age, education), country, infant sex, and surrogate measures of household level sanitation and socioeconomic status (tap water use, size of the house).
Results: Of the 1459 HEUs aged 2-5 years during the study period included in this analysis, 48.5% were female. Mean (sd) z-scores were below population norms for height (-1.2 +1.2) and weight (-0.5 +1.0) across all 4094 repeated measurements; 934 (22.9%) were stunted, 208 (5.1%) underweight and 72 (1.8%) wasted. We found that Malawi location when compared to South Africa [adjusted odds ratio; (95% CI): 2.50; 1.74-3.60] and being born to a mother who did not complete secondary school (1.47; 1.11-1.95) were associated with higher odds of stunting; whereas older children had lower odds of stunting (0.96; 0.95-0.96).
Conclusion: High rates of growth faltering were observed in this large multi-country cohort of predominantly breastfed African children who survived to at least 2 years and escaped HIV infection. Early interventions are necessary to address malnutrition in the growing population of HEUs in order to optimize their health and future human capital. Maternal factors, specifically education may be a key area of focus.

Nutrition status by country for observations from children aged 2-5 years during the study period

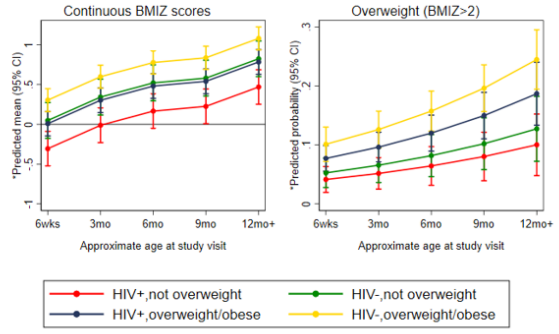
Variable	Malawi (N=1421)	South Africa (N=931)	Uganda (N=751)	Zimbabwe (N=991)	TOTAL (N=4094)
Number of children (% female)	514 (48.4%)	375 (49.6%)	240 (47.9%)	330 (47.6%)	1459 (48.5%)
Mean weight-for-age z-score (sd)	-0.7 ± 0.9	-0.2 ± 1.0	-0.5 ± 0.9	-0.6 ± 0.9	-0.5 ± 1.0
Mean height-for-age z-score (sd)	-1.6 ± 1.1	-0.7 ± 1.2	-1.2 ± 1.0	-1.0 ± 1.1	-1.2 ± 1.2
Mean weight-for-height z-score (sd)	0.5 ± 1.1	0.4 ± 1.3	0.3 ± 0.9	0.0 ± 1.0	0.3 ± 1.1
Number (%) stunted HAZ more than 2SD below the WHO population median	501 (35.4%)	137 (14.8%)	134 (17.9%)	162 (16.4%)	934 (22.9%)
Number (%) underweight WAZ more than 2SD below the WHO population median	101 (7.1%)	34 (3.7%)	24 (3.2%)	49 (4.9%)	208 (5.1%)
Number (%) wasted WHZ more than 2SD below the WHO population median	16 (1.1%)	28 (3.0%)	3 (0.4%)	25 (2.5%)	72 (1.8%)

801 HIGH BODY MASS IN HIV+ & HIV– WOMEN AND THEIR HIV-UNINFECTED INFANTS IN SOUTH AFRICA

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Background: HIV-exposed uninfected (HEU) infants may have altered growth relative to HIV-unexposed (HU) infants. Maternal body mass index (BMI) and obesity are strongly linked to child growth, but there are few data on associations between maternal BMI and HEU infant growth.
Methods: We followed cohorts of HIV+ (initiating TDF+XTC+EFV) and HIV- women from first antenatal visit (ANC) through 12 months postpartum with their breastfed infants. We estimated pre-pregnancy maternal BMI (kg/m$_2$) from routine antepartum measures; trained staff collected postpartum anthropometry (maternal BMI and infant BMI Z-scores). Virological testing excluded infant HIV infection. We examined relationships between a combined exposure of maternal HIV/ART (HIV+ vs HIV-) and pre-pregnancy BMI (not overweight (BMI<25) vs overweight/obese (BMI >25)) with mean infant BMIZ scores using multivariable linear mixed models and the probability of infant overweight (BMIZ >2 SD) using modified Poisson regression.
Results: In 780 mother-infant pairs (49% HIV+ mothers), 68% had pre-pregnancy BMI ≥25; 4% were underweight (BMI<18.5). HIV+ women were less likely to be overweight/obese (65% vs 71%), but more likely to report alcohol use (25% vs 7%) and food insecurity (17% vs 3%) vs HIV- women. HIV- women were more likely to breastfeed for ≥6 months (62% vs 44%); breastfeeding ≥6 months did not differ by BMI status (~54%). Throughout follow-up, infant BMIZ trajectories differed by maternal HIV-BMI status (Figure): scores were lowest among HIV+, not overweight women and highest among HIV-, overweight/obese women and similar among HIV-, not overweight and HIV+, overweight/obese women. At 12 months postpartum, the probability of infant overweight was highest for infants born to HIV-, overweight/obese women (0.24;95%CI 0.19, 0.30), followed by HIV+, overweight/obese women (0.19; 95%CI 0.13; 0.24), HIV-, not overweight women (0.13; 95% CI 0.07, 0.18), and lowest among HIV+ not overweight women (0.10; 95%CI 0.05, 0.15).
Conclusion: In this setting of high maternal BMI, HEU infants had lower mean BMI during the first year of life than HU infants, regardless of maternal BMI status. By 12 months postpartum, the probability of being overweight was >10% for all groups. However, infants born to overweight/obese women, compared to not overweight women, were more likely to be overweight, regardless of HIV status. Future research should examine if maternal HIV and BMI status increase the risk of cardio-metabolic complications for HEU infants later in life.

Figure. Body mass index-for age Z-scores (BMIZ) among HIV-uninfected children by maternal HIV and pre-pregnancy BMI status



*All models adjusted for poverty alcohol food insecurity education and maternal age.

802 DISTINCT CORD C-PEPTIDE, ADIPOKINE, AND LIPIDOMIC SIGNATURES BY IN UTERO HIV EXPOSURE

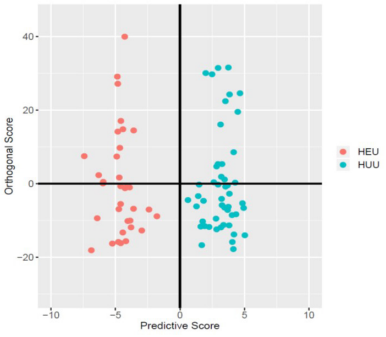
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Background: Metabolic derangements early in life of HIV-exposed uninfected (HEU) infants have been reported.
Methods: Pregnant HIV+ and HIV- women were enrolled with their infants in a US cohort from 2009-15. We measured insulin, C-peptide, and adipokines [metabolic (resistin, leptin) and inflammatory (Interleukin (IL)-6, Tumor Necrosis Factor-a (TNFa)] in cord blood of HEU and HIV-unexposed uninfected (HUU) infants using multiplex ELISA. Demographic, clinical, and in utero antiretroviral therapy (ART) exposure data were collected. Metabolites and lipid subspecies were measured via mass spectrometry. Linear regression models were fit to assess the association of in utero HIV exposure with cord insulin and C-peptide. Orthogonal partial least squares discriminant analysis (OPLS-DA) was used to assess if differences in metabolites and lipid subspecies discriminate between HEU and HUU infants. Elastic net regression was used to identify factors including metabolites and lipid subspecies most associated with increased cord C-peptide, stratified by in utero HIV exposure.
Results: Of 118 infants, 56 were HEU. No differences in maternal race/ethnicity, pre-pregnancy BMI, gestational diabetes (GDM) or infant preterm birth (PTB), birth weight/length were noted. All HEU were ART-exposed (52% PI, 21% NNRTI, 9% INSTI). After adjusting for maternal age, GDM, family diabetes history, pre-pregnancy BMI, as well as infant sex, PTB, and birth weight z score, mean cord insulin (ß=0.295, p=0.03) and C-peptide (ß=0.522, p<0.01) were significantly higher in HEU vs. HUU infants. IL-6 correlated positively with C-peptide in HEU (rho=0.30, p=0.05) but not HUU infants (rho=0.08, p=0.52) while resistin correlated inversely with C-peptide in HUU (rho= -0.40, p<0.01) but not HEU. Leptin correlated positively with C-peptide in both groups (rho=0.64, p<0.01 in HEU; rho=0.26, p=0.04 in HUU). OPLS-DA showed clear group separation by metabolites and lipid subspecies. (Fig)

Elastic net regression identified pre-pregnancy BMI and complex lipids with polyunsaturated side chains to be positively associated with cord C-peptide in both groups. However, in HEU but not HUU infants, arachidonic acid and microbial derivatives of tyrosine and tryptophan were associated with C-peptide.

Conclusion: Compared to HUU, HEU infants manifest with insulin resistance. Differences in cord metabolite, lipid subspecies, & adipokines are significant between HEU and HUU infants, suggesting altered fetal metabolic programming due to in utero HIV exposure.

Figure. Orthogonal Partial Least Squares Discriminant Analysis of Metabolites and Lipid Subspecies Showing Group Separation by *in utero* HIV Exposure Status



803 MORE SEVERE DISEASE IN HOSPITALIZED HIV-EXPOSED UNINFECTED VS HIV-UNEXPOSED NEONATES

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Background: Compared to children HIV unexposed and uninfected (CHUU), children HIV exposed and uninfected (CHEU) may have an increased risk of adverse birth outcomes, morbidity and hospitalization, but there are few insights into patterns of morbidity during the neonatal period.

Methods: We followed a prospective cohort of HIV+ and HIV- pregnant women recruited from a large antenatal clinic in Cape Town, South Africa. Their infants (CHEU=457; CHUU=475; n=2 HIV+ neonates excluded) were followed up from delivery. Medical records were reviewed to investigate all admissions during the neonatal period (day 0–28 of life). Infants who were in hospital for routine post-delivery observation were excluded.

Results: Rates of neonatal admission were similar between CHEU (59/457, 13%) and CHUU (75/475, 16%) (p=0.210). Most admissions occurred directly after birth (CHEU 88% vs CHUU 85%), and mode of delivery was by caesarean section in 64% CHEU vs 57% CHUU. Infectious causes were identified in 37% CHEU vs 35% CHUU (p=0.099); bloodstream infections accounted for most infectious admissions (34/48; 71%). Neonatal respiratory distress was the most common cause of non-infectious admissions, and did not differ between CHEU and CHUU (32% vs 35% of non-infectious admissions; p=0.20). Very preterm births (<32w) occurred more frequently among CHEU admissions (27% vs 9%; p=0.006) as well as very low birthweight (<1500 g) (36% CHEU vs 16% CHUU; p<0.001). Among those hospitalized, 54% CHEU required admission to an intensive care unit (ICU) vs 28% CHUU. Hospitalized CHEU had a 1.94 times increased risk of ICU admission compared to CHUU (95% CI 1.26–2.98). After adjusting for very preterm delivery, the risk of ICU admission remained higher among CHEU (RR=1.60; 95% CI 1.04–2.47).

Conclusion: There were no significant differences in overall hospitalization rates or frequency of infectious events during the neonatal period between CHEU and CHUU. However, hospitalized CHEU had increased risk of very preterm birth and very low birthweight, indicating increased severity of adverse birth outcomes. In addition, and independent of very preterm birth, hospitalized CHEU had higher risk of ICU admission, indicating increased disease severity during the neonatal period.

Table: Characteristics of neonatal hospitalizations

	CHEU	CHUU	Total	p-value
Neonatal hospitalizations (n/N)	59/457 (12.9%)	75/475 (15.8%)	134/932 (14.4%)	0.210
Admission duration (days): median (IQR)	9 (5-28)	7 (5-17)	8 (5-22)	0.171
Hospitalized directly after birth	52/59 (88.1%)	64/75 (85.3%)	116/134 (86.6%)	0.637
Admission to ICU	32/59 (54.2%)	21/75 (28.0%)	53/134 (39.6%)	0.002
Low birthweight (<2500g)	33/59 (55.9%)	40/75 (53.3%)	73/134 (54.5%)	0.764
Very low birthweight (<1500g)	21/59 (35.6%)	12/75 (16.0%)	33/134 (24.6%)	0.001
Preterm birth (gestational age <37 weeks)	36/59 (61.0%)	40/75 (53.3%)	76/134 (56.7%)	0.373
Very preterm birth (gestational age <32 weeks)	16/59 (27.1%)	7/75 (9.3%)	23/134 (17.2%)	0.007
Diagnosis of an infectious episode*	22/59 (37.3%)	26/75 (34.7%)	48/134 (35.8%)	0.099
Congenital abnormalities#	8/59 (13.6%)	6/75 (8.0%)	14/134 (10.4%)	0.790
Death during hospitalisation	4/59 (6.8%)	6/75 (8.0%)	10/134 (7.5%)	

**Includes: bloodstream infection, respiratory infection, meningitis, congenital syphilis, congenital tuberculosis, acute diarrhoea/dysentery, urinary tract infection, bacterial skin infection*
#Includes: hypospadias, G6PD deficiency, intestinal atresia, bilateral talipes equinovarus, Cornelia de Lange Syndrome, thoracic scoliosis, bilateral undescended testes, Klinefelter Syndrome, VACTERL association, polydactyly, cleft palate, myelomeningocoele, Trisomy 21

804 INFECTIOUS MORBIDITY OF BREASTFED, HIV-EXPOSED UNINFECTED INFANTS IN SOUTH AFRICA

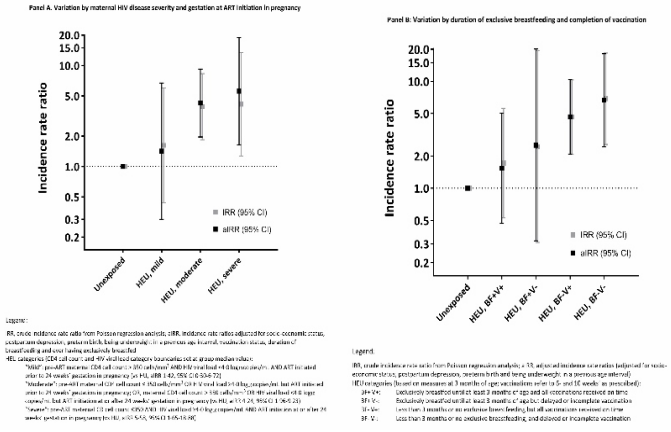
Stanzi M. Le Roux[1], Elaine J. Abrams[2], Kirsty Donald[1], Kirsty Brittain[1], Tamsin K. Phillips[1], Allison Zerbe[2], David M. Le Roux[1], Max Kroon[1], Landon Myer[1]
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Background: Without breastfeeding and maternal antiretroviral therapy (ART), HIV-exposed uninfected (HEU) infants experience greater infectious morbidity than HIV-unexposed (HU) infants. We hypothesized that with universal maternal ART, breastfed HEU and HU infants experience similar morbidity.

Methods: We recruited and followed pregnant women through delivery and with breastfeeding infants for ≥12 months. All HIV+ women initiated ART in pregnancy. Infection-related hospitalisation data abstracted from routine health records were analysed using incidence rate ratios (IRR) from Poisson regression.

Results: Mother-infant pairs (n=410 HU, n=459 HEU; pre-ART median CD4 count, 354 cells/μL; HIV viral load, HIV-VL 4•0 $\log_{10}$ copies/mL; gestation, 22 weeks) were followed for median 12 months. HEU (vs HU) infants experienced more infection-related hospitalizations between 7 days and 3 months (incidence/100 child-years, cy: 34•2 [95%CI 24•4-47•9] vs 9•8 [95%CI 5•1-18•8]; IRR 3•50 [95%CI 1•64-8•30]), but rates were similar at other ages. Rates for HEU infants with healthier mothers (n=84; ART initiation <24 weeks' gestation, CD4 count>350 cells/μL, HIV-VL<4•0 $\log_{10}$ copies/mL: 15•88/100cy [95%CI 5•12-49•23]) approximated those of HU infants (IRR vs HU, 1•62 [95%CI 0•44-6•00]); HEU infants of mothers with late ART initiation and advanced disease had the highest rates (n=44; ART≥24 weeks' gestation, CD4 count≤350 cells/μL, HIV-VL≥4•0 $\log_{10}$ copies/mL: 40•44/100cy [95%CI 15•18-107•74]; IRR vs HU, 4•14 [95%CI 1•27-13•44]). Reduced rates were seen among exclusively breastfed, timely-vaccinated HEU infants (n=165;16•82/100cy [95%CI 5•08-18•78]; IRR vs HU, 1•72 [95%CI 0•53-5•59]).

Conclusion: Despite ART in pregnancy, breastfed HEU vs HU infants had transiently increased infectious morbidity risks in early infancy. However, differences were driven by advanced maternal disease with late ART iniation, alongside suboptimal breastfeeding and vaccination. Interventions to increase early maternal HIV diagnosis and ART initiation, optimize vaccination and promote optimal breastfeeding should be prioritize to improve HEU child health.



805 HIV EXPOSURE AND HUMAN MILK OLIGOSACCHARIDES MODULATE THE INFANT GUT MICROBIOTA

Sarah L. Brooker[1], Nicole H. Tobin[1], Fan Li[1], Louise Kuhn[2], Grace M. Aldrovandi[1]

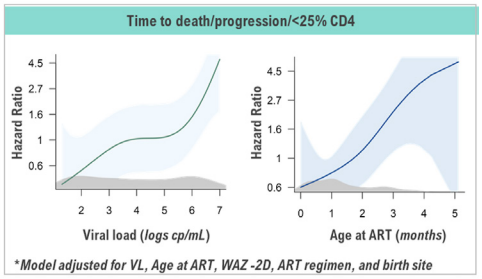
[1]University of California Los Angeles, Los Angeles, CA, USA, [2]Columbia University Medical Center, New York, NY, USA

Background: HIV-exposed, uninfected (HEU) infants experience almost twice the morbidity and mortality of their HIV-unexposed uninfected (HUU) counterparts. The mechanisms by which maternal HIV-infection alters infant immune development are under investigation. Maternal HIV infection is associated with alterations of breast milk human milk oligosaccharide (HMO) composition and the gut microbiome of HEU infants. Whether perturbations in maternal HMO composition in HIV-infected mothers alter the infant gut microbiome or whether infant gut microbial populations and maternal HMO profile are correlated for other reasons remains unknown.
Methods: 50 maternal-infant pairs were enrolled, half with maternal HIV, in a cross-sectional study at 1-3 months postpartum. 17 HEU and 25 HUU had stool shotgun metagenomics performed and maternal breast milk HMO data available. Host DNA removal followed by taxonomic classification using kraken v2.0 against the NCBI database resulted in 14.5 million reads assigned to 3720 taxa. 17 unique HMO isoforms were quantified using high-performance liquid chromatography. Statistical tests were performed in the R environment, v. 3.5.2.
Results: Alpha diversity tended to be lower in HEU compared to HUU infants. In contrast, maternal HMO alpha diversity tended to be increased in HIV-positive compared to HIV-negative mothers. In HEU infants, negative correlations were observed between Bifidobacterium breve and LNnT, Bacteroides vulgatus and LNFP III, Bacteroides fragilis and several other HMO including 2'FL, 3'SL, DSLNT, FLNH, LNFP I, as well as total HMO concentration. Escherichia coli was negatively correlated with DFLNH, DSLNT, and LNFP I, but had a positive correlation with LNFP II (FDR-adjusted $p < 0.1$). In HUU infants, the correlations were different: Bifidobacterium bifidum was negatively correlated with DFLNH, B. breve was negatively correlated with LNnT and LSTc, and Bacteroides fragilis was positively correlated with LSTb ($p < 0.1$). Correlations of pathways assessed by HUMAnN2 were found between chorismite biosynthesis I (found in B. fragilis and Akkermansia municiphila) and L-ornithine (found in B. breve and Bifidobacterium longum) and 3'FL, 3'SL, and DFLNT ($p < 0.1$).
Conclusion: Maternal HIV status modulates the associations between HMO profile and infant microbiota. These differential correlations suggest that bacterial utilization of HMO differs in HEU infants which may, in turn, contribute to altered GI and immune development and increased mortality of HEU infants.

806 POOR OUTCOME IN EARLY TREATED HIV PERINATALLY INFECTED INFANTS IN AFRICA

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Background: HIV-infected infants should be treated early after diagnosis. Mortality and morbidity peak in the first 6 months after ART initiation and in infants < 1-year-old. Mortality is linked to advanced disease at diagnosis. There are few data about determinants of poor outcome in early-treated infants. The aim is to assess risk factors for poor outcome despite early ART in a cohort of infants in South Africa and Mozambique.
Methods: EARTH is a multi-centre cohort enrolling HIV-infected infants diagnosed and treated in the first 3 months of life. Enrolment started in May 2018. ART regimens followed national guidelines. Poor outcome was defined as mortality or severe disease (progression to WHO clinical stage 3 or 4 or CD4 below 25%). Risk factors for poor outcome and viral load (VL) suppression adjusting for socio-demographics, clinical, immunological and virological measures were assessed by multivariable time-dependent Cox-proportional hazards model, including time-dependent coefficient for follow-up VL and CD4.
Results: To date, 135 infants were enrolled. Currently, the median follow-up time is 5.5 months (IQR 2.7-6.9). Median age at enrolment was 38 days (31-75), and median age at ART was 33 days (19-66). Fifty-four percent were male, 37% were premature and 30% had baseline weight-for-age Z-Score (WAZ) <-2SD. Prophylaxis after birth was prescribed to 80%. Median baseline VL was 5.1 logs (3.6-6.1). Median baseline CD4 was 35% (26.3-44.4). During the follow-up, 46% of mothers had health issues or serious life events but no mortality. 12 (9%) of infants died, 7 (5%) progressed to stage 3 or 4, and 16 (12%) had CD4 <25%. In total, 32 (24%) had poor outcomes. Only 34 (25%) infants suppressed VL during follow-up at a median time of 5.2 months. According to the model, determinants of poor outcome were VL and age at ART, after adjustment by site, baseline WAZ and ART regimen. The hazard of poor outcome was almost 3X higher (HR: 2.7 [1.3-5.8], p=0.010) per each VL log persistently elevated during the follow-up, and 50% higher for every month that ART was delayed (HR: 1.5 [1.01-2.2], p=0.049). At this point, time to suppression was influenced only by baseline VL (HR: 0.01 [0.002-0.1], p<0.001) and maternal severe life events/ health issues (HR: 0.4 [0.8-0.9], p=0.042).
Conclusion: Despite early ART, a high proportion of infants have a poor outcome during the first months of life. The poor outcome is mainly influenced by VL during follow-up and age at ART initiation



807 VIRAL RESPONSE IN HIV-INFECTED INFANTS STARTING ART AT 1 MONTH IN SOUTHERN MOZAMBIQUE

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Background: In perinatal HIV infection, early infant HIV diagnosis and initiation of antiretroviral treatment (ART) are critical for achievement of viral suppression and long-term remission into childhood and adolescence. This study was aimed at investigating viral response of a cohort of infants who started ART in the first month of life in southern Mozambique.
Methods: Project TARA (Towards AIDS Remission Approaches) included a descriptive cohort study of HIV perinatally infected infants who started ART at <2mo of age and were followed with frequent plasma virus load (VL) measures for two years under a NIH funded grant. VL monitoring was performed at 1, 2, 4, 5, 8, 9, 11, 17, 18 and 23mo and those with >4 measurements were included in the analysis. Kaplan–Meier estimator and descriptive analyses were used to summarize infants virologic response.
Results: Thirty infants started ART with ZDV/3TC/LPVr at 34 days (IQR 18). Median pre-ART VL was 1.988.708c/ml (IQR 4.661.355). 18/30 (60%) reached viral suppression (VS), defined as HIV RNA plasma < 1000copies/ml, within a median time of 7.86mo (1-24mo) after ART initiation. 9/18 (50%) infants who initially achieved VS had a rebound within 3.3 mo (1-10mo); 5/9 re-suppressed within 3mo (1-7mo). 14/30 (47%) infants had sustained VS defined as ≥ 2 consecutive VS measures. Cumulative probability of VS among all infants was 43% at 6mo, 56% at 12mo and 73% at 18mo (Fig1). Among 18 infants adherent to ART who reached VLS, the median time to control the virus was 3mo (0.92-16.41mo); at 12mo the probability of VS was 89%. There was no statistically significant difference in time to VS among infants with pre-ART VL>Log6 compared to those with VL<Log6. Strategies to promote adherence included intensified adherence and psycho-social sessions, but they showed limited success.
Conclusion: Despite early ART initiation and adherence efforts, only 60% HIV+ infants achieved virus suppression, and of these, about 50% had a virus rebound demonstrating adherence challenges in sustaining undetectable virus load faced by caregivers. Research to understand barriers to ART initiation and ART adherence in mothers along with innovative approaches to address problems that prevent timely delivery of medications to infants in low resource countries are urgently needed.

808 SEROSTATUS IS A MARKER FOR SUSTAINED VIRAL SUPPRESSION IN EARLY TREATED CHILDREN

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Background: Markers for sustained viral suppression over time are not available for HIV infection. We evaluated whether HIV serology was a useful marker for sustained RNA suppression or low cell-associated HIV reservoir among HIV-infected children treated very early in life.
Methods: The Early Infant Treatment Study (EIT) started antiretroviral treatment (ART) for HIV-infected children at < 7 days of age. Quantitative HIV DNA was evaluated every 1-3 months in PBMCs, and at 84 weeks with repeat qualitative whole blood DNA PCR testing and dual enzyme immunosorbent assay (EIA). Children starting ART at age 30-365 days in the Botswana ART program and sampled at 24-36 months of age served as controls. Comparisons were by Wilcoxon Rank Sum testing.
Results: Of 40 HIV+ children enrolled in EIT, 30 had reached 84 weeks by the time of this analysis; 14 (47%) had sustained RNA < 40 copies/mL at all visits from 24 to 84 weeks, including 12 (86%) with negative EIA at week 84, and 2 (14%) with indeterminate EIA. Among the 16 with > 40 copies/mL at one or more visits from 24 to 84 weeks, 5 (31%) had negative EIA, 10 (63%) had positive EIA, and 1 (6%) were indeterminate (Table). For a threshold of 40 copies/mL, the negative predictive value of the EIA was 71% (12/17) for sustained viral suppression from 24 to 84 weeks, and the positive predictive value was 100% (10/10) for lack of sustained suppression. For a threshold of 400 copies/mL, the negative predictive value was 100% (17/17), and the positive predictive value was 90% (9/10). Whole blood qualitative HIV DNA PCR at 84 weeks was negative for 14 (47%) children, positive for 15 (50%), and indeterminate for 1 (3%), and the DNA result was concordant with EIA testing for 73% (19/26) with interpretable results for both tests (Table). Among the first 17 EIT children with quantitative cell-associated DNA testing available at 84 weeks, the median DNA reservoir was significantly lower than among 10 control children (10.9 vs. 981.4 copies/million cells; p=<0.001). However, unlike plasma RNA, cell-associated DNA was not associated with the EIA test result at 84 weeks (p=0.63) in this first group of EIT children tested.
Conclusion: HIV serostatus at 84 weeks was a marker for sustained RNA suppression among HIV-infected children treated from the first week of life, and may be useful in longitudinal follow-up. Very low viral reservoirs continue to be noted among early-treated children.

Table: HIV viral suppression over time and 84 week qualitative DNA result,* by 84 week HIV serology (EIA test)

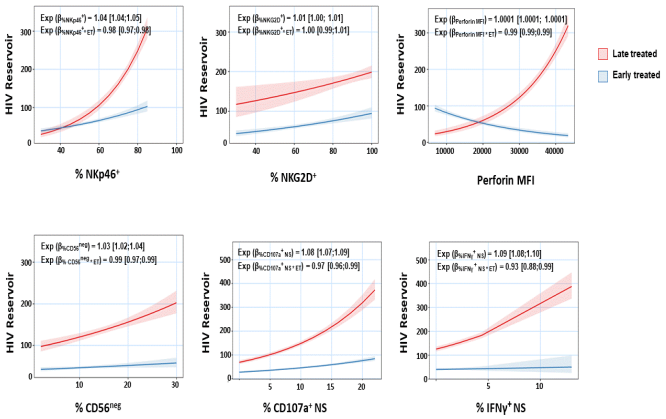
	<40 copies/mL 24-84 weeks (sustained)	≥40 copies/mL 24-84 weeks (at least once)	Negative qualitative DNA at 84 weeks	Positive qualitative DNA at 84 weeks
Negative HIV Serology*	12	5	11	5
Positive HIV Serology	0	10	2	8
Indeterminate HIV Serology	2	1	1	2

* Excludes 1 child with indeterminate Qualitative DNA test (with negative HIV serology)

809 NK CELLS ARE PRESERVED BY EARLY ART IN HIV-INFECTED CHILDREN WITH LOWER RESERVOIR

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Background: HIV infection causes pathologic changes in the natural killer (NK) cell compartment that can be only partially restored by antiretroviral therapy (ART). We studied NK cells phenotype and function in perinatally HIV-infected children (PHIV) enrolled in a multicenter cross-sectional study (CARMA, EPIICAL consortium), who started ART at different ages (early treated, ET ≤ 6 months; late treated, LT > 6 months to 2 years).
Methods: 40 PHIV who started ART< 2 years of life and had undetectable viremia (< 50 HIV copies/ml) for at least 5 years, were enrolled in 7 European research centers. HIV-1 DNA copies/10^6 PBMCs were measured by real-time PCR. NK cells were analyzed by flow cytometry for % of CD56high, CD56dim, CD56neg subsets, receptor expression, maturation profile, degranulation capacity (CD107a expression) in the presence or not of K562 cells, and IFNγ production after stimulation or not with cytokines. Data were analyzed by Spearman correlation plots and multivariable Poisson regression model (adjusted for baseline %CD4 and RNA HIV viral load and for age at ART start as interaction term, either ET or LT) to explore the association between NK cell parameters and HIV reservoir modulated by age at ART start.
Results: Later treatment in PHIV leads to a shift of NK cells to the anergic CD56neg subset that is associated with an increase of HIV reservoir size. For each 1% increase in %CD56neg, 3% upregulation of HIV reservoir is found and this effect is reduced in ET. LT display a persistent "activated" phenotype (i.e. NKp46+, NKG2D+, high Perforin expression) that is not present in ET: for each 1-unit increase in % of NKG2D+, % of NKp46+ or Perforin mean fluorescence intensity, there is an enrichment of 1%, 4% or 0,01% in HIV reservoir, respectively. Moreover, %CD107a+ and %IFNγ+ non-stimulated NK cells show a positive association with HIV DNA, but these effects are decreased in ET. Finally, among CD56dim cells, the frequencies of early differentiated and mature cells are associated with HIV DNA in a positive and inverse manner, respectively, whereas these effects were lower in ET.
Conclusion: Our results demonstrate that starting ART as soon as possible after birth in PHIV preserves NK cell features. Notably, we show for the first time that an intact NK cell compartment in PHIV is associated with lower HIV viral reservoir.



810 MARKERS OF HIV RESERVOIR SIZE IN INFECTED CHILDREN ON LONG-TERM VIRAL CONTROL

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Background: Curative strategies for HIV will need to eliminate the replication competent latent reservoir. Immune Checkpoint molecules (ICP) are promising therapeutic targets for the elimination of the HIV latent reservoir, as CD4 T cells expressing ICP have been shown to preferentially harbor latent, replication-competent HIV. T cells expressing ICP are also considered as being exhausted. T follicular helper cell subset of CD4 T cells are critical for B cell differentiation for which induction of IL-21 is favorable while IL-2 is inhibitory. Here a cohort of HIV vertically infected children and young adults under durable viral control (PHIV) were investigated for CD4 ICP, immune activation (IA) markers and function in relation to HIV reservoir size.

Methods: 40 PHIV (4-19yrs age) who started ART <2 years of life and had undetectable viremia (<50 HIV copies/ml) for the past 5 years, were enrolled in 7 European research centers. HIV DNA copies per million peripheral blood mononuclear cells (PBMC) were measured by real-time PCR. Flow cytometry was used to investigate CD4 T cells for 1) co-expression of PD1 with IA (ICOS, CD38, Ki67 and HLA-DR); 2) co-expression of PD1 with ICP (TIGIT, LAG3, TIM3 and CTLA4); 3) intracellular cytokine production (IL2, IFNg, TNFα, IL21) after stimulation with ENV peptides. Pearson correlations and 2 group comparisons were performed using the Mann-Whitney T Test. P value<0.05 was considered significant.
Results: Total PD1+ CD4 T cells positively correlated with HIV-DNA (r=0.46) as did CD4 T cells co-expressing PD1 with other ICP or IA (table 1). We then divided our cohort based on HIV DNA distribution into those with high (4th quartile) and low (1st quartile) HIV DNA. We found that PD1+ CD4 T cells co-expressing IA or ICP were higher in participants with high HIV DNA compared to low HIV DNA (table 1). PD1+ CD4 T cells (unstimulated) also showed correlations with ENV antigen activated circulating T follicular helper cells (Tfh) expressing CD40L (r=-0.41, p<0.05) with selective induction of IL2 (r=0.47, p<0.05) suggesting that PD-1 expression on CD4 can be associated with dysfunctional T:B cells interaction in response to HIV antigens.
Conclusion: This study confirms that vertically HIV infected children and young adults under long-term viral control maintain the association between expression of PD1 on CD4 T cells and size of viral reservoirs and also implicates the size of the viral reservoir in altered Tfh functionality.

Table 1: Relationship of ICP with HIV DNA in CD4 T cells

CD4+ T cell Markers	Correlation with HIV DNA in PBMC		Comparison of participants with high versus low HIV DNA (T-test)
	P Value	R value	P value
PD1+ICOS+CD38+Ki67+HLA-DR+	0.04	+0.35	NS
PD1+ICOS+CD38+Ki67+	0.02	+0.38	NS
PD1+ICOS+CD38+	0.001	+0.52	0.01
PD1+ICOS+	0.03	+0.35	0.04
PD1+CD38+	0.05	+0.33	0.005
PD1+TIGIT+LAG3+TIM3+	0.05	+0.33	0.04
PD1+TIGIT+LAG3+	0.04	+0.35	0.007
PD1+TIGIT+TIM3+	NS		0.04
PD1+TIGIT+	NS		0.01
PD1+LAG3+	NS		0.02
PD1+TIM3+	NS		0.02

NS: Not Significant

811 PROVIRAL LANDSCAPE IN CHILDREN PARALLELS ADULTS AND ENABLES RESERVOIR RECONSTRUCTION

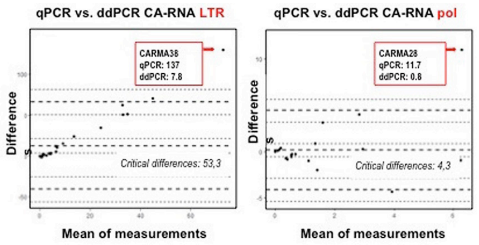
Jenna M. Hasson[1], Mary Grace K. Katusiime[2], Samuel Smith[3], Michael J. Bale[1], Liliana Perez-Rodriguez[3], Divya Kilam[3], Wei Shao[4], Mark Cotton[2], Eli A. Boritz[3], John M. Coffin[5], John W. Mellors[6], Sean Patro[1], Gert U. van Zyl[2], Mary F. Kearney[1]
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Background: Characterizing HIV-1 proviruses that lead to viral rebound upon ART interruption could inform design strategies towards a functional cure. Methods for measuring the HIV-1 reservoir, such as the quantitative viral outgrowth assay, require collecting large sample volumes that are difficult to obtain from children. Here, we profile the proviral landscape in children and demonstrate the utility of "viral reconstruction" to characterize the genetics of the HIV-1 reservoir when sample volumes or proviral copy numbers are low.
Methods: We performed near-full length (NFL) single-genome sequencing on 210 amplicons from PBMC of two children treated relatively early (9.0 and 9.3 months) and on ART for 7 years. The proviral landscape was compared to that of adults on ART (1056 genomes in the Proviral Sequence Database). Because recovering intact proviruses is rare in children and in adults who initiate ART early, we used the population of defective proviruses to reconstruct NFL ancestors that may be similar to the founder virus and/or to intact proviruses that persist on ART.
Results: Similar to adults, ~98% of the proviruses were defective including 60% with large 3' deletions of env/tat/rev. Proviral diversity (0.3% and 0.7% in p6-PR-RT) and proviral copy number (47 and 182 copies/10^6 PBMC) were low. In the child with the lower HIV-1 diversity and fewer 3' deletions, we identified defective proviruses with sequences identical except for non-overlapping deletions, allowing reconstruction of the ancestor that infected these cells and is likely similar to both the founder virus and to variants comprising the HIV-1 reservoir. Indeed, the reconstructed virus matched an intact provirus from the same sample, demonstrating the accuracy of the approach.
Conclusion: Despite very different immune systems, the HIV-1 proviral landscapes on ART were not obviously different between children and adults, with most proviruses containing large 3' deletions. The low numbers of infected cells in children and in early-treated adults makes it difficult to detect intact proviruses. Here, we demonstrate the utility of viral reconstruction to infer the genetics of possible transmitted founder viruses and of intact proviruses that may comprise the HIV-1 reservoir. Characterizing the genetics of the HIV-1 reservoir in early-treated individuals can help guide the design of therapeutic interventions towards HIV remission.

812 CELL-ASSOCIATED HIV-1 DNA/RNA IN CHILDREN: PERFORMANCE OF REAL-TIME AND DIGITAL PCR

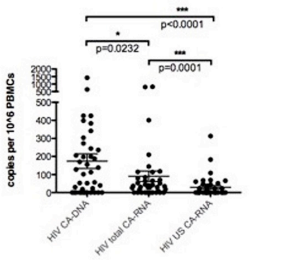
Kathleen Gärtner[1], Triantafylia Gkouleli[1], Judith Heaney[2], Paul Grant[2], Sara Dominguez Rodriguez[3], Eloise Busby[4], Denise O'Sullivan[4], Moira J. Spyer[1], Caroline Foster[5], Pablo Rojo Conejo[3], Deborah Persaud[6], Anita De Rossi[7], Jim Huggett[4], Eleni Nastouli[2], for the EPIICAL Consortium
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Background: Children perinatally infected with HIV-1 (PaHIV) require life-long antiretroviral treatment (ART). Despite ART, HIV persists in a latent reservoir, the cause of viral rebound after treatment interruption (TI). Robust methods to quantify the reservoir in perinatal infections are required. To detect cell-associated HIV-1 DNA (CA-DNA) and cell-associated HIV-1 RNA (CA-RNA) in suppressed PaHIV we compared two methods: quantitative Real Time PCR (qPCR) and digital droplet PCR (dPCR).
Methods: In the CARMA-EPIICAL study, 40 European PaHIV on suppressive ART for ≤5 years were recruited. Total CA-DNA, total CA-RNA and unspliced (US) CA-RNA were quantified using qPCR (C1000, Bio-Rad) and dPCR (QX100 Droplet Analyser, Bio-Rad). Nucleic acids were extracted from PBMCs using the DSP virus/pathogen mini kit (Qiagen) on the Qiasymphony. Quantitative qPCR and dPCR were performed using primers in the LTR region for total CA-DNA and total CA-RNA and the pol region for US CA-RNA. To normalise copy numbers of CA-DNA and CA-RNA per 10^6 PBMCs reference genes were included in multiplex reactions. For qPCR a standard curve with known copy numbers was used in a 10-fold dilution series. The concordance analysis of qPCR and dPCR was determined with the Bland-Altman test and significance with Wilcoxon rank test.
Results: HIV-1 CA-DNA could be detected in 36 of 40 PaHIV (<10-410 c/10^6 PBMCs for qPCR; <10-1420 c/10^6 PBMCs for dPCR). In seven of the 36 PaHIV CA-DNA copy numbers were below 10 c/10^6 PBMCs. Total CA-RNA was detected in 31 (<11-5789 c/10^6 PBMCs for qPCR, 11-857 for dPCR) and US CA-RNA in 23 of 40 patients (<11-274 c/10^6 PBMCs for qPCR, 11-325 for dPCR). Copy numbers of CA-DNA were significantly higher than CA-RNA, total CA-RNA copy numbers were significantly higher than US CA-RNA (see figure). Concordance analysis showed 97.4% agreement between qPCR and dPCR for total and US CA-RNA.
Conclusion: We have demonstrated the detection of very low HIV CA-DNA and CA-RNA levels using both qPCR and dPCR in well suppressed PaHIV. The high agreement of concordance analysis suggests comparability of qPCR and dPCR for detecting low copy numbers of CA-RNA and validates use of both methods for diagnostic applications. The very low levels of CA-RNA expression could contribute to chronic immune activation and/or lead to production of infectious viruses. Further work to determinate the sensitivity of both methods and validate lower thresholds for CA-DNA and CA-RNA will be done.



Bland-Altman concordance between qPCR and dPCR

CARMA38 and CARMA28 are outliers



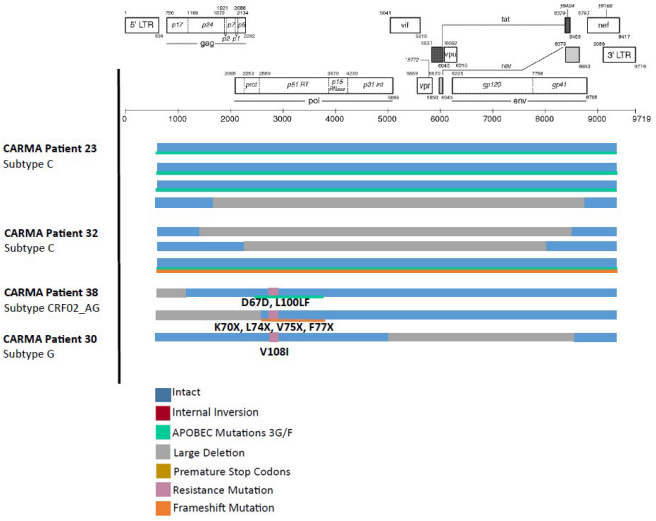
Detection of CA-DNA and CA-RNA

results from dPCR
(Wilcoxon matched-pairs signed rank test)

813 ASSESSMENT OF HIV-1 DNA BY SINGLE-GENOME SEQUENCING IN CHILDREN ON SUPPRESSIVE ART

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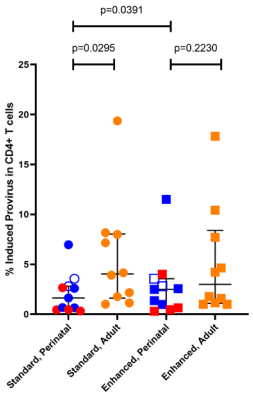
Background: Perinatally HIV-1 infected children on early suppressive ART (PaHIV) represent an important population in the era of cure. Reservoir characteristics can determine criteria and cut-offs in future trials. We present unique HIV-1 DNA single genome sequencing (SGS) data in PaHIV from a multicentre cross-sectional study. We describe the presence of intact proviruses, defective genomes and ART resistance associated mutations (RAMs).
Methods: In the CARMA-EPIICAL study, 40 PaHIV on ART since <2 years of life and suppressed for ≥5 years were recruited in 7 centers. HIV-1 DNA was measured by real-time PCR. Near full-length SGS was performed in positive samples: manual extraction and limiting dilution touchdown PCR generated amplicons across the genome using in house and published primers. Products were analysed by gel, libraries generated by Nextera®XT DNA Kit and sequenced on the Miseq (Illumina). De novo assembly of genomes was performed, using an in-house bioinformatics pipeline with open source software. SMALT and LASTZ for alignment and the HIVSeqinR pipeline were utilised to describe intact or otherwise defective viruses. The Stanford database was used for resistance/subtype analysis and the Geno2pheno tool for tropism assignment.
Results: The majority of patients, 34/40, had detectable HIV-1 DNA (median 115.1 c/10^6 PBMCs, range 49.1-260.7 c/10^6 PBMCs). Initial findings on 4 patients, where 10 near full-length sequences were generated, are included in the figure. 2 viruses were subtype C, 1 subtype G and 1 CRF02_AG. Tropism assignment was possible in 9/10 sequences, 4/9 were CCR5, 5/9 were CXCR4. Intact sequences were identified in 4/10, however all contained APOBEC 3G/F mutations. In 2 patients (3/10 sequences) RAMs in the pol/RT region were found. Defective genomes were frequent, 6/9 genomes contained deletions (4/6 were large), while 2/9 sequences had frameshift mutations. Inversions and stop codon mutations were not detected.
Conclusion: Our preliminary findings in this cohort suggest that the HIV-1 DNA landscape in PaHIV can be complex. Defective genomes with large deletions can be frequent but intact genomes are also present suggestive of a pool of virus that can rebound post treatment interruption. However, host driven APOBEC related hypermutations are present in long standing treated infection as well as RAMs. SGS represents a useful tool for reservoir assessment and further sequencing and analysis with respective clinical data is ongoing in the CARMA cohort.



814 DIFFERENCES IN THE INDUCED LATENT HIV RESERVOIR IN PERINATAL AND ADULT INFECTIONS

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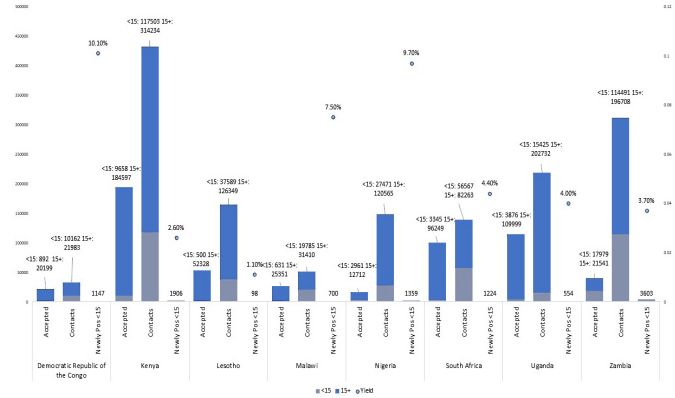
Background: The HIV latent reservoir in resting memory CD4+ T cells prevents cure. Novel therapies to reactivate and eliminate the reservoir are in clinical trials in adults, but not yet in pediatric populations.
Methods: HIV proviral reservoir size was determined in perinatal (N=11) and adult infections (N=10) by digital droplet PCR (ddPCR) and with the intact proviral DNA assay (IPDA) in perinatal samples. The inducibility of the latent reservoir was determined with the Tat/rev Induced Limiting Dilution Assay (TILDA) that uses single-round (12 hr) T cell stimulation of CD4+ T cells with PMA/ionomycin to maximally activate cells to induce proviral expression, measured as multiply-spliced HIV RNA Units per 10^6 CD4 cells (msRUPM). Markers of immune activation (CD69, CD25 and HLA-DR) and exhaustion (PD-1, TIM-3 and TIGIT) were also assessed. An enhanced TILDA with addition of PHA and for 18 hours was performed to enhance proviral expression in perinatal infections. Non-parametric tests were used for differences between paired and unpaired measurements; correlations were quantified by Spearman rank coefficient.
Results: The median age was 15.8 yrs with a median duration of suppression of 6.7 yrs for perinatal infections, and 40.5 yrs with a median duration of suppression of 7.3 yrs for adult infections. We found that despite a higher proviral reservoir size (median 132.1 vs. 66.7 c/10^6 PBMCs) and similar rates of T cell activation with PMA/ionomycin (median %CD69 = 96.7% and 93.0%) in perinatal and adult infections, respectively, the size of the induced reservoir was significantly lower in perinatal than in adult infections (median msRUPM of 2.99 vs 11.92, p=0.020). With the enhanced TILDA, the size of the induced reservoir increased significantly in perinatal infections (1.5-fold to a median of 4.5 msRUPM; p=0.034), but not in adult infections. The proportion of induced provirus was significantly lower in perinatal infections at 1.6% compared with 4.0% in adult infections (p=0.030). At baseline, the proportion of HLA-DR+ T cells was significantly lower in perinatal compared with adult infections (median HLA-DR+ cells = 4.56% vs 10.5%, p=0.012), but not correlated with the induced reservoir size.
Conclusion: The inducibility of the latent reservoir is substantially lower in perinatal compared with adult infections, possibly due to differences in baseline states of immune activation, with implications for latency reversal strategies towards ART-free remission.



815 CHILDREN <15 ARE LESS LIKELY TO BE AN INDEX TESTING CONTACT COMPARED TO ADULTS

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Background: According to UNAIDS, half of children with HIV globally remain undiagnosed. Children with HIV are being diagnosed after the first five years of life, and thus may have no routine contact with the health system until they become symptomatic. In April 2017, PEPFAR began to rapidly scale index testing of sexual contacts and biological children of people living with HIV across all sites and communities, as it has shown the highest testing yield across all countries. While some countries have been successful in scaling index testing among sexual contacts, many have struggled with using index testing effectively to find children with HIV who remain undiagnosed. This report evaluates the index testing cascade of pediatric contacts from October 2018 to June 2019.
Methods: A descriptive analysis was used to assess the number of children (aged 1-14) and adults (aged 15-49) who newly tested positive for HIV and accepted index testing services in eight countries in sub Saharan Africa. We then evaluated the number of pediatric contacts and adult contacts of index participants who were elicited for HIV testing, the number of children who received an HIV test, and the number of children who were seropositive for HIV (yield).
Results: Each index case elicited more adult contacts than pediatric contacts in all 8 countries, with noteworthy geographic variation. The percent of elicited contacts who were children ranged from 0.08% in Uganda to 40% in South Africa. For South Africa, Zambia and Malawi, >37% of elicited contacts were children, while for the Democratic Republic of Congo (DRC), Kenya, Lesotho, Nigeria, and Uganda, <25% of elicited contacts were children. HIV testing yield among children identified as contacts ranged from 1.1% in Lesotho to 10.1% in DRC, with an average yield of 4.5% across the 8 countries.
Conclusion: Our results demonstrate high yields of new pediatric cases in specific geographic regions from index testing services. Failure to identify all pediatric contacts of index clients represents a missed opportunity to find undiagnosed children. Although we are unable to link the number of clients who accept index testing with the number of contacts that are elicited from index testing and ultimately the number of children who test positive; attention to pediatric contacts of new adult cases will allow life-saving therapy to be delivered to a vulnerable population.



816 THE CASCADE OF HIV CARE FOR CHILDREN AND ADOLESCENTS IN WEST AFRICAN COHORTS

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Background: The attrition across the continuum of care for children and adolescents living with HIV (CALHIV) from their HIV diagnosis is unknown in West Africa. We assessed the progress to the second and third 90-90-90 targets in the International epidemiological Databases on AIDS (IeDEA) paediatric West African Cohort (pWADA).
Methods: The pWADA database, involves nine paediatric clinics in five countries (Benin, Côte d'Ivoire, Ghana, Mali, Togo). All CALHIV aged 0-18 years, ART-naïve at enrolment except for prevention of mother-to-child transmission, and diagnosed between 2004 and 2018 were included. We described the proportions of the CALHIV initiating ART, and attrition (death, loss to follow-up [LTFU]: last clinical visit >12 months) and the proportion of those on ART virally suppressed (first viral load <500cp/mL after 6-month post-ART). We presented cumulative incidence and factors associated with ART initiation, with death/LTFU as competing risks.
Results: Overall, 7570 CALHIV were enrolled in pWADA; 69% were enrolled before 2013. At enrolment, 49% were females, median age was 3.5 years [interquartile range (IQR): 1.2–7.6 years], 37% were <2 years, and 73% were eligible to initiate ART according to the WHO guidelines in effect at enrolment. During follow-up, 3% died, 3% were transferred out and 19% were LTFU before ART initiation; 3% were alive but had not initiated on ART while 72% (5475/7570) initiated ART. The median time between baseline and ART initiation was 1.4 months (IQR: 0.3-7.2 months]. At ART initiation, median age was 5.1 years (IQR: 2-9 years) and 80% were treated with a non-nucleoside reverse transcriptase inhibitors regimen. Adjusted for center, gender, clinical/immunological ART eligibility, children aged <2 years (Ajusted Hazard ratio [aHR]: 0.59; 95% Confidence Interval [95%CI]: 0.54-0.65) and aged 2-4 years (aHR: 0.84; 95%CI: 0.77-0.92) at baseline were significantly less likely to initiated ART compared to those aged 10-15 years, as well as CALHIV enrolled before 2016 compared to those enrolled later. Among CALHIV on ART, 65% (3562/5475) performed at least one viral load test during follow-up. The cumulative probability of reaching viral suppression was 17%, 26%, 36% and 43% at 6, 12, 24 and 36 months, respectively.
Conclusion: In West Africa, CALHIV had low retention in care, low access to viral load and far to meeting the second and third stages of the 90-90-90 targets. Additional supports is needed for this population to initiate ART earlier, using more potent drugs and to strengthen treatment adherence.

817 HIV VIRAL SUPPRESSION IN ADOLESCENTS AND YOUNG ADULTS: A NATIONAL SURVEY IN KENYA

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Background: Adolescents and young adults (AYA) living with HIV are at high risk of virologic failure. While HIV clinics have developed innovative approaches to address unique AYA challenges, it is unclear if these influence viral suppression. To achieve UNAIDS 95-95-95 goals, there is need to understand modifiable and fixed individual and clinic correlates of suppression.
Methods: We conducted a multi-level cross-sectional analysis using viral load data and facility surveys from HIV treatment programs throughout Kenya. We abstracted medical records of AYA in HIV care, analyzed the subset on ART for >6 months between January 2016-December 2017, and collected information on AYA services at each clinic. We used multi-level logistic regression models

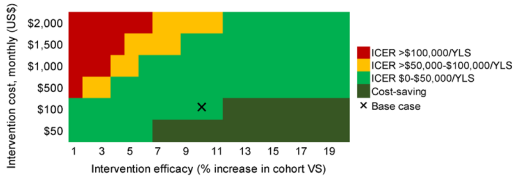
to determine individual-and clinic-level correlates of viral suppression at most recent assessment.
Results: In 99 HIV clinics, among 10,096 AYA on ART >6 months, 2,683 (27%) had unsuppressed viral load (VL).
Adjusted for individual-level factors, clinic-level correlates of individual suppression included designated adolescent spaces (aOR: 1.32, [95%CI: 1.07, 1.63]) and faster VL turnaround time (TAT) (aOR: 1.06 [95%CI: 1.03, 1.09]) per 10-day shorter TAT). Adjusted for clinic-level factors, AYA age 10-14 and 15-19 had lower odds of suppression compared to AYA age 20-24 years (aOR: 0.61 [95%CI: 0.54, 0.69] and 0.59 [95%CI: 0.52, 0.67], respectively). Compared to females, males had lower odds of suppression (aOR: 0.69 [95%CI: 0.62, 0.77]). Compared to ART duration of 6-12 months, ART for 2-5, >5-10 or >10 years was associated with poor suppression (p<0.001).
In 16% of clinics, ≥80% of AYA were suppressed. Clinics with ≥80% AYA viral suppression were more likely to be in hyper-endemic counties (56% versus 22% p=0.04), have separate adolescent space, and a shorter viral load TAT (39% versus 15% and 9 days versus 12 days p=0.03, <0.001, respectively).
Conclusion: Dedicated adolescent space, rapid VL TAT, and tailored approaches for specific groups may improve suppression. Routine summarization of VL suppression in clinics could provide benchmarking to motivate innovations in clinic- and individual-AYA care strategies.

818 CAN ADHERENCE INTERVENTIONS BE COST-EFFECTIVE AMONG YOUTH WITH HIV?

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Background: Viral suppression (VS) among US youth with HIV (YWH) in care is only 25-59%. The Adolescent Medicine Trials Network for HIV/AIDS Interventions is evaluating several interventions to improve ART adherence among YWH. Our objective was to model the impact of a hypothetical adherence intervention, based on electronic reminders, to identify combinations of effectiveness and cost at which these programs would be cost-effective for YWH.
Methods: Using the Cost-Effectiveness of Preventing AIDS Complications-Adolescent model, we simulated a cohort of YWH ages 13-24 using published YWH-specific data: cohort-level VS 59% (RNA <50c/mL), mean CD4 654/µL (SD 276). We compared 2 strategies: usual care (standard-of-care, SOC) and a 12 month (m) adherence intervention (AI) that led to an absolute increase in cohort-level VS (efficacy) of 10% compared to SOC at 12m and cost $100/m/person. We assumed all YWH were in care and on ART for the first 12m in both SOC and AI, after which YWH were lost-to-follow-up/returned to care at 0.62/0.015%/m. We examined a range of AI efficacies (VS +1-20%) and costs ($50-2,000/m). Projected outcomes included opportunistic infections (OIs), life expectancy (LE), primary HIV transmissions averted during the intervention, HIV-related costs, and incremental cost-effectiveness ratios (ICERs, $/year-of-life saved (YLS); threshold ≤$100,000/YLS; discounted 3%/year).
Results: Compared to SOC, AI reduced OIs by 15% and transmissions by 19% at 12m. Discounted LE for SOC vs. AI was 21.9 vs. 22.3 years. Discounted lifetime cost/person was $599,700 for AI and $599,500 for SOC. AI was +$200/person vs. SOC, a difference largely driven by added intervention costs (+$1,200) and ART (+$3,500); these costs were partially offset by savings from averted transmissions (-$3,800), less costly HIV-related care (-$300), and fewer OIs (-$200) and deaths (-$200). AI was cost-effective compared to SOC ($490/YLS). At base-case efficacy (10%), AI was cost-effective at costs up to $2,000/m; at base-case cost ($100/m), AI was cost-effective at efficacies ≥1% (Fig). When AI costs fell to $50/m, AI was cost-saving even when efficacy was as low as 7%.
Conclusion: Adherence interventions among YWH that increase VS could reduce OIs, deaths, and transmissions, and be cost-effective. As novel interventions are evaluated, modeling can identify benchmarks for efficacy and cost that would render these interventions clinically and economically valuable for this vulnerable population.

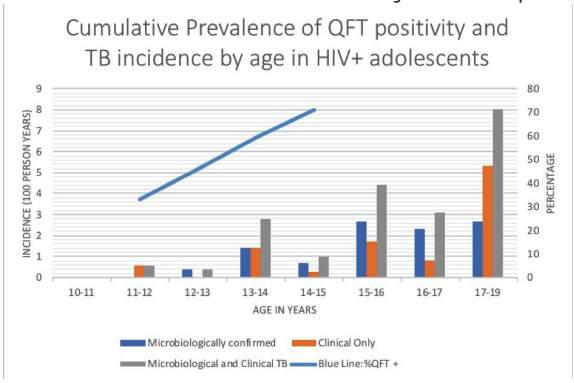
FIGURE. TWO-WAY SENSITIVITY ANALYSIS: INTERVENTION EFFICACY AND COST



819 TUBERCULOSIS INFECTION AND DISEASE IN HIV-INFECTED ADOLESCENTS ON ART: A COHORT STUDY

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[1]University of Cape Town, Cape Town, South Africa, [2]Stellenbosch University, Cape Town, South Africa

Background: There are limited data on TB in perinatally-infected adolescents living with HIV (PHIV+) in high burden settings. We examined the incidence of latent tuberculosis infection (LTBI) and TB disease in the Cape Town Adolescent Antiretroviral Cohort.
Methods: PHIV+ adolescents between 9-14y, on ART >6m in routine public sector care and age-matched HIV-uninfected children were enrolled between 2013-2015 and followed 6-monthly until end 2018. Symptomatic screening (including history of having a TB contact and or being on Isoniazid prophylaxis) for TB, chest radiograph and sputum for Xpert MTB/RIF, microscopy and culture, viral load and CD4 count were performed at enrolment and annually. QuantiFERON (QFT, Qiagen, South Africa) was done at enrollment and then annually if prior QFT was negative. LTBI was defined by a QFT of >0.35 IU/ml in the absence of signs and symptoms of TB. TB diagnosis was defined as definite (culture-confirmed) or probable (clinical case definition). Time to event analyses were used to describe the incidence of LTBI and TB disease.
Results: 485 PHIV+ and 95 HIV- adolescents (median age 12 years [IQR:10.6-13.3]; 50% male) had QFT results at enrolment. PHIV+ had a median CD4 of 715 cell/µL(IQR:564-959) and 365 (75%) had viral load <40 cps/ml. 61% of PHIV+ had a history of TB disease before enrolment (vs 3% in HIV-, p<0.01) and 27% were on INH prophylaxis (vs 4% in HIV-) but with no difference in QFT positivity at enrolment (33% vs 28%, p=0.34). Over 3 years of follow-up, HIV+ participants had a similar rate of QFT conversion compared to HIV- [7.4 (5.9-9.4) vs 8.7 (CI:5.6-13.7) per 100- person years (PY), p= 0.31]. HIV+ participants had a higher rate of TB disease [2.2 (CI:1.6-3.1) vs 0.3 (0.00-2.2) per 100- PY, p= 0.07]. 46% of HIV+ participants with TB disease were QFT+. Figure 1 describes the cumulative prevalence of QFT positivity and TB incidence by age in HIV+ participants.
Conclusion: In this high TB burden setting, the rate of QFT conversion did not differ between PHIV + and HIV- adolescents, but PHIV+ had a higher incidence of TB disease despite ART. INH prophylaxis, adequate viral suppression and other interventions are needed to reduce TB incidence during the adolescent period.



820 LOWER SIZE-ADJUSTED BONE DENSITY AND MUSCLE FUNCTION IN ZIMBABWEAN CHILDREN WITH HIV

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Background: Poor linear growth (i.e. stunting), is common in perinatally-acquired HIV infection, yet effects of HIV on adolescent musculoskeletal development remain poorly characterized in sub-Saharan Africa. We hypothesize that bone and muscle growth in children living with HIV (CWH) are impaired, putting them at risk of low bone mass and functional disability, which may increase future fracture risk. We aimed to determine the impact of HIV on size-adjusted (important in context of small stature) bone density and muscle function in peri-pubertal children in Zimbabwe.
Methods: CWH aged 8-16 years, established on ART for ≥2 years, from two public sector HIV clinics and sex and aged-band frequency-matched uninfected children from schools were recruited. Musculoskeletal assessments included grip strength, standing long jump and dual-energy X-ray absorptiometry (DXA). Total-body less-head (TBLH) bone mineral content (BMC) for lean mass adjusted for height (TBLH BMCLBM) and lumbar spine bone mineral apparent density (LS BMAD) values and Z-Scores were calculated. Differences by HIV status, and risk factors for impaired musculoskeletal measures, were determined using linear and logistic regression.
Results: A total of 284 CWH and 222 children without HIV were recruited (Table 1). CWH were more likely to have pubertal delay, stunting and wasting than children without HIV. Calcium and vitamin D intake were not significantly different between the two groups. However, CWH had significantly lower muscle mass, muscle strength, TBLH BMCLBM and LS BMAD compared to the uninfected controls.
Conclusion: This study, for the first time, investigated the effect of HIV on bone and muscle development sub-Saharan African children. HIV was found to have a profound effect on muscle function and bone mass. Whilst pubertal delay is more common in HIV, it does not account for these differences. The effect of HIV on musculoskeletal health may result in long-term disability and impaired quality of life in the future.

Table 1. Characteristics of Children With and Without HIV

	HIV + (n=284)	HIV – (n=222)	p value[a]
Mean age[b], years (SD)	11.8 (2.5)	12.2 (2.5)	0.070
Sex[b], female, N (%)	138 (48.5)	124 (55.8)	0.105
Pubertal delay (Tanner stage)[c], N (%)	7 (7.3)	0 (0.0)	0.020
Pubertal delay (Bone age)[d], N (%)	12 (21.4)	1 (2.7)	0.011
HIV characteristics			
Mean age at HIV diagnosis[b], years (SD)	3.7 (3.2)	-	-
Viral load at enrolment <1,000 copies/ml), N (%)	188 (66.2)	-	-
Mean ART duration[b], years (SD)	8.5 (2.6)	-	-
Tenofovir current use[b], N (%)	59 (20.8)	-	-
Anthropometry			
Stunted (height-for-age Z-score <-2), N (%)	51 (25.2)	17 (10.8)	<0.001
Wasted (weight-for-age Z-score <-2), N (%)	72 (25.4)	21 (9.5)	<0.001
Risk factors for musculoskeletal disease			
Mean calcium intake mg/week (SD)[f]	1197.1 (885.7)	1225.51 (863.8)	0.488
Mean vitamin D intake mcg/week (SD)[g]	30.8 (12.5)	32.3 (12.8)	0.190
Low physical activity level, < 600 MET minutes/week [h], N (%)	137 (48.2)	77 (34.7)	<0.001
Muscle Mass and Function			
Mean total body (TB) muscle (lean) mass, kg (SD)[i]	25.1 (6.3)	30.1 (8.2)	<0.001
Mean hand grip strength, kg (SD)	19.5 (6.8)	25.6 (8.7)	<0.001
Mean long jump distance, cm (SD)	124.3 (24.1)	130.7 (24.4)	<0.001
Bone outcomes[i]			
Mean TBLH BMC^{LBM} *Z-score (SD)	-1.30 (1.3)	-0.70 (1.07)	<0.001
Low TBLH BMC^{LBM} (Z-score <-2), N (%)	55 (27.1)	18 (11.0)	<0.001
Mean LS BMAD** Z-score (SD)	-0.34 (1.4)	-0.14 (1.3)	0.169
Low LS BMAD (Z-score <-2), N (%)	24 (11.8)	12 (7.3)	0.149

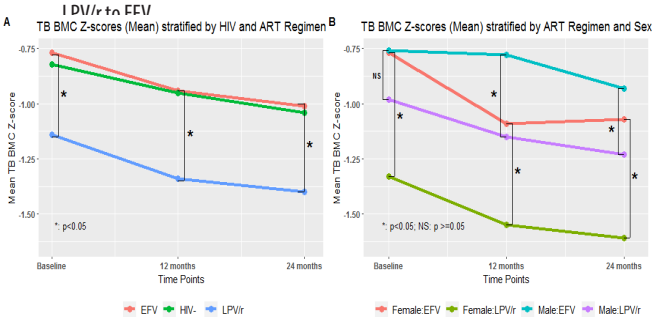
Footnotes and abbreviations
a) t test for continuous data and χ^2 or Fisher's exact test for categorical data
b) variables with no missing data
c) pubertal delay was defined here as <Tanner stage 2 in girls ≥13 years and boys ≥ 14 years. The denominator for pubertal delay is 96 (42 boys and 54 girls) in children with HIV and 90 (31 boys and 59 girls) in children without HIV
d) pubertal delay based on bone age data from hand x-rays available in 59 children with HIV and 41 children without HIV (Greulich-Pyle method). Pubertal delay is defined as chronological age minus bone age >2 years
e) socioeconomic status variable is a composite measure derived from data on household size, ownership and assets, using principle component analysis.
f) calcium intake estimated based on stated food frequency and lower reference range from UK calcium calculator http://www.caern.ed.ac.uk/research/rheumatological/calcium-calculator/
g) vitamin D intake estimated based on stated food frequency and lower reference range from UK vitamin D calculator https://theros.org.uk/media/2078/nos-healthy-living-ift-v4.pdf
h) physical activity calculated as metabolic equivalent minutes (MET minutes/ week) based on the international physical activity questionnaire (IPAQ)
i) Data based on baseline dual-energy X-ray absorptiometry (DXA) completed in 203 HIV+ and 164 HIV- children

*TBLH BMC^{LBM} - total body less head bone mineral content adjusted for lean body mass and height
** LS BMAD - lumbar spine bone mineral apparent density

821 BONE MASS REMAINS HIGHER AMONG CHILDREN ON EFAVIRENZ VS LOPINAVIR/RITONAVIR

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Background: We previously reported South African children living with HIV (HIV+) randomized to remain on a lopinavir/ritonavir (LPV/r)-based antiretroviral therapy (ART) regimen had lower bone mass compared to HIV+ children randomized to switch to efavirenz (EFV) and to controls without HIV (HIV-). This analysis presents two additional years of follow-up.
Methods: The CHANGES Bone Study tracks bone health in HIV+ and HIV- children at one site in Johannesburg, South Africa. A single technician blinded to HIV status and treatments analyzed total body (TB) bone mineral content (BMC) by dual-energy X-ray absorptiometry (DXA) at baseline, 12 and 24 months (mean 2.1, 3.1 and 4.1 years after ART switch, respectively). TB BMC Z-scores adjusted for sex, race, age, and height were generated using reference norms from the US Bone Mineral Density in Childhood Study. During follow-up three groups were compared: HIV+ children on LPV/r or EFV and HIV- children.
Results: 207 (94.1%) HIV+ children and 200 (90.9%) HIV- controls completed three visits. Mean ages at the third visit were 8.4 (SD=1.3) and 9.0 (SD=1.6) years respectively. Over 2 years of follow-up, TB BMC Z-scores declined for all three groups: HIV+ on EFV, HIV+ on LPV/r, and HIV- controls at a rate of -0.12, -0.13 and -0.11 per year, respectively. TB BMC Z-scores at baseline, 12 and 24 months were significantly higher among HIV+ on EFV compared to HIV+ on LPV/r (Figure 1A: -0.77 vs -1.14, p=0.04; -0.94 vs -1.34, p<0.01; -1.01 vs -1.40, p=0.04, respectively). With the exception of boys at baseline, differences in BMC Z-scores between ART groups were significant in girls and boys at all three visits (Figure 1B). TB BMC Z-scores at baseline, 12 and 24 months among HIV+ children on EFV were not significantly different from HIV- controls (-0.77 vs -0.82, p=0.54; -0.94 vs -0.95, p=0.95; -1.01 vs -1.04, p=0.71, respectively). Changes of TB BMC Z-scores from baseline to 24 months were not significantly different between children on EFV and those on LPV/r (-0.21 vs -0.26, p=0.53).
Conclusion: Despite a slight overall decline in bone mass among HIV+ compared with US population norms over 2 years, bone mass remained higher in HIV+ children switched to EFV compared to those continuing LPV/r, even 4 years after switching. Further, HIV+ children switched to EFV had similar BMC Z-scores as HIV- controls. These findings support our previous recommendations to switch children with sustained viral suppression on first line regimen with LPV/r to EFV.



822 BONE AND RENAL OUTCOMES IN VIROLOGICALLY CONTROLLED ADOLESCENTS SWITCHING TO TDF

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Background: Tenofovir disoproxil fumarate (TDF) is included in first line regimens for adolescents living with HIV (ALWH), however associated bone and renal toxicity are concerning. TDF used in combination for treatment-naïve ALWH or those with treatment failure is associated with decreased bone mass. Whether switching to TDF causes decreased bone accrual or bone loss in virologically controlled ALWH is not well established.
Methods: We recruited 50 adolescents, ages 15 - 20 years, Tanner stage 4/5, weight > 40 kg, viral load (VL) < 100 copies/mL, and no evidence of kidney or liver disease, that were switched from an abacavir (ABC)-based to TDF-based efavirenz regimen. Bone mass and renal function were assessed at enrolment and week 24 after switch to TDF using dual-x-ray absorptiometry (DXA) and serum renal markers. Undetectable VL was defined as < 50 copies/mL. Body mass index (BMI) was assessed using WHO BMI-for-age charts. Change in lumbar spine (LS) and total body (TB) bone mineral density (BMD) and Z-scores at 24 weeks and eGFR by Revised Schwartz Equation (2009) were assessed by paired t tests, stratified by sex.
Results: All participants (48% male) were perinatally infected, with median duration on antiretroviral therapy (ART) of 11.4 years. Six (12%) had a prior AIDS-defining illness. At time of ART switch, median CD4 count was 732 and 38 (76%) had undetectable VL. On BMI, 3 (6%) were classified as thin, and 5 (10%) as overweight by WHO criteria. Before ART switch, median (IQR) LS Z-score and TB Z-score were -1.15 (-2.3;-0.3) and -1.05 (-2.0;-0.3), respectively. Mean change (SD) in LS Z-score was -0.03 (0.25) and TB Z-score was 0.02 (0.24). None had a

decrease in LS Z-score from > -2 to < -2, but 1 ALWH had this outcome in TB Z-score. Among participants with 24 week DXA results, 15/47 (32%) had either no change or decreased LS BMD after switch, with a mean change of -1.6%; 14/15 (93%) of this group were female. Overall, a greater proportion of females than males had either no change or decreased LS BMD (58% vs 4%, p<0.0001; Fisher Exact). Overall, statistically significant increases in serum creatinine and decreases in eGFR were observed (p<0.0001 and 0.0003, respectively); however, final levels remained within clinically acceptable limits.
Conclusion: South African ALWH switching from ABC to TDF experienced statistically significant decreases in eGFR but not in LS and TB BMD overall. However, female ALWH experienced greater decreases in LS BMD and may require closer monitoring.

823 EPIGENETIC AGE IN YOUNG AFRICAN AMERICAN ADULTS WITH PERINATALLY ACQUIRED HIV

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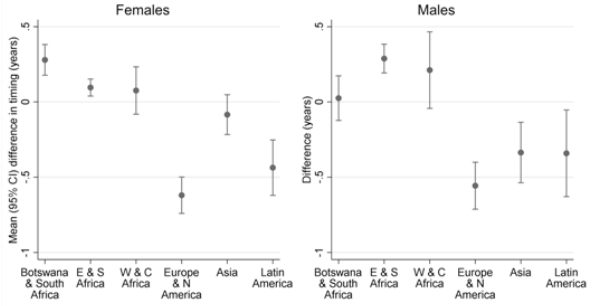
Background: Prior studies have measured accelerated aging in people living with HIV (PLWH) using a DNA methylation (DNAm)-based biomarker of aging, "epigenetic age", but data are limited in African Americans (AA). We assessed if perinatally-acquired HIV infection (PHIV) is associated with accelerated epigenetic age in AA young adults (20-35 years of age).
Methods: We enrolled 61 AA young adults living in NYC, including 31 youth living with PHIV and 30 youth confirmed to be HIV seronegative (Controls) and measured DNAm from whole blood samples using the Illumina EPIC Array. DNAm age (years) was estimated by the Horvath method. We estimated four age acceleration measures, where positive values indicate that the blood sample is older than expected based on chronological age: 1) age acceleration residual (AAR), considered to be robust with respect to cell composition changes; 2) extrinsic epigenetic age acceleration (EEAA), up-weights the contributions of age-related blood cell counts; 3) intrinsic epigenetic age acceleration (IEAA), adjusts for cell type counts; 4) Houseman-adjusted age acceleration residual (HAAAR), adjusts for cell type proportions estimated by the Houseman method.
Results: PHIV and Controls did not differ by sex (45 vs. 40% male), chronological age (26.2 vs. 28.0 years), or ethnicity (90% not Hispanic or Latino in both groups). Among PHIV, 63.0% had a viral load (VL) <50 copies/mL (cpm) and 37% >50 cpm. Blood cell composition differed between PHIV and Controls, largely driven by differential proportions of CD8 (0.36 vs. 0.25, p<0.01) and CD4 T-Cells (0.18 vs. 0.36, p<0.01). Chronological age and DNAm age were positively correlated (r=0.56, p<0.01). PHIV had a higher mean AAR (2.86±6.5 vs. -2.96±3.9, p<0.01) and EEAA (4.57±13.0 vs. -4.72±6.0, p<0.01) compared to controls. Among PHIV, AAR was higher in those with VL >50 cpm than those with VL <50 cpm (8.52±5.3 vs. 0.66±5.1, p<0.01). However, IEAA and HAAAR, the two age acceleration measures that adjust for blood cell composition did not differ between PHIV and Controls.
Conclusion: Epigenetic age acceleration in blood was observed in AA young adults with PHIV using measures unadjusted for blood cell composition. However, after accounting for blood cell composition, there was no longer evidence of age acceleration associated with HIV. Future studies of accelerated aging in PLWH should consider the relationships between CD8 and CD4 T-cells and epigenetic age.

824 GLOBAL VARIATIONS IN PUBERTAL GROWTH IN ADOLESCENTS LIVING WITH PERINATAL HIV

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Background: Adolescents living with perinatally-acquired HIV experience puberty later than HIV-exposed uninfected young people. This study describes growth during adolescence including regional variations.
Methods: The CIPHER Cohort Collaboration pooled observational data from 1994-2015 from 48 countries. Adolescents who initiated a combination ART regimen before age 10 years and had ≥4 height measurements aged ≥8 years (including ≥1 measurement aged≥12 years for females and ≥14 years for males based on expected age at peak height velocity) were included.
We used SITAR (Super Imposition by Translation And Rotation) models to describe growth from age 8-19 years using 3 parameters; mean height, timing and intensity (i.e. shape of the growth velocity curve) of the growth spurt. We then used multivariable regression models to explore characteristics (region, year of birth, initial ART regimen, age, height-for-age z-score (HAZ), and BMI-for-age z-score (zBMI) at ART initiation (baseline)) associated with the growth parameters from SITAR models.
Results: Of 9397 female and 9585 males on ART by age 10, 4535 and 2202, respectively, were included. 1125(17%) were from Botswana and South Africa, 3312(49%) Eastern and rest of Southern Africa, 442(7%) Western and Central Africa, 880(13%) Europe and North America, 649(10%) Asia, 329(5%) Latin America.
Timing of the growth spurt varied by region and sex (Figure). In multivariable analyses the association between baseline HAZ and timing of growth spurt in females differed by region (p=0.017); a 1SD decrease in HAZ was associated with a 0.30(95%CI 0.21,0.39) year delay in Asia and 0.11(0.07,0.14) year delay elsewhere. In males, there was an interaction between baseline age and HAZ (p=0.009); for males starting ART age <4 years, baseline HAZ was not associated with timing but for those initiating ART at older ages, lower baseline HAZ was associated with later growth spurts.
Later calendar year of birth was associated with earlier growth spurt in females (-0.04(-0.07,-0.02)) but not in males. A 1SD decrease in zBMI was associated with a delay of 0.04(0.01,0.07) years in females and 0.07 (0.02,0.12) years in males. Differences in intensity of the growth spurt were observed across regions, age and HAZ at ART initiation.
Conclusion: Starting ART when stunted is associated with delayed pubertal growth spurt globally. Longer term follow-up is important to understand the impact of these delays on outcomes later in life.

Figure: Regional variations in timing of the pubertal growth spurt



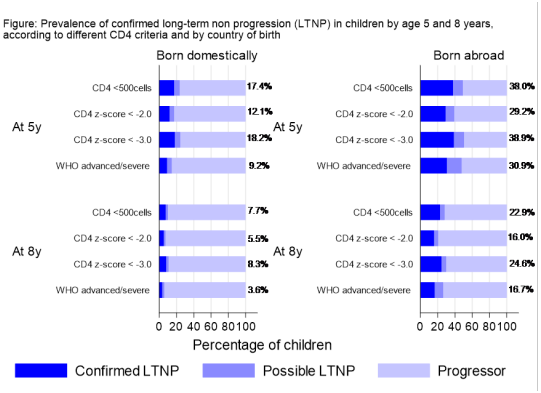
Note: The y-axis represents the difference (in years) between the average timing of the growth spurt in each region and the average timing across all regions/adolescents included in the analysis.

825 LONG-TERM NONPROGRESSION IN CHILDREN WITH PERINATALLY ACQUIRED HIV

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Background: Long-term non-progression (LTNP) refers to long-term survival with HIV without disease progression or antiretroviral treatment (ART). LTNP prevalence estimates in children range from 2-42% using varied definitions, often in small samples. Understanding LTNP in children can potentially inform

HIV cure research. We assessed the prevalence of paediatric LTNP in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC).
Methods: 16 cohorts from 12 European countries and Thailand contributed follow-up data from 1980-2016. Confirmed LTNP was defined as having none of these events during the first 5 (or 8) years of life: AIDS diagnosis, initiating ART, death or ever meeting defined CD4 progression criteria. Possible LTNP was defined as no clinical events but unclear timing of CD4 progression relative to age/ART initiation. We explored 4 different CD4 criteria: a)CD4 z-score<-2 relative to HIV-exposed uninfected children, b)CD4 z-score<-3, c)CD4 count<500cells/μL, d)WHO advanced/severe immunodeficiency for age (CD4%<30, <25, <20, <15 at age <11m, 12-35m, 36-59m, >5y, or CD4 count<350/μL at >5y). Inclusion criteria for analysis were perinatal infection or <10years at first visit, ≥1 CD4 record, born pre-2011 (or 2008), not lost to follow-up by age 5/8y.
Associations between LTNP and sex, region and birth year were assessed with logistic regression. Data were analysed separately for children born domestically (country of reporting cohort) vs abroad.
Results: Of 9621 children followed in EPPICC, 6642 (69%) met the inclusion criteria. Median age at entry to HIV care was 1.6y [IQR 0.2-4.3] and follow-up duration 10.5y [6.6-15.1]. 1468 (22.1%) were born abroad. LTNP prevalence was 9.2-38.9% at 5y and 3.6-24.6% at 8y, 2-3 times higher in those born abroad vs domestically (Figure).
In multivariable analysis, for all CD4 criteria and those born domestically and abroad, prevalence was lower in Thailand and Western/Central Europe, higher in Eastern Europe (vs UK/Ireland, p<0.01) and lower in children born in later years.
Conclusion: This is the largest multi-country paediatric collaboration to explore LTNP prevalence. Higher prevalence in children born abroad likely reflects selection bias of survivors well enough to migrate. Age 5y may be too early to define LTNP, as prevalence falls by 8y. Introduction of "treat all" approaches likely explains recent declines in prevalence. Data before these changes allow study of the natural history of LTNP, especially in domestic born children.

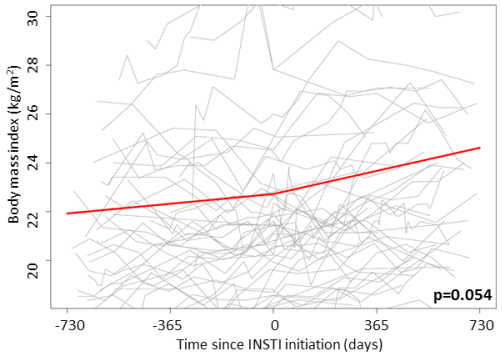


826 EFFECT OF INTEGRASE INHIBITORS ON WEIGHT GAIN IN CHILDREN AND ADOLESCENTS WITH HIV

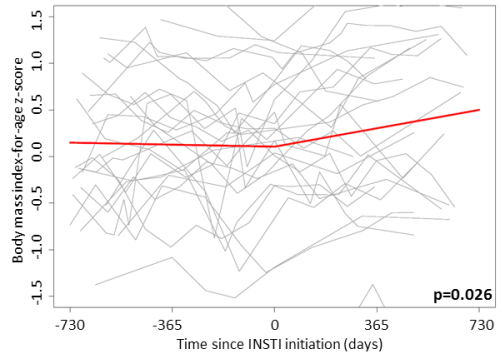
Sahera Dirajlal-Fargo[1], Wei Li A. Koay[2], Matthew E. Levy[3], Anne K. Monroe[3], Amanda D. Castel[3], Natella Rakhmanina[2], for the DC Cohort Executive Committee
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Background: Weight gain has been associated with integrase strand transfer inhibitor (INSTI) based regimens in adults, but this has not been studied in children and youth with perinatally acquired HIV. We investigated the change in body mass index (BMI) among young persons living with HIV (YPLWH) initiating INSTI-based regimens for the first time within an observational cohort in Washington DC (DC Cohort).
Methods: YPLWH (0-24 years of age) who initiated INSTI-based regimens between Jan 2011 and Mar 2018, and had ≥2 BMIs recorded at least 6 months apart within 2 years pre- and post-INSTI initiation were eligible. We compared the trajectory of BMI (or BMI-for-age z-score for those ≤19 years of age) pre- and post-INSTI initiation using piecewise linear mixed effects models, and adjusted for potential confounders.
Results: We enrolled 51 YPLWH (median age 18 years (IQR 15-21), 47% male, 94% black, 72% perinatally infected, 59% initiated dolutegravir, 57% had a history of AIDS). Pre-INSTI, 59% were on a protease inhibitor based regimen and 4% were ART-naive. At INSTI initiation, median BMI was 21.4 m/kg2 (IQR: 19.6-24.3), CD4 count was 574 cells/mL (IQR: 348-834), 43% had HIV viral load < 200 copies/mL. Fifty one YPLWH had 720 BMI measurements (median BMI measurements per YLPWH 13 (IQR: 11-17)) with a mean BMI change of +0.37 (p=0.04) and +0.98 kg/m_2/year (p<0.0001), in the two years pre- and post-INSTI initiation respectively. There was a greater rate of BMI change post- vs. pre-INSTI of +0.6 kg/m_2/year (p=0.05, Fig. 1a). Sub-cohort of YPLWH (≤19 years of age (n=27)) had 312 BMI-for-age z-score measurements (median z-score measurements per YLPWH 12 (IQR: 10-15)) with a mean z-score change of -0.04 (p=0.51) and +0.21 units/year (p=0.01), pre- and post-INSTI initiation respectively. YPLHIV ≤19 years had a significantly greater rate of BMI-for-age z-score change of +0.25 units/year (p=0.03, Fig. 1b) when comparing trajectories post- vs. pre-INSTI after adjusting for age at INSTI initiation, sex, race, mode of HIV acquisition and most recent CD4 count and VL (β=0.22, p=0.05).
Conclusion: Similar to adults, we report a greater rate of BMI and BMI-for-age z-score change following switch to INSTI in predominantly perinatally infected YPLWH. Although the final BMI remained in the normal range, our findings support the need for continued monitoring of BMI trends and potential cardiometabolic implications in YPLWH receiving INSTIs to assess if this represents more than a return to health phenomenon.

a. Spaghetti plot of BMI rate of change pre and post-INSTI in 0-24 years old



b. Spaghetti plot of BMI-for-age-z-score rate of change pre and post-INSTI in 0-19 years old



827 BODY FAT AND LIPID PROFILE CHANGES IN HIV-INFECTED YOUTHS SWITCHED TO DOLUTEGRAVIR

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Background: HIV-lipodystrophy syndrome consists in abnormal distribution of adipose tissue and alteration of glucose and lipids blood concentration. Many studies established a key role of older NRTIs and PIs in lipodystrophy development, but few data are available for newer drugs, such as dolutegravir, a second-generation INSTI assumed to be responsible for weight gain in adults. The aim of this study was to evaluate the effects of dolutegravir on body composition and glico-lipidic metabolism in HIV-infected youths.
Methods: We enrolled 14 patients (mean age 16.1 years, 12 girls) previously treated with PI or NNRTI-based regimen and switched to ABC/3TC/DTG. Blood concentration of glucose, total and fractionated cholesterol and triglycerides were measured at baseline and after 3, 6 and 12 months. Body composition was evaluated by dual-energy X-ray absorptiometry and body mass index (BMI)

was calculated at baseline and after 12 months. Statistical comparisons were performed by ANOVA for repeated measures.
Results: Mean blood concentration of glucose and HDL cholesterol did not change significantly during the follow-up. Conversely, mean total cholesterol concentration was 190, 159, 161 and 168 mg/dL at baseline, 3, 6 and 12 months, respectively ($p = 0.0057$). Mean LDL cholesterol values were 109, 90, 92 and 96 mg/dL at baseline, 3, 6 and 12 months ($p = 0.025$). Mean triglycerides concentration decreased significantly after 3 months of therapy (114 and 64 mg/dL, $p = 0.007$). BMI was 20.4 at baseline and 20.9 Kg/m$_2$ after 12 months ($p = 0.09$). Body fat percent did not change significantly during the study ($p = 0.16$), but we observed a remarkable increase in trunk body fat percent ($p = 0.0413$). In particular, trunk/total body less head (TBLH) fat ratio increased significantly ($p = 0.0485$), while limbs/trunk fat ratio decreased significantly ($p = 0.0495$) (Table 1).
Conclusion: Our study shows that a dolutegravir-based regimen induces a significant improvement in lipids blood concentration, but no interference on glucose metabolism. On the other hand, we observed a relevant increase in trunk fat without alterations of BMI and body fat percent. Future studies are needed to evaluate if this increase in trunk fat could impact on body metabolism.

Table 1. Body composition measurements

Fat percent (%)	*Baseline*	*12 months*	*p-value*
TBLH	28.0	27.2	0.16
Trunk	24.9	25.1	0.0413
Legs	31.6	29.9	0.65
Arms	29.2	27.0	0.97
Fat ratio	*Baseline*	*12 months*	*p-value*
Trunk/TBLH	0.45	0.46	0.0485
Legs/TBLH	0.44	0.43	0.089
Limbs/trunk	1.29	1.23	0.0495

828 CHER TRIAL COHORT SHOWS GREATER INSULIN RESISTANCE INTO ADOLESCENCE

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Background: Few longitudinal studies have examined insulin resistance in HIV-infected children, and of those most have been conducted in developed countries. Our aim was to examine whether the trajectory of insulin resistance differs in perinatally-HIV-infected children (PHIV) who received early antiretroviral therapy (ART) below 12 weeks of age; HIV-exposed uninfected children (HEU); and HIV-unexposed uninfected children (HU).
Methods: This longitudinal cohort study consists of 90 PHIV, 317 well-matched controls (156 HEU and 161 HU) from the same communities and socio-economic background, attending the Family Clinical Research Centre with Ubuntu (FAM-CRU) at Tygerberg Children's Hospital, South Africa. This cohort was the first to begin ART from below 12 weeks of age with normal CD4 percentages and without clinical HIV disease (CHER trial, Lancet 2013). The cohort has now been followed until 16 years of age. For the present study, children required ≥1 set of simultaneously-obtained fasted serum glucose and insulin measurements. The main outcome was the Homeostatic Model Assessment (HOMA) insulin resistance index (HOMA-IR) (Insulin mIU/L X glucose mg/dL) modelled using log HOMA-IR given skewness.
Results: Using linear mixed effects modelling, PHIV had a geometric mean HOMA-IR 1.2 (95% CI 1.1 – 1.3) times above HU (table 1), after adjusting for gender, height (as a surrogate for age, puberty onset and growth), waist circumference (as a surrogate for visceral adiposity), and the random effect of child, given each child had multiple measurements. Elevated HOMA-IR was unlikely linked to differences in environmental or household circumstances in HIV-affected versus -unaffected households, as no significant difference was found between the HOMA-IR of HEU and HU.
Conclusion: Despite being closely monitored and on ART since soon after birth, PHIV exhibit elevated insulin resistance that has persisted into adolescence. This has long term implications for cardiovascular risk. Further research needs to identify which PHIV are at risk.

Table 1: Longitudinal linear mixed effects model for the association between HIV infection and log HOMA-IR (insulin resistance index)

Parameters	Beta	Standard Error	Z value	P value
Fixed effects				
Intercept	-1.260	0.171	-7.378	<0.001
HEU	-0.010	0.026	-0.397	0.692
HIV+	0.075	0.026	2.946	0.004
Gender: Male	-0.040	0.021	-1.912	0.057
Height	0.005	0.001	3.158	0.002
Waist circumference	0.123	0.002	7.566	<0.001
Random effects	Variance	Standard Deviation		
Study ID (Intercept)	0.009	0.097		
Residual	0.067	0.259		

829 CARDIOVASCULAR RISK PROFILE: A CLINIC-BASED SAMPLE OF YOUTH LIVING WITH HIV IN THE US

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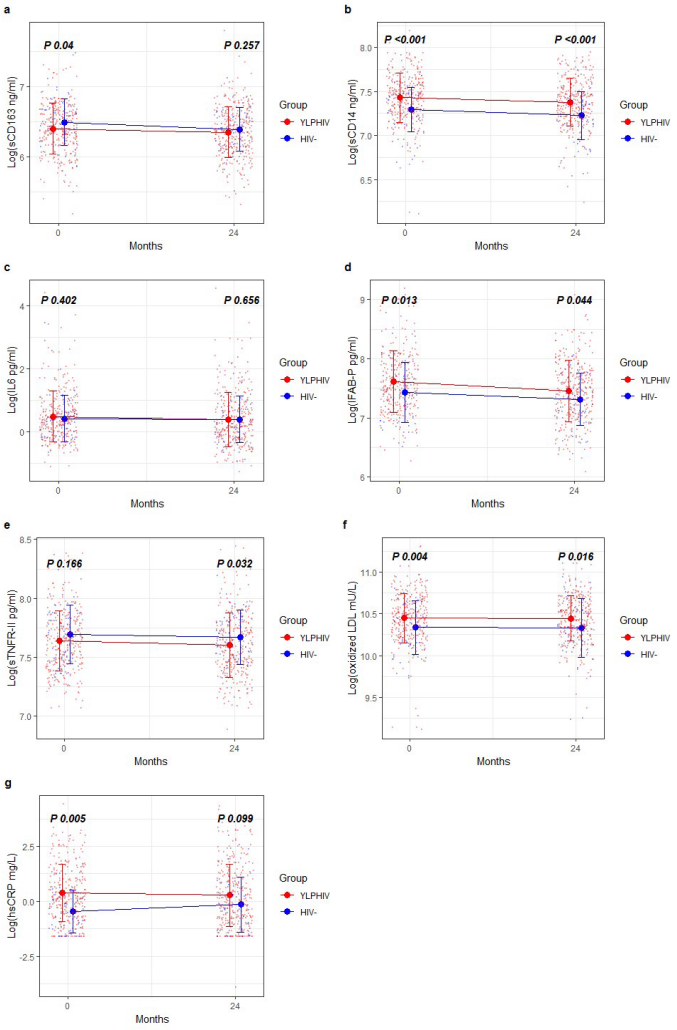
Background: Accelerated atherosclerosis has been found in young individuals diagnosed with HIV. Previous research indicates that lower CD4 and higher plasma viral load (VL) significantly increased the risk of cardiovascular disease (CVD); however, this link is largely under-investigated among youth living with HIV (YLH). We examined whether detectable VL and low CD4 increased the risk of CVD among YLH aged 14-26y.
Methods: This study used electronic health records from the Adolescent Medicine Trials Network 154 Cascade Monitoring baseline data extracted from multidisciplinary adolescent HIV care settings across the United States. Multivariable linear regression was used to assess the association between detectable VL and CD4 of ≤ 200 with Cardiac Risk Score1 (for those who had systolic blood pressure, cigarette smoking, diabetes, and anti-hypertensive medication use data, n =813) and Cardiac Risk Score2 (for those who had systolic blood pressure, cigarette smoking, diabetes, anti-hypertensive medications use, total cholesterol, and HDL data, n = 398) adapted from the Framingham gender-specific algorithm.
Results: The sample was predominantly black and male with mean age of 21y. Overall, 47.8% had a detectable VL and 8.6% had a baseline CD4 of ≤ 200 indicating immune dysfunction. In bivariate analyses, both scores (Cardiac Risk Score1, $p < 0.001$; Cardiac Risk Score2, $p < 0.01$) demonstrated significantly increased risk of CVD in patients who had detectable VL compared with those who had undetectable VL. Comparing patients who had CD4 ≤ 200 with those who had CD4 > 200, the risk of CVD was significantly increased in patients who had CD4 ≤ 200 compared with those who had CD4 > 200 using Cardiac Risk Score2 ($p < 0.01$) but not Cardiac Risk Score1. In the multivariable models, after adjusting for demographic and clinical covariates, a log 10 increase in VL copies/mL was associated with increased odds of cardiovascular risk (Cardiac Risk Score1, $\beta = 0.088$, $p < 0.01$; Cardiac Risk Score2, $\beta = 0.146$, $p < 0.05$). CD4 models were not significant.
Conclusion: Our findings demonstrate the independent contribution of detectable VL on cardiovascular risk in YLH.

830 SOLUBLE CD14 IS ASSOCIATED WITH ENDOTHELIAL DYSFUNCTION IN SOUTH AFRICAN YOUTH ON ART

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Background: There is evidence for endothelial dysfunction in youth living with perinatally acquired HIV (YLPHIV). We assessed gut and inflammatory biomarkers associated with endothelial dysfunction in South African YLPHIV.
Methods: YLPHIV and age-matched HIV-uninfected (HIV-) youth enrolled in the Cape Town Adolescent Antiretroviral Cohort (CTAAC) in South Africa between 9-14 years of age were included. YLPHIV were on ART> 6 months with viral load <400 copies/mL. Endothelial function was measured using reactive hyperemic index (RHI) by Peripheral Arterial Tonometry. Endothelial dysfunction was defined as RHI <1.35. Serum levels of systemic inflammation, monocyte activation, intestinal integrity and oxidized lipids were measured at baseline and 24 months. RHI was measured at 24 months. Spearman correlations were used and quantile regression models assessed associations with RHI.
Results: We included 283 YLPHIV and 69 HIV- participants. At baseline, median (Q1, Q3) age was 12 years (11, 13), 53% were females. There was no difference in age, sex or Tanner stages between the groups. At baseline, median CD4 cell count was 744 cells/μL (603, 951). PHIVs had poorer endothelial function compared to HIV- (RHI=1.36 vs 1.52, p<0.01). At baseline and 24 months, YLPHIV had lower BMI but higher waist-to-hip ratio, LDL cholesterol, triglycerides, markers of monocyte activation (sCD14), gut barrier dysfunction (intestinal fatty acid binding protein, IFAB-P) and oxidized LDL cholesterol (p≤0.04). Several biomarkers decreased at 24 months in YLPHIV but remained elevated compared to HIV- (Figure). In univariate analyses, higher levels of IFAB-P at baseline and sCD14 at 24 months correlated with endothelial dysfunction at 24

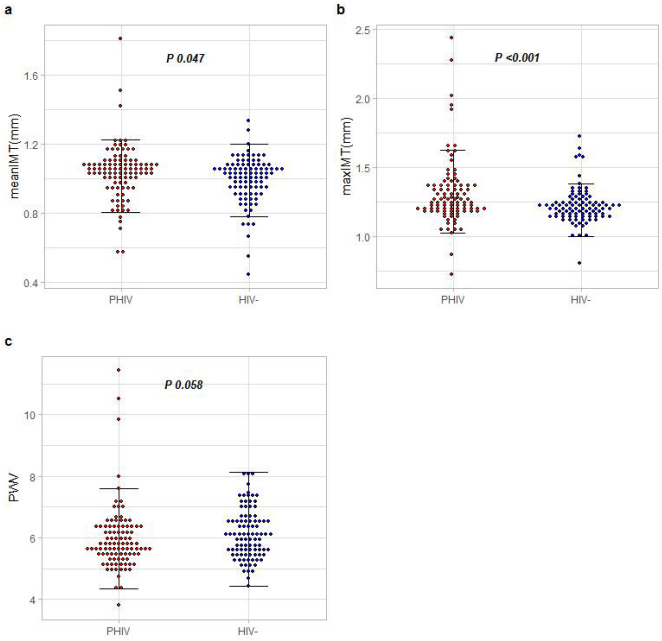
months (p≤0.04). In quantile regression analyses, in YLPHIV with endothelial dysfunction, sCD14 remained associated with lower RHI after adjusting for age, sex, Tanner stage, viral load and ART duration (β-0.05, p=0.01).
Conclusion: Despite viral suppression, South African YLPHIV have poor endothelial function and persistent evidence of monocyte activation and gut barrier dysfunction compared to uninfected youth. A key finding in our results is that higher sCD14 is independently associated with endothelial dysfunction in this population. The long-term clinical significance of gut integrity and monocyte activation needs to be further assessed in YLPHIV.



831 VASCULAR DISEASE, IMMUNE ACTIVATION, AND GUT DYSFUNCTION IN HIV+ UGANDAN CHILDREN

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Background: Sub-Saharan Africa is facing new challenges in HIV care including management of non- communicable diseases and a growing younger generation. The risk of cardiovascular disease (CVD) and its mechanisms in children living with perinatally acquired HIV (PHIV) in sub-Saharan Africa has been understudied.
Methods: Mean common carotid artery intima-media thickness (IMT) and pulse wave velocity (PWV) were evaluated in 101 PHIV and 96 HIV negative participants (HIV-). Participants were between 10-18 years of age with no active infections including tuberculosis. PHIVs were on ART with HIV-1 RNA level ≤400 copies/mL. We measured plasma (soluble CD14 and CD163) and cellular markers of monocyte activation (proportions of monocyte subsets), T-cell activation (expression of CD38 and HLA-DR on CD4+ and CD8+), as well as plasma markers of systemic inflammation, oxidized lipids, gut integrity.
Results: Overall median (Q1, Q3) age was 13 years (11,15) and 52% were females. Groupswere similar by age, sex and BMI. Median CD4+ cell counts were 988 cells/μL (638, 1308), 86% had viral load < 20 copies/mL and median ART duration was 10 years (8, 11). 72% were on an NNRTI based regimen. PHIVs were more likely to have traditional CVD risk factors including higher waist-hip ratio, triglycerides, and insulin resistance (p≤ 0.03). Median IMT was slightly thicker in PHIVs compared to controls, while PWV did not differ between groups (Figure). PHIVs had higher monocyte and T-cell activation; higher CD14 (p<0.01), higher frequencies of non-classical monocytes (p=0.02) and activated CD4+ and CD8+ T-cells (p<0.001 for both). In univariate analyses, lower BMI and oxidized LDL, and higher waist-hip ratio, hsCRP and zonulin correlated with thicker IMT in PHIV (p≤0.05). After adjustment for age, BMI, sex, CD4 cell count, triglycerides, HOMA, sCD163 and hsCRP were added separately, higher levels of intestinal permeability (zonulin) remained associated with IMT (β=0.02, p≤0.03).
Conclusion: Our study shows for the first time that African PHIV with viral suppression have evidence of worse CVD risk, structural vascular disease, ongoing immune activation and a leaky gut compared to age matched uninfected children. Gut barrier dysfunction may be involved in the pathogenesis of subclinical vascular disease in this population.



832 DEPRESSION ASSOCIATED WITH LOWER EXECUTIVE FUNCTIONING IN ASIAN YOUTH LIVING WITH HIV

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Background: Youth with perinatally acquired HIV (YPHIV) and youth who are PHIV-exposed but uninfected (YPHEU) may be at risk for depression in the presence of HIV-related health, cognitive, and/or psychosocial challenges. Our objective is to describe the prevalence of persistent depressive symptoms (PDS) and associated factors among YPHIV, YPHEU, and youth who are HIV-unexposed

and uninfected (YHUU) in Asia, as well as the relationship of depression and stigma.

Methods: Data from the PREDICT Resilience longitudinal cohort study of 482 Cambodian and Thai adolescents aged ≥ 10 years (223 YPHIV, 117 YPHEU and 142 YHUU) were analyzed. Depression screening was performed annually using the Child Depression Inventory (CDI) for those aged 10-15 years and the Center for Epidemiological Studies Depression Scale (CES-D) for those aged 15-24 years. PDS were defined as CDI or CES-D scores ≥ 16 in ≥ 2 consecutive visits. Executive function (EF) was measured annually by the Delis-Kaplan Executive Function System (D-KEFS) verbal and design fluency tests; self-reported stigma was identified at annual interview. We compared the prevalence of PDS by PHIV status and adolescent time period (early, mid-, and late adolescence). Generalized estimating equations with Poisson regression were used to identify associations of EF, age group, and stigma experiences with persistent depressive symptoms.

Results: Between July 2015 to July 2019, 482 adolescents completed baseline evaluations; median age was 13.8 years (IQR=11.8-16.1). Prevalence of PDS was highest among YPHIV (23.8%), followed by YPHEU (17.9%) and YHUU (14.1%) (p=0.09). Adjusted incidence rate ratios (aIRR) of PDS were 2.05 (95% CI of aIRR=1.03-4.07) and 2.66 (95% CI=1.21-5.85) among adolescents aged 15-17 and 18-24 years compared to those 13-15 years, respectively. Across 144 weeks of follow-up, adolescents with PDS performed worse on measures of EF compared to those without symptoms (p<0.001). Among the 223 YPHIV youth, stigma at baseline (26%) was associated with PDS (p=0.045).

Conclusion: Persistent depressive symptoms were present among all 3 groups of youth in Cambodia and Thailand, and are more likely as youth age towards young adulthood. Transition to adult responsibilities and self-care, especially for YPHIV, may be complicated by associated psychosocial and EF challenges. Comprehensive mental health diagnosis and care should be integrated into HIV services.

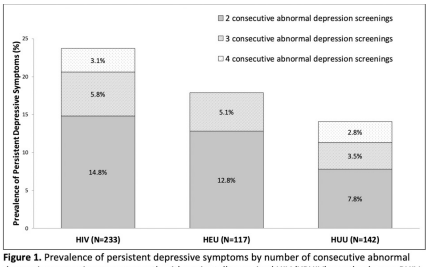


Figure 1. Prevalence of persistent depressive symptoms by number of consecutive abnormal depression screenings among youth with perinatally acquired HIV (YPHIV), youth who are PHIV-exposed but uninfected (YPHEU), and youth who are HIV-unexposed and uninfected (YHUU).

833 DEPRESSION, SUBSTANCE USE, AND ADHERENCE AMONG LATIN AMERICAN YOUTH LIVING WITH HIV

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Background: Adolescents and young adults living with HIV are situated within a dynamic confluence of behavioral, developmental, and care transitions that pose unique challenges to provide optimal healthcare. Depression and substance use may impact antiretroviral therapy (ART) adherence, but data from Latin America are scarce. We evaluated the prevalence and factors associated with depression, substance use, and self-reported adherence among youth in HIV care.

Methods: Cross-sectional study including adolescents (10 to <18 years) and young adults (18 to <25 years) on ART for ≥6 months within the Caribbean, Central and South America network for HIV epidemiology (CCASAnet) in Brazil, Chile, Haiti, Honduras, Mexico and Peru. Individuals were screened for depression (Patient Health Questionnaires,PHQ- 2/9/A), substance use (The Alcohol, Smoking and Substance Involvement Screening Test) and ART adherence (The Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol). Multivariable logistic regression models were used to evaluate factors associated with each outcome.

Results: Of 592 participants included in the analysis, 308 (52%) were female, 235 (40%) were 10-17 years old and 355 (60%) had undetectable viral load. The prevalence of depression was 16%. Regarding substance use in previous 3 months, 338 (57%) used alcohol, 170 (29%) tobacco, and 110 (19%) illicit drugs. Non-adherence in previous week was reported by 213 (36%) participants. Females were more likely to report depression (adjusted odds ratio (aOR) 2.9, 95% CI 1.6–5.1) and less likely to report illicit drug use (aOR 0.34, 95%CI 0.2–0.7) than males. Alcohol use in previous 3 months was associated with the use of tobacco (aOR 10.4, 95%CI 4.6–23.9) and illicit drugs (aOR6.9, 95%CI 1.8–26.4). Tobacco was the only substance associated with non-adherence (Table).

Conclusion: The prevalence of substance use was higher than found among CCASAnet adults in a previous analysis. Youth reporting alcohol and tobacco use should be screened for illicit drug use. Although alcohol and illicit drugs were not associated with ART adherence, youth using these substances may be at increased risk for mortality related to violence and traffic accidents - which are the main cause of death in many Latin American countries. Further studies and interventions are needed.

Table: Factors associated with depression, substance use, and non-adherence to antiretroviral therapy (ART) among Latin American adolescents and young adults (n=536) in multivariable logistic regression analyses, 2018-2019.

	Depression	Alcohol use in previous 3 months	Tobacco use in previous 3 months	Any illicit drug use in previous 3 months	Missed ART doses in last week
Factor	aOR(95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)
Sex: Female vs. Male	**2.89 (1.65–5.07)**	1.25 (0.80–1.96)	0.57 (0.32–1.01)	**0.34 (0.17–0.68)**	1.38 (0.94–2.03)
Age: 18-24 vs. 10-17	3.66 (0.86–15.6)	1.87 (0.63–5.54)	0.86 (0.20–3.74)	0.91 (0.17–4.74)	0.85 (0.32–2.27)
Education: (vs. **0-6 years**)					
7-8 years	1.86 (0.72–4.84)	1.11 (0.58–2.12)	1.35 (0.46–4.01)	1.08 (0.25–4.63)	1.37 (0.75–2.49)
9-12 years	1.49 (0.61–3.66)	1.23 (0.64–2.38)	**2.99 (1.13–7.91)**	0.67 (0.18–2.41)	**2.09 (1.16–3.77)**
>12 years	1.14 (0.41–3.13)	**3.86 (1.69–8.83)**	1.66 (0.55–5.01)	0.45 (0.11–1.80)	1.47 (0.71–3.03)
Alcohol use: Yes vs. No	1.44 (0.72–2.89)	-	**10.45 (4.57–23.9)**	**6.92 (1.81–26.4)**	1.08 (0.68–1.72)
Tobacco use: Yes vs. No	1.45 (0.71–2.96)	**10.25 (4.48–23.4)**	-	**19.2 (8.73–42.2)**	**1.82 (1.02–3.22)**
Sedative use: Yes vs. No	**3.99 (1.57–10.1)**	1.64 (0.70–3.86)	2.60 (0.91–7.38)	0.78 (0.20–3.04)	1.89 (0.94–3.80)
Any illicit drug: Yes vs. No	1.36 (0.65–2.84)	**7.86 (2.19–28.19)**	**19.65 (8.94–43.2)**	-	1.71 (0.91–3.21)
Depression: Yes vs. No	-	1.45 (0.71–2.94)	1.72 (0.84–3.54)	1.64 (0.78–3.47)	1.05 (0.62–1.80)
ART doses missed last week: ≥1 vs. none	1.03 (0.60–1.76)	1.13 (0.71–1.81)	**2.00 (1.10–3.65)**	1.87 (0.95–3.67)	-
Viral load: Detectable vs. Undetectable	-	-	1.01 (0.55–1.84)	0.59 (0.30–1.18)	**2.28 (1.54–3.39)**

aOR: adjusted odds ratio; CI: confidence interval
Bold font indicates p<0.05
All models were adjusted for Country and the presence of a parent/guardian during the interview.
Observations with missing data were not included in the logistic regression models

834 SUBSTANCE USE IN PERINATALLY INFECTED AND SAME-AGE HIV– ADOLESCENTS IN SOUTH AFRICA

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Background: Experimentation with substances is common among adolescents, but there are few longitudinal data exploring the prevalence among perinatally-infected adolescents living with HIV (PHIV+) in sub-Saharan Africa, including comparisons with HIV- adolescents.

Methods: The Cape Town Adolescent Antiretroviral Cohort follows PHIV+ and age- and gender-matched HIV- adolescents in South Africa. Self-reported substance use was assessed annually, and a 6-panel urine toxicology screen tested for common substances (marijuana, methaqualone, cocaine, methamphetamine, MDMA, opiates) at enrolment and after 36 and 48 months of follow-up; HIV viral load (VL) was measured annually. Using repeated measures, we describe substance use during pre-adolescence (ages 9-11 years), early (12-14 years) and middle-late adolescence (15-19 years).

Results: A total of 515 PHIV+ (median age at enrolment: 11.9 years; 49% female) and 110 HIV- adolescents (11.7 years; 55% female) contributed 1491 toxicology screens over a median of 4 years. Overall, 5.5% of tests were positive. The most commonly used substance was marijuana (95% of all positive tests), followed by methaqualone/mandrax (17%) and methamphetamine (9%). Among females, neither age nor HIV status was associated with a positive test. Among males, older age was strongly associated with a positive screen (p<0.001); male PHIV+ were significantly less likely to screen positive across study visits after adjusting for age (aOR: 0.15 [0.04-0.60]; Figure A). Self-report of ever using alcohol was common: among PHIV+, report of use increased from 3% in pre-adolescence to 7% and 29% in early and middle-late adolescence; with levels of use even higher

in HIV- adolescents (from 5% to 18% and 54%; p<0.001). Self-reported use of tobacco increased with age but did not differ by HIV status (from 0.9% to 2% and 11% in PHIV+; 0% to 3% and 10% in HIV-). Self-report performed poorly in detecting use of the most common substances (Figure B). At enrolment and after 36 and 48 months, approximately 22% of PHIV+ had VL>50 copies/mL; 13% had VL>1000 copies/mL. Adjusting for age and gender, positive toxicology screen was not associated with VL at any time point.

Conclusion: Among male PHIV+, the prevalence of substance use increased dramatically with older age but was lower than that of same-age, HIV- peers. Further efforts are needed to refine self-report measures and to explore the clinical and behavioral effects of substance use.

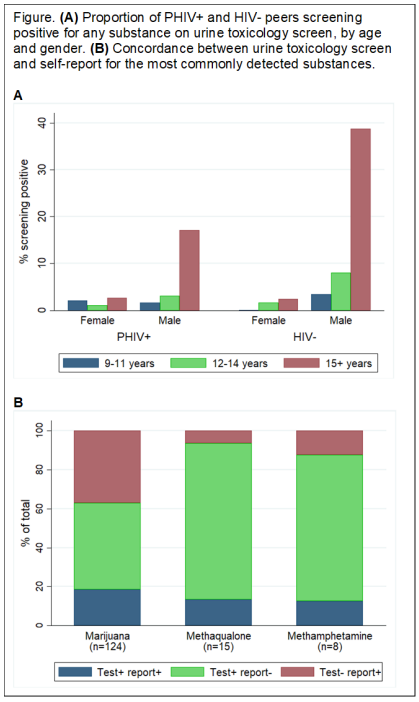


Figure. **(A)** Proportion of PHIV+ and HIV- peers screening positive for any substance on urine toxicology screen, by age and gender. **(B)** Concordance between urine toxicology screen and self-report for the most commonly detected substances.

835 VIRAL SUPPRESSION AND MARIJUANA MODULATE TRANSCRIPTOME BIOPROFILE IN YOUTH WITH HIV

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Background: Viral suppression by antiretroviral therapy (ART) modulates many inflammatory pathways perturbed by HIV, but does not completely normalize inflammation. Substance use, particularly marijuana, affects pro-inflammatory pathways. A systems biology approach was used to define the transcriptome profiles associated with viral suppression and marijuana use in youth with HIV (YWH).

Methods: The study included 20 YWH with long-term (3 years) viral suppression on ART (viral load < 50 copies), 8 virally suppressed YWH who regularly used recreational marijuana based on toxicology and self-report, 7 age-balanced YWH who failed the same 3-year ART regimen (median viral load 2,379 copies/ml), and 25 healthy, HIV-uninfected youth balanced for age, gender and race. Peripheral blood cell mRNA was profiled using Affymetrix HG-U133 Plus 2.0 Arrays. Differentially expressed genes (DEGs) were identified by Significance Analysis for Microarrays (FC > 1.3). Pathway enrichment analysis was performed using Ingenuity Pathways Analysis to identify enriched pathways (p < 0.001).

Results: Active HIV-1 replication in 7 viral failures perturbed 127 pathways including 602 DEGs. Sustained long-term viral suppression by ART significantly reduced the perturbed pathways to 25 with 70 DEGs. Although 22 pathways remained perturbed in viral suppressors, ~70% genes dysregulated in viral failures were normalized, while DEGs identified in viral suppressors, including up-regulation of RAP2B, ITGB1, KLRD1 and KLRC3, and down-regulation of SLC8A1, E2F3 and COL4A3BP, were not observed in viral failures. Three pathways, including IL-6 signaling, macropinocytosis signaling and GDNF family ligand-receptor interactions, were unique to viral suppressors. Four genes, RAP2A, RAP2B, PIK3C2A and PIK3CB, were enriched in almost all pathways perturbed in viral suppressors, potentially serving as networking hubs. Among virally suppressed YWH, marijuana normalized all pathways and genes except for Protein Ubiquitination Pathway.

Conclusion: HIV replication and long-term viral suppression display unique blood transcriptome bioprofiles. Surprisingly recreational use of marijuana normalized many pathways and genes dysregulated by HIV.

836 PROMISING RESULTS FROM A PILOT RCT MENTAL HEALTH INTERVENTION FOR HIV-INFECTED YOUTH

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Background: There are increasing numbers of youth living with HIV (YLWH) with unaddressed mental health challenges. Mental health challenges are associated with poor antiretroviral therapy (ART) adherence which lead to unacceptably high mortality. Few evidence-based mental health interventions exist to address mental health challenges and improve HIV outcomes specifically for YLWH.

Methods: This pilot group treatment trial, which individually randomized YLWH from two clinical sites in Tanzania, evaluated a mental health intervention, Sauti ya Vijana (SYV), compared to standard-of-care (SOC) for improving ART adherence and virologic suppression. SYV consisted of ten group and two individual sessions held weekly, delivered by lay counselors. Participants were living with HIV and 12-24 years of age. Demographics, mental health questionnaires (PHQ-9, SDQ, UCLA Trauma), stigma, self-report and objective measures of adherence (ART concentration in hair), and HIV RNA were obtained at baseline and 6-months (post-intervention). Potential effectiveness was assessed by comparing outcomes between arms in exploratory analyses using mixed effects modeling.

Results: Between June 2016 and July 2017, 128 YLWH enrolled, of whom 105 were randomized and 93 (55 in SYV) followed-up at 6 months and were included in this analysis. Mean age of participants was 18.1 years with 51% female; 84% were infected perinatally. Exploratory analyses of effectiveness outcomes demonstrated change in mental health symptoms and internal stigma improved in both arms baseline to 6-months, but were not significantly different between arms. Self-reported adherence improved by 7.3 percentage points (95% CI: 2.2, 12.3) more in SYV compared to SOC; standardized levels of ART concentration increased by 0.17 ng/mg (95% CI: -0.52, 0.85) more in SYV compared to SOC. Virologic suppression (HIV RNA <400 copies/mL) at baseline was 65% in both arms, but increased to 75% in the SYV arm and stayed the same in the SOC arm (RR 1.13; 95% CI: 0.94, 1.36).

Conclusion: YLWH worldwide are an important population, but often have poor HIV outcomes due to stigma and mental health difficulties. Very few interventions exist to improve outcomes in this critical population. This pilot trial of SYV demonstrated trends towards improvement in ART adherence, measured objectively, and virologic outcomes among YLWH in Tanzania supporting efforts to scale the intervention into a fully powered effectiveness trial.

Mental Health and HIV Measures Pre-Intervention and 6-Month Follow Up (Post Intervention)

		Standard of care (N=38)			*SYV* Intervention (N=55)		
		Baseline	6-mo (post)	Difference baseline-post	Baseline	6-mo (Post)	Difference baseline-post
PHQ-9	Mean (SD)	6.3 (4.1)	5.1 (3.9)	-0.9 (3.7)	4.9 (3.3)	4.1 (3.4)	-0.8 (4.0)
	Cutoff ≥ 10	10 (27.0%)	4 (11.1%)		4 (7.3%)	5 (9.1%)	
SDQ	Mean (SD)	7.1 (3.6)	7.3 (4.4)	0.1 (3.9)	7.3 (4.0)	6.7 (4.4)	-0.6 (3.9)
	Cutoff ≥ 17	0 (0.0%)	2 (5.6%)		0 (0.0%)	2 (3.6%)	
UCLA Trauma	Mean (SD)	9.3 (6.9)	8.9 (6.3)	-0.3 (5.9)	8.6 (7.4)	8.6 (7.5)	0.0 (7.3)
	Cutoff ≥ 18	5 (13.5%)	4 (10.8%)		9 (16.4%)	8 (14.5%)	
Composite Mental Health Difficulties*		12 (35.3%)	7 (19.4%)		13 (23.6%)	11 (20.0%)	
Stigma Mean (SD)	Overall	23.5 (3.7)	21.5 (5.1)	-2.3 (4.7)	21.9 (5.1)	22.7 (5.3)	0.6 (4.2)
	Internal	8.1 (1.8)	7.1 (2.0)	-1.1 (1.7)	7.7 (1.9)	7.5 (2.1)	-0.2 (2.5)
	External	15.5 (3.7)	14.3 (4.2)	-1.2 (3.9)	14.4 (4.3)	15.1 (4.5)	0.7 (3.3)
Adherence	Self-report	57.7 (15.2)	57.7 (14.9)	-0.1 (12.4)	60.5 (11.6)	65.5 (12.3)	5.1 (17.0) *
ART concentration in Hair (ng/mg)	NVP (N=13)	44.2 (15.4)	49.7 (20.8)	5.4 (16.1)	47.1 (19.2)	45.9 (20.0)	2.4 (32.2)*
	EFV (N=29)	9.3 (7.3)	10.0 (8.2)	-1.1 (4.1)	6.0 (5.4)	5.7 (3.3)	-0.3 (4.8)
	LPV (N=15)	6.1 (5.9)	11.0 (11.7)	4.9 (9.2)	6.3 (6.6)	6.9 (5.9)	0.6 (6.5)*
	ATV (N=20)	4.7 (4.0)	4.4 (3.2)	-0.4 (2.3)	5.8 (3.8)	6.1 (3.1)	0.4 (1.7)*
	Standardized (N= 77)	-0.4 (2.0)	-0.5 (2.0)	-0.1 (1.5)	-0.7 (2.3)	-0.6 (1.7)	0.1 (2.1)*
HIV RNA Copies/mL	Log_{10}	5.1 (2.8)	5.3 (3.3)	0.2 (1.8)	5.4 (3.3)	4.7 (2.6)	-0.7 (2.5)
	<400 (Suppression)	25 (65.8%)	25 (65.8%)		35 (64.8%)	41 (74.5%)	

Continuous variables reported as Mean (SD) where SD is standard deviation.
*Negative value favors the intervention except for adherence where a positive value signifies improved adherence
*Scoring at or above the cutoff on one or more of the mental health measures

837 LONGITUDINAL STUDY OF NEUROCOGNITIVE DISORDERS AND BRAIN STRUCTURE IN ADOLESCENT HIV

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Background: Neurocognitive disorders (NCD) despite ART are well known in perinatally-infected HIV+ adolescents (PHIV) but there are few data on longitudinal changes in NCD and brain structure in PHIV over time.

Methods: Within this sub-study of the Cape Town Adolescent Antiretroviral Cohort, PHIV on ART >6m completed baseline and 3-year follow-up assessments including a comprehensive neurocognitive battery assessing function in 10 domains. We applied the youth HIV-associated NCD diagnostic criteriato classify each as having either a major NCD, a minor NCD, or no impairment. Diffusion tensor imaging and structural brain magnetic resonance imaging was done to determine fractional anisotropy (FA), mean diffusivity (MD), grey and white matter volumes, cortical thickness and cortical surface area. In analysis we examined changes over the 3-year period in NCD and neurostructural measures in PHIV compared to age- and sex-matched HIV- controls.

Results: Overall 122 PHIV ages 9-12 years (mean CD4 cell count 953 cells/μL and 85.3% VL<50 copies/mL) and 37 age-matched HIV- controls completed baseline and 3-year follow-up assessments. 48% PHIV had a NCD at baseline and 60% at follow-up: NCD diagnosis was stable over time in 60 (49%) of participants, 22 (18%) improved NCD status and 40 (33%) deteriorated. At baseline, PHIV with major NCD showed the highest whole brain MD (p=.007); at follow-up whole brain grey (p=.004) and white matter volumes (p=.032) were lowest in PHIV, with whole brain MD remaining highest in PHIV with a major NCD (p=.02). Higher MD is suggestive of inflammation and myelin loss. In addition significant regional brain changes were observed at follow-up compared to baseline in PHIV vs controls. Structural changes over time were observed mainly in cortical surface area of the bilateral orbitofrontal, anterior cingulate, medial orbitofrontal, middle frontal, superior temporal, transverse temporal gyri and insula (all p<.05). White matter microstructural changes over time were observed in the internal capsule, cerebral peduncle and the cingulum (all p<.05).

Conclusion: NCD and brain structural alterations in PHIV increased over the 3 years of follow-up compared to HIV- controls. Studying the participants who improved vs deteriorated over time may provide insight into future interventions for NCD in PHIV.

838 BRAIN DEVELOPMENT IN TREATED PERINATAL HIV: A LONGITUDINAL NEUROIMAGING STUDY

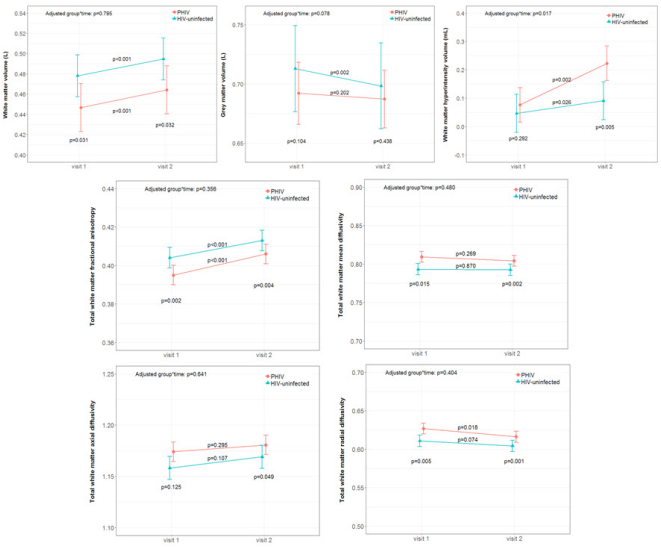
Malon Van den Hof[1], Pien Jellema[1], Anne Marleen Ter Haar[1], Henriëtte J. Scherpbier[1], Anouk Schrantee[2], Antonia Kaiser[2], Matthan W. Caan[2], Peter Reiss[3], Ferdinand Wit[3], Henk-Jan M. Mutsaerts[2], Dasja Pajkrt[4]
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Background: Cross-sectional studies, including our NOVICE study (Neurological Visual and Cognitive performance in treated perinatally HIV-infected [PHIV] children compared to age-, sex-, ethnicity- and socioeconomic status [SES]-matched HIV-uninfected controls), have reported lower white matter (WM) and grey matter (GM) volumes, higher WM hyperintensity (WMH) volume and poorer WM integrity measures in treated PHIV children. It is however unknown whether these differences originated before treatment initiation, or may be progressive over time. This longitudinal study compares the rates of change over time.

Methods: We approached all NOVICE participants, to repeat 3T magnetic resonance imaging (MRI) at the Amsterdam University Medical Centers, the Netherlands, after a mean of 4.6±0.3 years. We repeated GM and WM volume, WMH volume and WM integrity measures (total fractional anisotropy [FA], mean diffusivity [MD], radial diffusivity [RD], and axial diffusivity [AD]), obtained by T1-weighted-, FLAIR and DTI MRI, respectively. We compared rates of change between groups using multivariable linear mixed effects models, adjusted for sex and age at first MRI, and we investigated disease- and treatment related factors as determinants of poorer outcomes.¬

Results: 20 out of 31(65%) PHIV and 20 out of 37(54%) controls completed a second MRI examination. Those who gave consent for follow-up MRI were not statistically different compared to those who did not gave consent in volumetric outcomes and FA at first MRI (all p-values>0.05). Those who completed two MRI examinations had a mean age of 13.0±3.1 years and 17.6±3.1 years at first and second MRI, respectively. PHIV and controls were not statistically different in age, sex, ethnicity, and SES (all p-values>0.05). At p<0.1, WMH volume increased significantly more in PHIV participants (group*time 0.10mL, 95%CI 0.02–0.18, p=0.017) compared to controls (figure 1), which was not associated with disease- and treatment related factors (all p-values>0.05). GM volume decreased significantly less in PHIV (group*time 0.010L, 95% CI -0.001–0.020, p=0.078). We found no statistically different changes over time in WM volume (group*time 0.001, 95%CI -0.006–0.008, p=0.795), nor in WM integrity measures (group*time p-values>0.356).

Conclusion: Results indicate progressive cerebral differences as WMH progress over time in long-term cART-treated PHIV adolescents. Future analyses should further investigate determinants of WMH progression.



839 IDENTIFICATION OF AGE-APPROPRIATE DOSING STRATEGIES OF BICTEGRAVIR IN NEONATES

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Background: Paediatric patients differ from older patients in terms of drug metabolism and disposition, which necessitates evaluation of age-appropriate dosing strategies. Historically, this has complicated drug development resulting in fewer treatment options for neonates. PBPK modelling can be employed in early drug development to help inform selection of appropriate medicines at appropriate doses for paediatric patients. Bictegravir (BIC) is a HIV-1 integrase inhibitor that elicits a potent virological response and has potential for treatment and prophylaxis within neonatal populations. The safety and pharmacokinetics (PK) of BIC have previously been studied in children older than 6 years and adolescents but not neonates. The aim of this study was to use PBPK modelling to inform identification of an age-appropriate dose within this population.

Methods: A whole-body PBPK model was constructed in Simbiology (MATLAB 2018b) using neonatal physiological and anatomical descriptors. Neonatal PK simulations also utilised published experimental in vitro data for BIC. The ontogenies of key metabolic enzymes such as CYP3A4 and UGT1A1 were refined and validated using observed neonatal clinical data for raltegravir (RAL) and midazolam (MDZ). Published adult PK data for BIC were used to partially validate the simulated parameters, where the model was assumed to be qualified if simulated values were within 0.5 -1.5-fold of the mean reported values as per modelling convention.

Results: All models were acceptably qualified with RAL, MDZ and BIC exhibiting absolute average fold errors of 1.05, 1.31 and 1.12, respectively. Several multi-dose regimens for orally administered BIC were simulated in 100 healthy neonates with the aim of achieving equivalent plasma concentrations to therapeutic exposures observed in adults (C_{trough}: 2.61 mg/L and AUC24: 102 mg.h/L). These regimens and their resulting PK parameters are summarised in Table 1. Regimens 2 & 3 resulted in exposures comparable to that observed in

adults, and involved starting neonates on a 5 mg once daily dose, increasing to 7.5 – 10 mg once daily after day 11.

Conclusion: Dose adjustments are predicted between adult and paediatric patients. Drug approval in infants and neonates is often hindered by a lack of suitable formulations and difficulty in examining drug exposure. Several potential regimens have been identified, which are worthy of empirical investigation within this patient group.

Table 1 Summary of pharmacokinetic parameters of orally administered bictegravir (BIC) in neonates

Regimen	Total Dose (mg)	C_{max}[1] (mg/L)	AUC_{av} (mg.h/L)	C_{max}[2] (mg/L)	AUC_{24hr} (mg.h/L)	C_{trough} (mg/L)
1	Day 1-28 = 5 QD	5.71 ± 1.17	57.29 ± 22.6	2.43 ± 0.68	33.49 ± 14.87	0.65 ± 0.57
2	Day 1-10 = 5 QD; Day 11-28 = 10 QD	6.25 ± 1.60	80.00 ± 29.57	4.32 ± 1.18	63.78 ± 40.91	1.29 ± 0.99
3	Day 1-10 = 5 QD; Day 11-28 = 7.5 QD	6.00 ± 1.52	74.00 ± 32.20	3.67 ± 1.21	47.05 ± 19.58	1.10 ± 0.97
4	Day 1-28 = 10 QD	10.30 ± 2.26	106.66 ± 45.57	4.39 ± 1.56	61.22 ± 20.00	1.32 ± 1.45

C_{max}[1], Average maximum plasma concentration over 28-day simulation; AUC_{av}, Average conc. over 28-day simulation; C_{max}[2], Max plasma conc. after final dose; AUC_{24hr}, Final dose; C_{trough}, Min conc. after final dose.

840 SAFETY, PK, AND EFFICACY OF LOW DOSE B/F/TAF IN CHILDREN ≥2 YEARS OLD LIVING WITH HIV

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Background: Few antiretroviral options exist for smaller children living with HIV and no single-tablet regimen (STR) is used or approved for this population. STR of bictegravir, emtricitabine and tenofovir alafenamide (B/F/TAF) is approved for use in HIV-infected children weighing ≥25 kg. We report safety, pharmacokinetics (PK), and efficacy from an interim analysis of the first clinical trial of a low dose B/F/TAF tablet in young children living with HIV.

Methods: Virologically suppressed children (≥2 yrs) weighing 14 to <25 kg with HIV-1 RNA <50 c/mL for ≥6 months and CD4 ≥200 cells/µL at screening, received low dose B/F/TAF (30/120/15 mg) once daily in a prospective, 48-week (W), single-arm, open-label trial. Adverse events (AE), laboratory tests, and the proportion of participants with HIV-1 RNA <50 c/mL were assessed through W12. Steady-state PK of B/F/TAF was evaluated; BIC PK in children were compared to B/F/TAF-treated adults (50/200/25 mg) using a 50-200% equivalence boundary.

Results: Twelve children were enrolled; median age 6 (range 3-9) years, median weight 20.1 (range 14.6-24.1) kg, 58% female, 58% black, median CD4 count 841 cells/µL, all vertically infected. Through a median (Q1, Q3) duration of exposure to study drug of 20.1 (18.0, 27.1) weeks, most common AEs were abdominal pain, diarrhea, and upper respiratory tract infection (n=2 participants each); all AEs were grade 1 or 2; no child discontinued STR for AE. Related-AEs included neutropenia, irritability, and social avoidant behavior (n=1 each). Mean (SD) adherence to study drug was high (97.1% [7.02]). Ten of 11 (91%) children had HIV-1 RNA <50 c/mL at W12. Mean increase in CD4 count from baseline was 42 cells/mL. Geometric least squares mean ratios and 90% CIs for BIC AUC_{tau} and C_{max} in children vs adults were within 50-200%; BIC C_{tau} was 32% lower (Table). FTC and TAF exposures were within the range of historical data.

Conclusion: The B/F/TAF pediatric STR had high levels of adherence and virologic suppression. Exposures of all B/F/TAF drug components in young children were in the range of older populations, with mean BIC C_{tau} 12-fold above the paEC95 for wild type virus. Efficacy and safety of the pediatric STR in young children are consistent with adult strength STR efficacy in older populations. These data support further evaluation of low dose B/F/TAF as an unboosted INSTI-based STR for young children living with HIV.

Table. PK parameters of bictegravir (BIC) with B/F/TAF 30/120/15 mg STR administration in young children and adults

	Parameter	Young children[a]	Adults[b]	%GLSM Ratio (90% CI)
BIC	AUC_{tau}, ng*h/mL	110,000 (24)	102,000 (27)	108, (96.7, 122)
	C_{max}, ng/mL	10,100 (21)	6,150 (23)	166 (149, 184)
	C_{tau}, ng/mL	2,000 (78)[c]	2610 (35)	67.7 (49.6, 92.4)

Values presented to 3 significant figures. Statistical comparisons of the PK parameters in children (test) versus adults from Phase 3 studies (reference) were made using geometric least-squares mean (GLSM) ratios and associated 90% confidence intervals (CI). PK Parameters are presented as arithmetic mean (%CV).

GLSM, Geometric least-squares mean

[a] n=11 from intensive PK substudy in current child cohort, 1 participant excluded due to non-compliance with study drug

[b] n = 1193 from pooled population PK data from 4 Phase 3 Studies in adults with HIV

[c] n=10

841 B/F/TAF LOW-DOSE TABLET RELATIVE BIOAVAILABILITY IN HVs AND PK IN CHILDREN WITH HIV

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Background: Bictegravir (BIC)/emtricitabine (FTC)/tenofovir alafenamide (B/F/TAF 50/200/25 mg) single tablet regimen (bilayer tablet) is FDA-approved for the treatment of HIV in adults and pediatrics ≥25 kg. A low-dose monolayer B/F/TAF tablet (LDT) has been developed; the relative bioavailability (rBA) and food-effect of the LDT were evaluated in a Phase 1 study. The PK of the LDT was then confirmed in children with HIV 14-< 25kg.

Methods: Adult healthy volunteers (HV) received single doses of adult-strength B/F/TAF 50/200/25 mg fasted, or B/F/TAF 30/120/15 mg LDT fasted or fed (high-fat meal) in a randomized, 3-period, crossover study. PK parameters of BIC, FTC and TAF were compared between test and reference treatments using geometric least-squares mean (GLSM) ratios and 90% confidence intervals (CI) with a stringent 70-143% equivalence boundary. The PK of the B/F/TAF LDT was then assessed in virologically suppressed children ≥2 yrs, 14-<25kg (N=12) at W2. BIC exposures in children were compared to B/F/TAF-treated adults using clinically relevant boundaries of 50-200%. The PK of FTC, TAF and TAF-metabolite tenofovir (TFV) were compared descriptively to historical data. Safety was assessed throughout the studies.

Results: 52/54 HVs completed the Ph1 study. GLSM ratios and 90% CIs for BIC, FTC, and TAF PK parameter comparisons between LDT and adult tablet were within 70-143% (Table). Compared to fasted, high-fat meal did not alter BIC or FTC PK; TAF AUCinf increased 42%, C_{max} decreased 44%. 15% (adult tab fasted, or LDT fed) and 19% (LDT fasted) of HVs had an AE (all Grade 1). There were no discontinuations due to AEs. GLSM ratios and 90% CIs for BIC AUC_{tau} and C_{max} in children vs adults were within 50-200%. Mean BIC C_{tau} was 32% lower (Table). Exposures of FTC (mean AUC_{tau}=14,900 h*ng/mL), TAF (mean AUC_{tau}=305 h*ng/mL) and TFV (mean $AUCC_{tau}$=339 h*ng/mL) were within the range of historical data. 75% had an AE (all Grade 1/2).

Conclusion: B/F/TAF was well tolerated in HVs and children with HIV. The B/F/TAF LDT provided exposures equivalent to adult tablet with no clinically relevant food-effect. Like the adult tablet, LDT can be taken without regard to food. In children 14-< 25kg with HIV taking the LDT, no clinically meaningful differences in PK were identified compared to adults; mean BIC C_{tau} was 12-fold above paEC95, supporting its continued evaluation in pediatric trials.

Table. Comparisons of PK Parameters between the B/F/TAF LDT and Adult Tablet Formulations, and between Children 14 to < 25 kg and Adults Treated with B/F/TAF

Analyte	PK Parameter	BIC/FTC/TAF 30/120/15 mg (Low-dose Tablet)[a] vs BIC/FTC/TAF 50/200/25 mg (Adult Tablet) Dose-normalized %GLSM Ratio (90% CI)[b] N=53		
BIC	AUC_{inf} ng*h/mL	112 (106, 117)		
	C_{max} ng/mL	117 (112, 123)		
FTC	AUC_{inf} ng*h/mL	101 (99.1,103)		
	C_{max} ng/mL	104 (98.2,109)		
TAF	AUC_{inf} ng*h/mL[c]	90.5 (84.7,96.6)		
	C_{max} ng/mL	95.4 (83.0,109)		
Analyte	PK Parameter Mean (CV%)	Children 14 to < 25 kg (B/F/TAF 30/120/15 mg) N=11[d]	Adults (B/F/TAF 50/200/25 mg) N=1193[e]	Children 14 to < 25 kg vs Adults %GLSM Ratio (90% CI)
BIC	AUC_{inf} ng*h/mL	110,000 (24)	102,000 (27)	108, (96.7, 122)
	C_{max} ng/mL	10,100 (21)	6,150 (23)	166 (149, 184)
	C_{tau}, ng/mL	2,000 (78)[f]	2,600 (35)	67.7 (49.6, 92.4)

Values presented to 3 significant figures; GLSM= geometric least squares mean; CI= Confidence Interval
•PK parameter was dose-normalized by dividing by value of the ratio of the test dose/reference dose [0.6]
•Dose-normalized %GLSM Ratio and 90% CI were calculated by dividing the dose-normalized GLSM of the PK parameter from the test treatment with the GLSM of the PK parameter from the reference treatment
•N=52
•PK parameters estimated by non-compartmental analysis; 1 participant excluded from PK analysis as undetectable predose drug concentrations indicated non-compliance
•Population PK estimated data from 4 Phase 3 Studies in adults with HIV
•N=10

842 MARAVIROC SAFETY & PHARMACOKINETICS IN HIV-EXPOSED NEONATES

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Background: Lack of adequate safety and pharmacokinetic (PK) data limits antiretroviral (ARV) prophylaxis and treatment options in HIV-exposed neonates. Maraviroc (MVC), a CCR5 receptor antagonist approved for use in adults, has potential for use in prophylaxis and treatment of HIV-exposed or infected neonates.
Methods: IMPAACT 2007 is an ongoing Phase I, multi-center, open-label study of MVC safety and PK in HIV-exposed neonates on standard ARV prophylaxis. Study design includes two sequential dosing cohorts starting MVC by day 3 of life. Cohort 1 infants received two single 8mg/kg MVC doses one week apart with intensive PK sampling after the initial dose. Based on PK data from Cohort 1, Cohort 2 infants receive 8 mg/kg MVC twice daily through 6 weeks of life with intensive PK sampling at Weeks 1 and 4. Due to a known PK interaction between MVC and efavirenz (EFV) in adults, cohorts were stratified by exposure to maternal EFV. PK samples were analyzed for MVC concentration by validated high-performance liquid chromatography. PK parameters were estimated using standard non-compartmental methods. MVC exposure target is Cavg ≥ 75ng/mL, from adult treatment studies. Laboratory and clinical evaluations assessed infant safety at entry and Weeks 1, 2, 6, 16 in Cohort 1; Weeks 1, 4, 6, 12, 16 in Cohort 2.
Results: Forty-seven MVC-naïve, HIV-exposed neonates have enrolled; 15 in Cohort 1, 32 in Cohort 2 (median gestational age 39 weeks, 51% male) from the USA(20), Thailand(3), Kenya(2), and South Africa(22). PK data are available for 13 Cohort 1 infants and 21 Cohort 2 infants; data from 4 additional infants pending. All Cohort 1 infants (n=13) met the PK target after the initial dose. Median exposure for Cohort 2 infants (n=22) exceeded the PK target but variability in exposure was high, with 17-33% of infants below the PK target at Weeks 1 and 4, respectively (Table 1). The proportion of infants who achieved the PK target was similar between EFV-naïve and EFV-exposed infants. No Grade 3+ toxicities or early study discontinuations noted due to MVC.
Conclusion: Maraviroc appears safe when used in the first 6 weeks of life. MVC exposures met treatment PK targets in most infants receiving 8 mg/kg twice daily, but with considerable variability in exposure. Maternal EFV use appeared to have no effect on MVC exposure and there were no study discontinuations due to toxicity or intolerance. The final MVC dose recommendation will be determined accounting for patient variability.

Table 1: PK Parameters by Study Strata[a]

		N	Dose (mg/kg)	AUC (ng*h/mL)	C_{avg} (ng/mL)	$C_{avg} \geq$ 75 ng/mL	Cl/F (L/h)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)
Cohort 1										
Initial dose	EFV-naive	6	8.3 [8.0-8.9]	2,286 [1,422-3,648]	190 [119-304]	6 / 6 (100%)	10.8 [4.9-13.3]	227 [125-457]	4.7 [3-6]	4.6 [4.1-6.8]
	EFV-exposed	7	8.7 [8.6-9.0]	4,506 [3,629-6,882]	375 [302-574]	7 / 7 (100%)	6.7 [4.5-7.6]	551 [506-916]	1.5 [1.3-1.7]	3.7 [3.4-4.6]
Cohort 2										
Week 1	EFV-naive	12	8.5 [8.2-8.9]	1,862 [988-2,220]	155 [82-185]	10 / 12 (83%)	14.9 [12.7-25.3]	325 [204-761]	1.5 [1.3-1.9]	3.3 [2.6-3.8]
	EFV-exposed	10	7.8 [7.6-8.1]	1,851 [1,070-2,523]	154 [89-210]	8 / 10 (80%)	15.5 [11.4-31.0]	355 [224-634]	3 [1.5-3.0]	3.3 [2.8-4.7]
Week 4	EFV-naive	12	7.5 [7.3-8.1]	1,806 [783-3,485]	151 [65-290]	8 / 12 (67%)	16.1 [7.4-31.1]	467 [161-649]	1.5 [1.2-3.5]	3.9 [3.4-7.1]
	EFV-exposed	9	6.9 [6.8-8.4]	1,530 [793-1,819]	127 [66-152]	6 / 9 (67%)	19.0 [16.3-27.7]	230 [162-448]	3 [1.0-3.0]	7.9 [4.1-10.6]

[a]Median [Interquartile range: IQR] except for N, number of patients with $C_{avg} \geq 75$ ng/mL, number/total (% achieving PK target); AUC=Area under the concentration time curve to infinity for Cohort 1 (single dose), and to 12 hours for Cohort 2 (steady-state); C_{avg} = average concentration (AUC divided by tau set to 12 hours); Cl/F = oral clearance; C_{max} = maximum observed concentration; T_{max} = time of C_{max}; $t_{1/2}$ = half-life

843 ABACAVIR SAFETY AND PHARMACOKINETICS IN NORMAL AND LOW BIRTH WEIGHT INFANTS WITH HIV

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Background: Abacavir (ABC) is licensed for infants >3 months of age while WHO recommends use in HIV-infected children ≥4 weeks of age and ≥3 kg. ABC is metabolized in the liver via UDPGT and ADH enzymes, and information describing ABC disposition during the first few months of life is lacking. We describe ABC pharmacokinetic (PK) and safety data in HIV-infected normal and low birth weight (LBW) infants initiating ABC within the first 3 months of life.
Methods: IMPAACT P1106 is an opportunistic, multi-arm study of PK and safety in LBW infants conducted in South Africa on antiretroviral and antituberculosis medicines. Arm 5 included HIV-infected infants receiving ABC, lamivudine and lopinavir/ritonavir. Plasma samples for ABC PK assessment were collected pre-dose (C0), 1.5- and 4-hours post-dose at study weeks 2, 10, and 24, with C0 samples at weeks 6 and 16. ABC concentrations were measured by LC-MS/MS and ABC PK parameters estimated using a population approach. Adverse events (AE) were evaluated from entry to week 24.
Results: Twenty-five infants (18 LBW) were included in the analysis. Median entry age was 44 days (range 11 to 78 days). Twelve (48%) infants were male and 22 (88%) black African. Median ABC dose was 10 (6-13) mg/kg BID and ABC concentrations were available for 24 (195 observations) infants with median (range) birth weight 2190 g (1360-3260) and median gestational age 36 weeks (32-37). ABC plasma concentrations were described by a 1-compartment model. Infant body weight (BW) and post-menstrual age (PMA=gestational age+postnatal age [PNA]) influenced ABC PK parameters. ABC oral clearance (CL/F) increased by 2% per PMA week. Infant characteristics and ABC PK parameters per PK visit are shown in Table 1. One infant died of unknown cause 3 days after entry. Fourteen infants had Grade 3/4 AEs, among which most common were gastroenteritis (n=4) and respiratory infection (n=4) and all of which improved except for malnutrition (n=1), underweight (n=1) and a respiratory infection (n=1) present at the last study visit. No hypersensitivity was reported. All AEs were assessed as unrelated to ABC, except for one possibly related Grade 2 alanine aminotransferase where all antiretrovirals were stopped for 2 weeks until resolution then restarted without further complications.
Conclusion: ABC was well tolerated in LBW infants. ABC exposures were relatively high compared to older infants during the first 3 months of life but decreased rapidly as infants matured.

Table 1. Median (range) of Infant Characteristics and Abacavir PK parameters

Study Visit	ABC Dose (mg/kg)	Weight (kg)	PNA (Days)	PMA (Weeks)	CL/F (L/hr/kg)	*AUC_{0-12} (mg.hr/L)
Week 2 (n=16)	11 (6-13)	3.6 (2.4-5.4)	63 (41-93)	44 (38-50)	0.67 (0.24-1.42)	16.9 (4.6-48.7)
Week 10 (n=20)	9 (6-12)	5.2 (3.8-6.8)	118 (93-148)	52 (46-58)	0.79 (0.28-1.56)	10.7 (6.9-30.6)
Week 24 (n=20)	10 (7-12)	6.8 (5.1-8.9)	216 (186-247)	66 (59-71)	1.03 (0.34-1.97)	9.8 (4.4-33.9)

**Historical ABC PK data in children 3 to 6 years old: AUC_{0-12}: 7.8 mg.hr/L [ARROW Trial: Musiime et al Antivir Ther. 2010;15(8):1115-24.]*

844 ABACAVIR DOSING, EFFECTIVENESS, AND SAFETY IN YOUNG INFANTS LIVING WITH HIV IN EUROPE

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Background: The World Health Organization recommends abacavir (ABC) as the preferred/alternative backbone for 1st line regimens in children with HIV from age 28 days. There are limited data available on safety and tolerability of ABC in young infants aged <3 months.

Methods: All children in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) who initiated ABC aged <3 months between 2000-2016 were included. We describe infant and regimen characteristics at the start of ABC (including drug combinations and dosing) and outcomes up to 12 months after first use of ABC. Outcomes include drug discontinuations (defined as interruption of treatment for >30 days), clinical adverse events (AE, reported from start of ABC up to 30 days after discontinuation) and viral suppression <400c/ml (VS) at 6 and 12 months of treatment for children who remained on ABC.
Results: Of 498 children in EPPICC who received antiretroviral therapy (ART) whilst aged <3 months, 139(28%) received an ABC-containing regimen (n=20 aged<28 days) and were followed for median 4.6 [IQR 1.5,9.7] years. Median year of birth was 2010 [2006,2012], age at HIV diagnosis was 39 [11,62] days and 84(60%) were female. 53(38%) were from UK and Ireland, 23(17%) Ukraine, 19(14%) Spain, 14(10%) Russia, 12(9%) Belgium and 18(13%) elsewhere in Europe. 63(45%) received post-exposure prophylaxis (PEP) prior to ABC-based treatment (4 PEP regimens included ABC, with the ABC continuing following HIV diagnosis). 54(39%) were taking ABC with lamivudine and lopinavir/ritonavir and for 44 infants with ABC dosing/weight data available, 30(68%) started on an 8mg/kg twice daily (BD) dose (Table).
Overall 66/92(70%) and 59/77(77%) on ABC-containing regimens had VS after 6 and 12 months, respectively. During the first 12 months on ABC, AEs were reported in 8 infants with 4 events leading to discontinuation of ABC, all occurring within the first 7 days of treatment (Table). By 12 months after start of ABC, cumulative incidence of discontinuation of ABC due to a safety concern was 3.6% (95% CI 1.4,7.8%). A further 11 infants discontinued ABC for other reasons (5 of 11 later restarted ABC) and the cumulative incidence of any discontinuation by 12 months was 11.8% (7.3,18.9%). There were no deaths reported during follow-up.
Conclusion: ABC is safe and well tolerated in infants, with rare discontinuations for safety concerns, supporting WHO treatment recommendation. More data on ABC use are required in neonates.

Table: Regimen characteristics, adverse events and drug discontinuations in infants who initiated abacavir aged <3 months

Characterises of ABC regimen		n(%)
Weight at start of ABC (n=71):	<3kg	8(11%)
	3 to <6kg	60(85%)
	6 to <10kg	3(4%)
Initial ABC dose (n=44):	<4mg/kg BD	3(7%)
	4-6mg/kg BD	6(14%)
	8mg/kg BD	30(68%)
	>8mg/kg BD	5(11%)
Initial regimen:	ABC+3TC+LPV/r	54(39%)
	ABC+3TC+AZT+NVP	45(32%)
	ABC+3TC +NVP	19(14%)
	Other	21(15%)

AEs and ABC discontinuations up to 12 months after ABC start	n
Treatment emergent AEs	8
Events leading to ABC discontinuation[1]	4
Other discontinuations	11
Non-compliance	3
Structured interruption	2
Treatment failure	2
More effective treatment available	1
Parents' wish	1
Unknown	2

Abbreviations: ABC – abacavir, 3TC – lamivudine, LPV/r – lopinavir/ritonavir, AZT – zidovudine, NVP – nevirapine
[1] Of 8 AEs, 4 led to ABC discontinuation within 7 days of starting ABC (1 in 2003, 1 in 2007 and 2 in 2011): 1 severe metabolic acidosis (initially thought to be ABC reaction, later confirmed rotavirus gastroenteritis; HLA-B 5701 negative); 1 diarrhoea and vomiting (considered unlikely related to ABC; HLA-B 5701 negative); 1 possible HLAB5701 positivity (unconfirmed); 1 hypersensitivity reaction. Other 4 AEs were: 3 pneumonia and 1 anaemia (possibly related to zidovudine).

845 ABACAVIR SAFETY AND EFFICACY IN YOUNG INFANTS IN SOUTH AFRICAN OBSERVATIONAL COHORTS

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Background: World Health Organization guidelines recommend abacavir as part of the preferred first line antiretroviral treatment (ART) regimen in children aged >28 days. However, there is no approved dose under 3 months of age, and with increasing access to early infant HIV diagnosis, more data are necessary to guide dosing recommendations in neonates. We describe the safety and effectiveness of abacavir in young infants in 9 South African cohorts participating in the IeDEA collaboration.
Methods: We included all infants who initiated ART (≥3 antiretroviral drugs from ≥2 classes) before 3 months of age, between 2006–2017. In those who received abacavir we described characteristics at abacavir initiation; the proportion who discontinued abacavir; and viral load suppression at 12 months. We compared infants who started abacavir aged <28 days with older infants, and those who weighed <3 kg with those who weighed ≥3 kg, in terms of abacavir discontinuations and viral load suppression, using Chi-squared or Fisher's exact tests.
Results: Of 1847 infants who started ART aged <3 months, 931 (50%) received abacavir: 96 were aged <28 days. At abacavir start, median (interquartile range, IQR) age was 67 days (48 to 80), CD4 percentage was 26.9 (19.0 to 37.0), viral load was 1 000 000 copies/mL (146 036 to 3 792 175), and weight was 4.2 kg (3.2 to 5.0). ART regimens included lamivudine and ritonavir-boosted lopinavir in 858 infants (92%), lamivudine and nevirapine in 9 (1%) and other antiretrovirals in 64 (7%). In those with ≥1 month's follow-up after abacavir initiation, 61/789 (8%) infants discontinued abacavir permanently, at a median of 13.3 months (IQR 6.4 to 26.8). There were no significant differences in the proportion of discontinuations by age or weight category (p=0.6 and 0.9 respectively, Table 1). Reasons for discontinuation were documented in 20 infants (33%): non-compliance or transfer out in 11, treatment failure in 6, and hypersensitivity in 1. Viral load was measured at 12 months in 353/527 infants with ≥12 months' follow up. The proportion of infants with viral load <400 copies/mL was 15/27 (56%) and 188/326 (58%) in those who started abacavir aged <28 days and 28 days to 3 months respectively (p=0.8); and 17/24 (71%) and 67/111 (60%) in those who weighed <3 kg and ≥3 kg respectively (p=0.4).
Conclusion: Half of the infants who started ART before three months of age in our cohort received abacavir. Our data suggest that abacavir may be used safely in infants <28 days old or who weigh <3 kg.

Table1. Abacavir discontinuations by age and weight categories in infants with at least one month's follow up

	Weight at abacavir start (±7 days) in kg						
	<3	3-3.9	4-4.9	5-5.9	≥6	Missing	Total
Overall							
n	37	62	70	42	24	554	789
Discontinuation (%)	3 (8.1)	3 (4.8)	5 (7.1)	4 (9.5)	1 (4.2)	45 (8.1)	61 (7.7)
Age <28 days at abacavir start							
n	8	7	0	0	1	60	76
Discontinuation (%)	1 (12.5)	1 (14.3)	0	0	0	5 (8.0)	7 (9.2)
Age 28 days to 3 months at abacavir start							
n	29	55	70	42	23	494	713
Discontinuation (%)	2 (6.9)	2 (3.6)	5 (7.1)	4 (9.5)	1 (4.4)	40 (8.1)	54 (7.6)

846 PHARMACOKINETICS OF RALTEGRAVIR IN HIV/TB COTREATED INFANTS AND YOUNG CHILDREN

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Background: Current Antiretroviral (ARV) options for HIV/TB co-infected children are limited. Rifampin (RIF) induces UDP-glucuronosyltransferase activity, increasing clearance of raltegravir (RAL). We sought to establish the optimal and safe dose of RAL when administered with RIF in HIV/TB co-infected infants and children.
Methods: P1101 is a dose finding study of RAL in HIV-infected children at four South African sites receiving RIF-containing TB therapy for at least 1 wk, with three age cohorts spanning 4 wks to <12 yrs of age, aiming to enroll 12 evaluable participants for PK and safety in each. At entry, participants start RAL at 12 mg/kg/dose twice daily (twice the approved pediatric dose) and two nucleoside reverse transcriptase inhibitors. Intensive RAL PK sampling is done 5-8 days after ARV initiation and then a fourth ARV is added. RAL is stopped at the end of TB treatment with follow-up for another 3 mo. PK targets are a geometric mean (GM) AUC0-12h of 14-45 µMxh and GM C12h ≥75 nM. Here we report the results from Cohort 3 (4 wks to <2 yrs) using RAL chewable tablets as a dispersible tablet; Cohorts 1 and 2 (ages 2 yrs to <12 yrs) were previously reported.
Results: Of 13 participants, 8 were male with a median age 12.3 mo and baseline $\log_{10}$ HIV (RNA cpy/mL) of 5.13 (5.01-5.60), CD4 count/µL of 1513 (1337-2008), and CD4% 16.8% (15.4-19.1). Wk 1 PK showed GM AUC12h (%CV) of 32.7 µMxh (49%) and GM C12h of 106.5 nM (57%). No adverse events were related to RAL. 12/13 had evaluable efficacy data at wk 8 (1/13 stopped RAL early due to use of a disallowed medication). By wk 8, 10/12 (83%) had HIV RNA <400 copies/mL; median changes from baseline were $\log_{10}$ RNA cpy/mL -3.05, CD4 count +105.5 cells/µL and CD4% +4.9%. RAL was permanently stopped

in 6/13 participants,one each for Grade 4 neutropenia (likely related to TB medication), use of a disallowed medication, or AUC12h exceeding the allowed AUC12h maximum (asymptomatic). Three stopped RAL for virologic failure (VF): 1 at wk 8 (above) who was very ill; 1 at wk 12 (non-adherence); 1 at wk 12 (VF unexplained).

Conclusion: A 12 mg/kg dose twice daily of RAL chewable tablets appears to safely achieve PK targets in HIV/TB co-infected children 4 wks to <2 yrs receiving rifampin, with high rates of virologic suppression by Week 8.

847 ADEQUATE DOLUTEGRAVIR EXPOSURE DOSED BID WITH RIFAMPICIN IN CHILDREN 6 TO <18 YEARS

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Background: Adults with HIV/TB co-infection on dolutegravir (DTG)-based antiretroviral therapy (ART) can overcome the induction effect of rifampicin (RIF) by doubling the DTG dose (50mg twice(BID) instead of once(QD) daily. We undertook a pharmacokinetic (PK) substudy nested within the ongoing ODYSSEY randomised controlled trial (#NCT02259127) to evaluate DTG PK in HIV/TB co-infected children while receiving DTG BID+RIF and DTG QD.

Methods: Children aged 6-<18 years receiving DTG BID+RIF were eligible; we aimed to include 6 children aged 6-<12 years and 6 children 12-<18 years. A 12h PK curve was constructed for children on DTG BID in the last month of RIF treatment and subsequently, a 24h PK curve on DTG QD ≥4 weeks after stopping RIF. Geometric mean ratios (GMRs) were estimated comparing DTG PK parameters between the 2 periods and individual C_{trough} levels below EC_{90} (0.32 mg/L) were summarised. All children who received DTG BID+RIF aged ≥6 years were followed for serious adverse events(SAEs), grade 3/4 clinical/laboratory adverse events(AEs) and any AEs resulting in ART modification from start of DTG BID to 30 days after return to DTG QD.

Results: Of 30 eligible children, 17 were enrolled in the PK substudy; 13/17 participants undertaking PK had ≥1 evaluable PK curve. 12/13 were black African, median (range) age 12.3 (6.8-16.1) years and 31.3 (19.8-48.5) kg. 12 PK curves were evaluable for DTG BID+RIF (5 on 25mg BID and 7 on 50mg BID) and 11 for DTG QD (5 on 25mg QD and 6 on 50mg QD). GMRs (90% CI) for DTG BID+RIF versus DTG QD (reference) for C_{trough}, AUC0-24h and C_{max} were 1.59 (1.09-2.33), 1.20 (0.90-1.59), and 0.98 (0.79-1.21), respectively. Oral clearance of DTG with RIF was increased 1.7-fold, with 41% reduction in elimination half-life. Findings were similar in children above and below 12 years old. AUC0-24h GMRs in children ≥20kg receiving WHO 2019-recommended DTG 50mg dose was 1.00 (0.61-1.62) and 1.47 (0.99-2.19) for children on 25mg dose. One child on DTG 25mg QD without RIF had C_{trough}<EC_{90}. 30 children were followed for median (IQR) of 32(30,40) weeks; 8 participants had 13 reportable AEs (9 SAEs including 1 DTG discontinuation). All events were considered unrelated to DTG by investigators and independent reviewers.

Conclusion: Twice daily dolutegravir dosing was safe and sufficient to overcome rifampicin enzyme-inducing effect in HIV/TB co-infected children aged 6-<18 years, including in children ≥20kg receiving new WHO doses (DTG 50mg).

Table 1: Participant characteristics and PK parameters on DTG BID+RIF and GMRs for DTG BID+RIF versus DTG QD

		Children 6 to <18 years		
Parameter		**DTG 25mg (n=5)**	**DTG 50mg (n=8)**	**Overall (n=13)**
Age, years	Median (range)	8.9 (6.8-10.3)	13.1 (10.7-16.1)	12.3 (6.8-16.1)
Weight, kg	Median (range)	24.9 (19.8-27.7)	33.0 (28.1-48.5)	31.3 (19.8-48.5)
DTG BID dose, mg/kg	Mean (range)	2.1 (1.8-2.5)	2.8 (2.1-3.6)	2.5 (1.8-3.6)
C_{trough} (mg/L) on DTG BID+RIF	GM (CV%)	0.90 (16)	1.11 (99)‡	-
AUC_{0-24h} (h*mg/L) on DTG BID+RIF	GM (CV%)	53.4 (21)	60.3 (63) ‡	-
C_{max} (mg/L) on DTG BID+RIF	GM (CV%)	3.62 (24)	4.50 (47) ‡	-
C_{trough} (mg/L)*	GMR (90% CI)	2.10 (1.20-3.68)	1.23 (0.64-2.36)	1.59 (1.09-2.33)
AUC_{0-24h} (h*mg/L)*	GMR (90% CI)	1.47 (0.99-2.19) †	1.00 (0.61-1.62) †	1.20 (0.90-1.59)
C_{max} (mg/L)*	GMR (90% CI)	1.02 (0.73-1.41)	0.94 (0.64-1.37)	0.98 (0.79-1.21)
$T_{1/2}$ (h)*	GMR (90% CI)	0.60 (0.46-0.78)	0.56 (0.39-0.80)	0.59 (0.49-0.72)
Vd/F (L)*	GMR (90% CI)	0.81 (0.48-1.37)	1.20 (0.75-1.94)	1.03 (0.7.-1.45)
CL/F (L/h)*	GMR (90% CI)	1.36 (0.91-2.01)	2.01 (1.24-3.26)	1.70 (1.25-2.32)

* GMRs (90% CI) for DTG BID+RIF versus DTG QD (reference).
‡ 7 participants have evaluable PK on 50mg DTG BID + RIF
† Individual AUC_{0-12h} while on BID dosing were multiplied by 2 for extrapolation to AUC_{0-24h} and used for calculation of GMR for AUC_{0-24h} on BID versus QD.

848 RISK FACTORS FOR NEW HIV INFECTIONS IN THE GENERAL POPULATION IN SUB-SAHARAN AFRICA

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Background: Previous work identified risk factors for new HIV infections in sub-Saharan African populations but patterns of association are not consistent across studies. Different risk factor definitions and low power may explain some inconsistencies. Statistical power has not previously been estimated in these risk factor analyses. We harmonised population-based longitudinal data from general population studies in 6 sub-Saharan African countries, partners in the Network for Analysing Longitudinal Population-based HIV/AIDS data on Africa, to assess risk factors for new HIV infections. Potential risk factors were identified from the literature and a modified version of the proximate determinants framework.

Methods: Individual level data covering 2005 to the end of follow up (2012-2016) were obtained for each study. Data were arranged for survival analysis with first HIV negative test as the start of observation and HIV seroconversion as the failure event. Indviduals were censored at death, out migration and end of follow up. 70 imputations of seroconversion date were used to overcome interval censoring.

Time-varying risk factors were: residence, residential mobility, time since first sex, marital status, numbers of partners in lifetime and last year, acquisition of new partners, types and combinations of partnerships, male circumcision, condom use and age gaps between partners. Piecewise exponential regression models were fitted separately by study for men and women aged 15-24 and 25-49. Crude hazard ratios were compared between studies. We estimated the statistical power to detect each association. Study- and sex- and age-specific multivariate models were fitted and consistency of risk factors evaluated. Where warranted, the pooled effects of risk factors are estimated.

Results: 99097 people contributed 351457 person years (203266 from women). There were 5274 seroconversions (3711 among women). Figure 1 shows the crude hazard ratio for HIV infection by selected risk factors. Most consistent findings across studies were that new & multiple partners and being formerly married increased risk whilst being circumcised decreased risk. Condom use was protective among people who had higher risk partnerships.

Conclusion: Effect size and strength of evidence varied across studies and age groups and for each risk factor. Whilst lack of statistical power explains some heterogeneity there are likely to be real differences in the importance of some risk factors between populations.

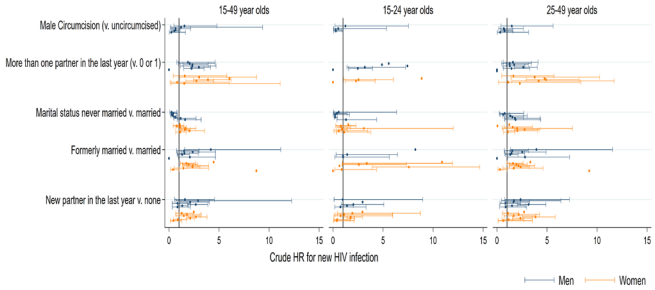


Figure 1: Crude hazard ratios for new HIV infections by study, sex and age group.
Points shown without CI have very wide CI; each point represents the estimate for one study

849 METRICS OF MOBILITY BY SEX ARE ASSOCIATED WITH HIV INCIDENCE IN RURAL KENYA & UGANDA

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Background: There are few longitudinal studies conducted with clear ascertainment of exposures and outcomes to understand pathways linking mobility and HIV acquisition; multiple measures and sex-stratified analyses are needed to measure the complex and dynamic nature of mobility and its influence on HIV risk in specific settings.
Methods: This study examined risk of HIV acquisition over 3 years among mobile and non-mobile adults in 32 rural communities in Uganda and Kenya in SEARCH, a cluster randomized trial conducted from 2013 through 2017. We examined HIV incidence by mobility pre-baseline and over 3 years, and evaluated differences by sex. Poisson regression was used to estimate incidence rate ratios (IRRs) of HIV acquisition among mobile relative to non-mobile adults, with sex-stratified multivariate models adjusted for region, demographic characteristics, and clustering by community.
Results: In a cohort of 117,114 adults who were aged ≥15 years, stable residents, and HIV-negative at baseline, 704 new HIV infections occurred by year 3; 11,337 adults (9.7%) had lived ≥1 month outside of their community in past 12 months (8% of women & 11.8% of men, p<0.001). By year 3, 8,511 (7.3%) had out-migrated (7.6% of women & 6.9% of men, p<0.001). In multivariate analyses, risk of HIV acquisition by year 3 was higher in adults who reported pre-baseline mobility (relative to no mobility): IRR=1.47 [95%CI 1.18-1.82]) for having lived ≥1 month outside community in past 12 months (similar effects for women & men), and IRR=1.42 [95%CI 1.11-1.81], for having spent some nights away in past month in men only. Temporal ordering of exposure and outcome cannot be definitively ascertained for mobility reported at year 3, but magnitude of association was highest for having lived >12 months in past 3 years outside community (IRR=3.2 [95%CI 2.21-4.64]), and having changed residence in past 12 months (IRR=2.3 [95%CI 1.8-2.95]). Significant heterogeneity was seen by sex for HIV incidence and mobility, with effects for women but not men in year 3 report of living outside community >12 months in past 3 years, IRR=3.9 [95%CI 2.63-5.78], and >6 months in past year IRR=1.84 [95%CI 1.23-2.76]).
Conclusion: Mobility is significantly associated with risk of HIV acquisition in rural Kenya and Uganda; its effect on HIV incidence is influenced by both sex and type of mobility.

Table 1: Risk of HIV acquisition associated with forms of mobility, total population, and by sex

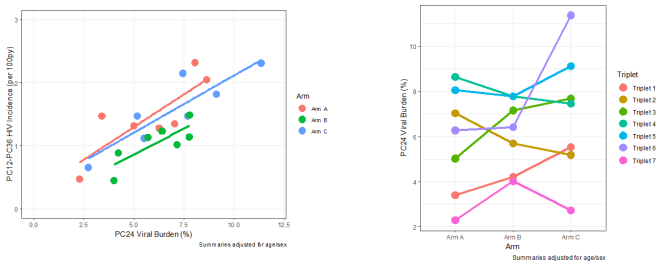
Measures of mobility at baseline and year 3	Adjusted HIV Incidence Rate Ratios											
	Total population				Women				Men			
	Adj IRR	p	95% CI		Adj IRR	p	95% CI		Adj IRR	p	95% CI	
≥1 month lived outside community in past 12 months, baseline	1.47	0.001	1.18	1.82	1.41	0.038	1.02	1.95	1.49	0.013	1.09	2.05
Away at least some nights in past month, baseline	1.17	0.070	0.99	1.40	1.06	0.627	0.85	1.32	1.42	0.006	1.11	1.81
Spent >6 months in past 12 months outside community, year3	1.70	0.001	1.24	2.34	1.84	0.003	1.23	2.76	1.35	0.235	0.83	2.19
Spent >12 months in past 3 years outside community, year 3	3.20	<0.001	2.21	4.64	3.90	<0.001	2.63	5.78	1.68	0.209	0.75	3.80
≥1 month lived outside community in past 12 months, year 3	1.88	<0.001	1.48	2.38	1.83	0.001	1.27	2.64	1.85	0.001	1.31	2.60
Changed residence in past 12 months, year 3	2.30	<0.001	1.80	2.95	2.28	<0.001	1.68	3.09	2.03	0.016	1.14	3.61
Away at least some nights in past month, year 3	1.41	<0.001	1.12	1.78	1.27	0.152	0.92	1.75	1.59	0.003	1.17	2.17
Lived for some time outside community in past 5 years, year 3	1.78	0.005	1.19	2.66	1.82	0.014	1.13	2.92	1.65	0.284	0.66	4.16

IIR=Incidence rate ratio. Poisson regression models adjusted for sex (in pooled models), age, region, marital status, education level, household wealth index, occupation category, and circumcision (men only), and adjusted for clustering by community.

850 HIV INCIDENCE AND VIRAL BURDEN AT THE COMMUNITY LEVEL IN HPTN 071 (POPART)

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Background: HPTN 071 (PopART) was a 3-arm cluster-randomized trial that evaluated use of a combination HIV prevention strategy to reduce HIV incidence. The intervention package included universal HIV testing and treatment (UTT). The trial was conducted in 21 high HIV prevalence communities in Zambia and South Africa (7 matched community triplets). The study primary outcome was HIV incidence in the period 12 to 36 months after the start of the study, measured in a Population Cohort (PC) of ~2000 randomly-selected adults per community (aged 18-44). The intervention effect was greatest in the study arm that included treatment according to national guidelines (Arm B); a lesser effect was observed in the full UTT arm (Arm A), compared to standard of care (Arm C).
Methods: For each community, HIV incidence was estimated in the primary analysis period (PC12-PC36), weighted by age and sex. HIV viral load was measured in all HIV-positive PC participants 2 years after the start of the study (PC24). Viral suppression was defined as a viral load <400 copies/mL. Viral burden was defined as the estimated proportion of the entire community (both HIV positive and HIV negative persons) that were not virally suppressed at PC24, weighted by age and sex. We examined associations of viral burden at PC24 with HIV incidence, and whether it mediated the PopART intervention effect on HIV incidence.
Results: HIV viral burden at PC24 was strongly associated with HIV incidence (Figure 1; p<0.001). We estimated a mean difference of -1.2% in viral burden for Arm A vs C (95% CI: -2.8%, 0.4%) and a mean difference of -0.85% for Arm B vs C: (95% CI: -2.5%, 0.8%). The average causal mediation effect of viral burden on HIV incidence was not significant (Arm A vs. C p=0.50; Arm B vs. C p=0.77).
Conclusion: In HPTN 071 (PopART), higher HIV incidence was associated with higher viral burden. However, the reduction in viral burden did not explain the differential reduction of HIV incidence observed in the two trial intervention arms.



Association between community-level viral burden and HIV-incidence; Arm differences in viral burden at PC24.

851 AGE-SPECIFIC HIV INCIDENCE PATTERNS AMONG POPULATION COHORTS IN SUB-SAHARAN AFRICA

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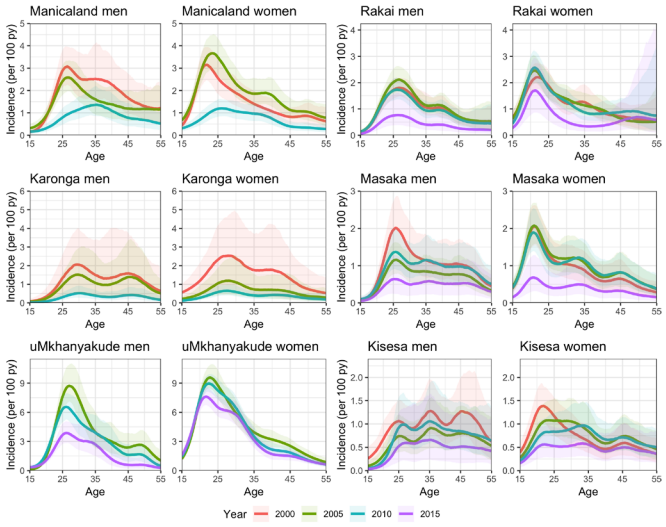
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Background: As the HIV epidemic in sub-Saharan Africa matures, it is unclear how patterns of HIV incidence by sex and age have changed.

Methods: We used a Bayesian model to jointly reconstruct age-specific HIV incidence and mortality from population-based sero-survey and HIV survival data collected among rural population HIV cohorts in Tanzania (Kisesa), Uganda (Masaka and Rakai), Malawi (Karonga), Zimbabwe (Manicaland) and South Africa (uMkhanyakude). HIV incidence hazard was flexibly modelled using penalised B-splines with knots every 5 years over age and time. The model was fit separately for each sex in each site. Modelled incidence and prevalence results are applied to national standard populations to estimate average age of infection and percentage of new infections at given ages.

Results: Age-specific incidence decreased over time across age groups in most studies (Figure). In the earlier years of the epidemic, almost all studies had peak incidence among 20-24 year old women and 25-29 year old men. Over time, age-specific incidence flattened in Masaka, Kisesa, Karonga and Rakai men, while in Manicaland the age-specific incidence peaks at a later age and uMkhanyakude and Rakai women maintained the same peaks. Average age at infection is higher in men than women across all studies. While relatively stable across time, average age at infection increases from 2000 to 2017 (or max year of data collection) in Kisesa (+1.8 years among men and +2.7 among women), Masaka (+1.3 men, +1.2 women), Manicaland (+2.3 men, +1.7 women), and Karonga women (+0.2), though there were decreases in Karonga men (-0.2), Rakai (-0.1 men, -0.3 women) and uMkhanyakude (-2.0 men, -2.4 women). The percentage of women's infections occurring among 15-24 year olds, the age range targeted in major HIV prevention, is above 50% in the most recent year for 3 of 6 studies: Rakai (64%, 95% CI=44-76%), uMkhanyakude (58%, 95% CI=54-62%), and Masaka (51%, 95% CI=35-64%). In the other three sites, this proportion was: Kisesa (38%, 95% CI=26-53%), Karonga (35%, 95% CI=25-44%), and Manicaland (41%, 95% CI=33-49%).

Conclusion: Our evidence suggests that age-specific incidence is declining over time in these six study sites, though the magnitude and timing of this decline varied by site. Among adult women, between 35-65% of new infections occurred among adolescent girls and young women aged 15-24.



852 HIGH HIV INCIDENCE AND VOLUNTEER RETENTION IN A BANGKOK-BASED COHORT OF MSM AND TGW

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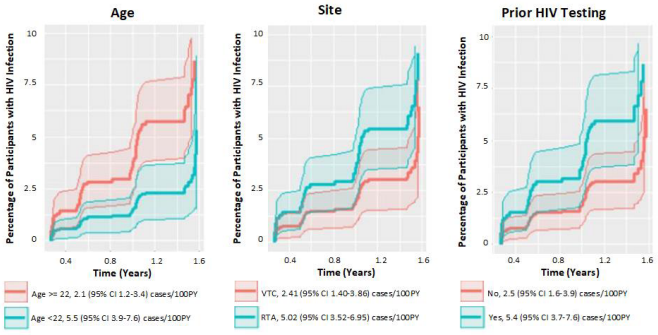
Background: Men who have sex with men (MSM) and transgender women (TGW) bear a disproportionate burden of new HIV infections. We characterized HIV incidence and retention in MSM and TGW in Bangkok, Thailand, to evaluate suitability and preparedness for potential future efficacy trials of preventive HIV vaccines.

Methods: From April to October 2017, HIV-uninfected Thai MSM and TGW aged 18-35 years were recruited into an 18-month prospective cohort at two sites independently: Royal Thai Army (RTA) and Vaccine Trial Centre at Mahidol University (VTC). Participants had been assigned male sex at birth and reported anal intercourse in the preceding six months with at least one of the following: condomless anal intercourse with a man or TGW living with HIV or of unknown HIV status; ≥3 sexual partners; exchange of sex for money or goods; or diagnosis of any sexually transmitted infection. Participants answered comprehensive behavioral questionnaires and were screened for HIV using sequential rapid tests. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) associated with HIV acquisition.

Results: Of 1184 screened, 87 (7.1%) were excluded due to prevalent HIV infection, and 1017 were prospectively enrolled with median age 22 years (interquartile range 20-25), including 349 (34.3%) TGW. At enrollment, syphilis was diagnosed in 39 (3.8%), hepatitis B in 15 (1.5%), and hepatitis C in 2 (0.2%). 805 (79%) participants expressed willingness to participate in a HIV vaccine trial, 532 (55.2%) reported having heard of pre-exposure prophylaxis (PrEP), and none reported current PrEP use. A total of 942 (92.6%) participants were retained through the end of the study. During 1422 person-years (PY) of observation, 53 incident HIV infections were diagnosed (3.73 [95% CI 2.79-4.87] cases/100PY). Among 256 candidate models evaluated, the one with the lowest Akaike's information criterion contained age, site, and prior HIV testing (Fig.1). Increased age was associated with lower hazard of incident HIV (HR 0.84 [95%CI 0.76-0.93]) and prior HIV testing was associated with increased hazard of incident HIV (2.16 [95%CI 1.23-3.79].

Conclusion: Thai MSM and TGW in this study demonstrated high HIV incidence and are in need of effective HIV prevention interventions. Good retention in this cohort demonstrates the feasibility of future efficacy testing of such interventions.

Figure 1. Unadjusted Hazard Curves Depicting the Proportion of MSM and TGW Diagnosed with HIV Over Time by (A) Age, (B) Site, and (C) Prior History of HIV Testing



Curves were calculated using unadjusted Cox proportional hazards models. Shaded areas represent the upper and lower limits of 95% confidence intervals around the proportion of participants diagnosed with HIV. HIV incidence rates were calculated for each group of interest by dividing the number of observed cases by the sum of the observed person-time and multiplying by 100 to standardize reporting as cases per 100 person-years (PY).

853 HIV AMONG FEMALE SEX WORKERS: RISK FACTORS AND LESSONS FROM A NATIONAL SURVEY

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Background: HIV prevention programming among female sex workers (FSW) is of national priority in the implementation of Nigeria HIV Research Agenda. FSWs are high risk group with the second highest HIV prevalence among the key populations in Nigeria. Generating evidence needed for implementable prevention strategies is vital to future national prevention and control efforts. The 2014 Integrated Biological Behavioral Surveillance Survey (IBBSS) provided the most recent national progress and performance data among the key populations. This study assessed HIV prevalence among FSWs and risk factors to HIV infection.
Methods: Secondary data analysis of 2014 IBBSS was undertaken among 8050 FSWs in brothels (BFSW) and non-brothels (NBFSW). Two-stage cluster and time location sampling techniques were used in selecting the FSWs in 13 states and Federal Capital Territory in the six geo-political zones. The survey involved HIV testing, and collected information on demographic, and sexual and reproductive health indicators. A random-effects logistic regression model was fitted with HIV infection as the outcome, and was used to ascertain state level variation.
Results: The mean age of FSW was 27.1±6.2years; mean age at first sex was 17.0±2.8years and average number of clients/day was 4.4. About 36.1% were married. About 38.8% had sex partners that were 10years older. Condom use at last sex was 91.8% among the FSWs; 40.3% experienced condom breakage in the last month prior to the survey and consistent condom use was 29.1%. About 55.0% completed at least secondary education, 46.2% had been away from home for more than one month and 72.6% received information/education on HIV/STIs in the last 12 months. HIV prevalence among FSW was 14.4% (BFSW was 19.4% and NBFSW was 8.6%). Factors associated with HIV infection were brothel-based FSW OR=2.6 95%CI 1.4-4.2; being away from home for at least one month OR=1.8 95%CI 1.1-2.9; consistent condom use OR=0.7 95%CI 0.5-0.8 and receiving information/education on HIV/STIs OR=0.7 95%CI 0.4-0.8. The estimated variance between states was 0.4 with a standard error of 0.1.
Conclusion: Although consistent condom use was low, it was protective against HIV in addition to information materials given to FSWs. There was state-level variation. Thus, there is a need for state-level intervention with more emphasis on BFSWs. Also, targeted health education programs are needed to increase consistent condom use.

854 HIV RISK, BEHAVIOUR, AND SERVICE UPTAKE IN ADOLESCENT GIRLS SELLING SEX IN ZIMBABWE

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Background: Adolescent girls who sell sex (AGSS) in sub-Saharan Africa are disproportionally affected by HIV, yet little is known about how these vulnerabilities intersect and its implications for programming. Using a representative sample of AGSS in Zimbabwe, we estimate population size, determine risk factors for, and the prevalence of, HIV infection, and explore engagement with HIV services.
Methods: In 2017 rapid ethnographic mapping of the spatial and social organization of AGSS (aged 16-19 years) was conducted, followed by a bio-behavioural survey using respondent driven sampling (RDS) in Harare and Bulawayo, and a census method in Gokwe, and Beitbridge. Unique objects were distributed to all women at sites identified as sex work locations during mapping in Harare and Bulawayo. All recruited women were tested for HIV and completed an interviewer administered questionnaire. Data were analysed using RDS-II weighting in Harare and Bulawayo and pooled across sites to run a logistic regression examining sociodemographic and sex work characteristics associated with being HIV-positive.
Results: In total, 615 AGSS were recruited. HIV prevalence varied between 7.2% and 38.0% by site. HIV prevalence rose sharply with age from 2.1% among AGSS aged 16 to 26.9% among those aged 19 years. AGSS who were in school and had more years of education were less likely to be infected. Overall, more than half of HIV positive AGSS were aware of their HIV status (range 45.5-61.5% by site). Of those, 68.2% to 100% were on antiretroviral treatment (ART). Among HIV negative women, rates of HIV testing in the preceding 6 months was 62.0-71.4%. Reported alcohol and drug use was common, as was past history of physical and sexual violence.
The size of the population of adolescent girls selling sex was estimated to be 1342 (95% CI 498-2186) in Harare and 1462 (95% CI 845-2079) in Bulawayo using the unique object multiplier method. For Gokwe (n=41) and Beitbridge (n=79) all AGSS were contacted.
Conclusion: AGSS aged 16-19 years in Zimbabwe have a high HIV prevalence that increases rapidly by age, often report high alcohol and drug use, have commonly experienced both sexual and physical violence and, as a consequence, are extremely vulnerable. Among HIV positive AGSS just over 50% knew their HIV status, and the proportion taking ART varied by site. Testing rates in HIV negatives were high. Programmes specifically aimed at the needs of AGSS are urgently needed, offering regular HIV testing to improve knowledge of HIV status.

855 TRANSACTIONAL SEX WITH OLDER PARTNERS HEIGHTENS HIV RISKS AMONG AGYW IN TANZANIA

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Background: Across sub-Saharan Africa, transactional sex and sexual relationships with older partners both affect HIV risk in adolescent girls and young women (AGYW). The extent to which these behaviors operate either independently or together to impact HIV acquisition is not well known.
Methods: Data were collected through the Sauti Project, a PEPFAR/USAID funded project which provides combination HIV prevention services to AGYW and key and vulnerable populations across Tanzania. Out-of-school AGYW aged 15-24 years who were accessing HIV-prevention services through Sauti completed a questionnaire to assess demographics and other psychosocial measures between 2016-2018. AGYW were tested for HIV and those who tested positive were linked to HIV care and treatment as per Tanzania national guidelines. We estimated adjusted prevalence ratios (aPR) and 95% confidence intervals (CI) for the associations of transactional sex (any sex in exchange for money, services or gifts) and intergenerational sex (reporting a sexual partner ≥10 years older) with prevalent HIV infection. We assessed potential synergism between both exposures by comparing their observed and expected joint associations using additive and multiplicative criteria.
Results: Among 12,708 sexually active AGYW, median age was 21 years (IQR 19, 23). Transactional sex and intergenerational sex were common (43% and 33%, respectively); 5% reported engaging in both behaviors. Two percent were living with HIV. The association of transactional sex with HIV prevalence was 1.27 (95% CI 0.97, 1.67) and the association of intergenerational sex with HIV prevalence was 0.97 (95% CI 0.50, 1.89) when setting AGYW who reported neither behavior as a reference category. AGYW who reported both transactional sex and intergenerational sex had nearly twice the HIV prevalence of AGYW who reported neither behavior (aPR 1.74; 95% CI 1.03, 2.94). Evidence of interaction was present, suggesting transactional sex and intergenerational sex operate synergistically to heighten HIV risks in AGYW.
Conclusion: Transactional sex was not strongly associated with HIV prevalence in the absence of intergenerational sex, and intergenerational sex was not associated with HIV prevalence in the absence of transactional sex. Targeting AGYW who are likely to engage in commodified sex with older partners, such as AGYW who are economically and socially vulnerable, may maximize effectiveness of behavioral and biomedical HIV prevention efforts.

Table. Unadjusted and adjusted joint associations of transactional sex and intergenerational sex with HIV prevalence among AGYW in Tanzania, 2016-2018[a,b]

Exposure strata defined by transactional sex and intergenerational sex status[c]	Prevalent HIV infection n/N (%)	Unadjusted PR (95% CI)	Adjusted PR (95% CI)	p for interaction[d]
No transactional sex, no intergenerational sex	120/6863 (1.7)	1 (REF.)	1 (REF.)	0.037
No transactional sex, intergenerational sex	10/526 (1.9)	1.09 (0.57, 2.06)	0.97 (0.50, 1.89)	
Transactional sex, no intergenerational sex	107/4606 (2.3)	1.33 (1.03, 1.72)	1.27 (0.97, 1.67)	
Transactional sex, intergenerational sex	16/547 (2.9)	1.67 (1.00, 2.80)	1.74 (1.03, 2.94)	

Abbreviations. AGYW: adolescent girls and young women, PR: prevalence ratio, CI: confidence interval

[a] Among 12,708 sexually active AGYW, excluding 166 (1.31%) AGYW who were missing measures of transactional sex and/or partner age.
[b] A directed acyclic graph (DAG) was used to identify a minimally sufficient adjustment set of covariates, and potential confounders were included based on prior literature. Confounders included in the adjustment set were age, family support, marital status, prior pregnancy, food insecurity, early sexual debut, and survey version.
[c] Defined as a sexual relationship with a male partner ≥10 years older than the participating AGYW.
[d] P value for the term for interaction between the two joint exposures, transactional sex and intergenerational sex.

856 FACTORS ASSOCIATED WITH HIV SEROCONVERSION IN YOUNG WOMEN IN SOUTH AFRICA

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Background: High HIV incidence in young women in Sub-Saharan Africa remains a key challenge to HIV epidemic control. HIV incidence rates in young women exceed those of men and older women, and the proportion of young HIV-positive women who know their status and are virally suppressed falls well short of the UNAIDS '90-90-90' targets. This study examined the factors associated with seroconversion in young women in a hyperendemic area of South Africa.

Methods: We analysed prospective cohort data of HIV-negative women (15-24 years) from the HIV Incidence Provincial Surveillance System conducted in KwaZulu-Natal, South Africa. Participants (n=2,710) completed a questionnaire and provided blood samples for laboratory testing (pregnancy, HIV and other STIs) at enrolment and follow-up approximately 18 months later. The association between risk factors and HIV-seroconversion was assessed using Cox proportional hazards models.

Results: The incidence rate of young women was 3.92 (95% confidence interval (CI): 3.27-4.69) per 100 women-years; 3.74 (95% CI: 2.87-4.86) and 4.13 (95% CI: 3.20-5.33) per 100 women-years for women aged 15-19 and 20-24 years respectively. At follow-up, median (interquartile range) viral load of seroconverters was 4,400 (280-50,000) copies/ml and 17% reported knowing their HIV-positive status. Risk of seroconversion in young women increased significantly with the number of lifetime partners reported at baseline. Among teenage girls (15-19), risk of seroconversion was positively associated with being an orphan (adjusted hazard ratio (aHR)=4.38, p=0.005) and having a baseline STI (aHR=2.37; p=0.016), and negatively associated with having family support (aHR=0.46, p=0.022) and having a circumcised partner (aHR=0.58, p=0.047). For women aged 20-24 years, failure to complete high-school (aHR=1.78; p=0.042) and inconsistent condom use (aHR=2.72; p=0.024) were associated with HIV acquisition.

Conclusion: This study suggests that structural factors contribute to the high HIV incidence rates observed in young women in this population. However, programs supporting sexual health, male circumcision and condom use remain effective ways to reduce risk. In addition to supporting such programs, it is imperative that HIV testing frequency of young women be increased so that infections can be diagnosed timeously, treatment can be provided and transmission risk reduced.

857 SOCIOECONOMIC DISPARITIES ARE ASSOCIATED WITH HIV IN YOUNG MSM WITHIN LATIN AMERICA

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Background: Despite efforts to stop HIV epidemic in Latin America, new HIV cases continue to increase in the region especially among young MSM (YMSM). This study aims to assess social-economic and behavioral factors associated with HIV self-reported prevalence among YMSM participating in a survey conducted in Brazil, Mexico and Peru.

Methods: Through March to May, 2018, MSM were recruited to complete a web-based survey through advertisements on geosocial network (GSN) dating apps (Grindr and Hornet) and Facebook. Inclusion criteria were cisgender men, ≥18 years, living in Brazil, Mexico or Peru. For this analysis, we included YMSM aged 18-24 years who self-reported their HIV status (negative/positive). Multivariable logistic regression models assessed factors associated with HIV self-reported prevalence among YMSM for each country. The models were adjusted for geographical region within each country, race (only Brazil and Peru: white vs. non-white), monthly income (low vs. middle/high, according to countries definition), schooling (>secondary school vs. ≤), steady partner (yes/no), sexual attraction (men, women or both) and time since last HIV testing (≤1 year vs. >1 year).

Results: Among 43,687 MSM that started the questionnaire, 27,475 (62.9%) reported their HIV status; 7,055 (25.7%) were YMSM and were included in the analysis. The majority of YMSM (83.1%) were recruited on GSN apps. Most (83.3%) reported an HIV test in the past year, and 15.3% reported HIV positive status in Peru, 8.4% in Mexico and 7.7% in Brazil. Among YMSM, low-income was associated with higher odds of HIV self-reported prevalence in Brazil (aOR=1.31, 95%CI:1.00-1.74) and Peru (aOR=1.59, 95%CI:1.04-2.48) but not in Mexico (aOR=0.81, 95%CI:0.56-1.18). Lower education was also associated with higher odds of HIV self-reported prevalence in Brazil (aOR=1.34, 95%CI:1.03-1.76) but not in Mexico nor in Peru. YMSM from the three countries sexually attracted to men had at least twice higher odds of HIV self-reported prevalence than those preferring women or both (Table 1).

Conclusion: In this large, cross-country study, HIV prevalence among YMSM was high. Social-economic disparities were associated with higher odds of HIV self-reported prevalence. Interventions to increase awareness to prevention technologies including PrEP targeting socio-economic disadvantaged YMSM are urgent in Latin America.

Table 1. Factors associated with HIV self-reported prevalence among YMSM aged 18-24 years in Brazil, Mexico and Peru, 2018.

		Brazil [N=4288; HIV+ = 329 (7.7%)]		Mexico [N=1766; HIV+ = 148 (8.4%)]		Peru [N=1001; HIV+: 153 (15.3%)]	
		HIV- (%) vs. HIV+ (%)	aOR (95%CI)	HIV- (%) vs. HIV+ (%)	aOR (95%CI)	HIV- (%) vs. HIV+ (%)	aOR (95%CI)
Income	Low	2708 (68.4) vs. 246 (74.8)	**1.31 (1.00-1.74)**	783 (54.1) vs. 68 (51.1)	0.81 (0.56-1.18)	448 (69.3) vs. 85 (62.0)	**1.59 (1.04-2.48)**
	Middle/High	1251 (31.6) vs. 83 (25.2)	Ref.	665 (45.9) vs. 65 (48.9)	Ref.	307 (40.7) vs. 52 (38.0)	Ref.
Schooling	≤Secondary education	2601 (67.3) vs. 239 (73.8)	**1.34 (1.03-1.76)**	651 (40.2) vs. 63 (42.6)	1.14 (0.78-1.65)	301 (36.0) vs. 46 (31.3)	0.77 (0.49-1.20)
	>Secondary education	1262 (32.7) vs. 85 (26.2)	Ref.	967 (59.8) vs. 85 (57.4)	Ref.	536 (64.0) vs. 101 (68.7)	Ref.
Race	White	1692 (42.7) vs. 120 (36.5)	Ref.	N/A	N/A	153 (18.9) vs. 30 (20.7)	Ref.
	Non-white	2267 (57.3) vs. 209 (63.5)	1.19 (0.93-1.54)	N/A	N/A	657 (81.1) vs. 115 (79.3)	0.84 (0.52-1.40)
Steady partner	No	3226 (82.2) vs. 253 (78.1)	Ref.	1254 (78.5) vs. 103 (71.0)	Ref.	600 (72.6) vs. 91 (60.3)	Ref.
	Yes	698 (17.8) vs. 71 (21.9)	1.28 (0.95-1.70)	344 (21.5) vs. 42 (29.0)	1.39 (0.91-2.07)	227 (27.4) vs. 60 (39.7)	1.50 (0.98-2.27)
Sexual Attraction	Men	3543 (89.9) vs. 312 (95.7)	**2.87 (1.67-5.48)**	1380 (85.7) vs. 137 (92.6)	**2.08 (1.09-4.50)**	641 (75.9) vs. 131 (85.6)	**1.98 (1.14-3.67)**
	Women/both	399 (10.1) vs. 14 (4.3)	Ref.	230 (14.3) vs. 11 (7.4)	Ref.	204 (24.1) vs. 22 (14.4)	Ref.

858 FORCED SEX IN HAITI: IMPLICATIONS FOR THE HIV EPIDEMIC AMONG MSM AND TRANS WOMEN

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Background: Sexual violence is an often perpetrated, but rarely studied risk factor for HIV, particularly among men who have sex with men (MSM) and transgender women (TW) living in the Caribbean. This study aimed to describe the prevalence of forced sex and HIV among MSM and TW and the association between forced sex and HIV prevalence in Haiti.

Methods: Five-hundred and twenty MSM and 109 TW were recruited from 2,339 venues where men and women meet new sexual partners, such as bars, nightclubs, and hotels, in nine of the ten departments in Haiti. Venues were selected using the Priorities for Local AIDS Control Efforts (PLACE) methodology. All MSM and TW completed an interview and HIV test. History of forced sex was defined as ever having experienced forced sexual intercourse or forced sex without a condom.

Results: HIV prevalence among MSM and TW in the study population was 2.15% and 27.64%, respectively, while 40.77% and 64.22% reported a history of forced sex. In general, MSM and TW were young, educated, in a primary relationship, and received money or gifts in exchange for sex in the past 12 months (MSM: 54.62%; TG: 59.63%). In an unadjusted log binomial regression, MSM with a history of forced sex were 8.19 (95% CI, 3.09-21.67) and TW were 7.02 (95% CI 1.90-26.00) times more likely to be HIV positive than those without a history of forced sex. When adjusting for age, education, in a primary relationship, receiving money or gifts for sex in the past 12 months, the number of sexual partners in the past four weeks, if a condom was used at last anal sex and self-identification as LGBTQ in a log binomial regression, MSM with a history of forced sex were 5.67 (95% CI, 2.63-12.24) times as likely to be HIV positive than those without a history of forced sex. When adjusting for age, education, in a primary relationship, the total number of sexual partners in the past four weeks, if a condom was used at last anal sex and perceived risk of acquiring HIV in a log Poisson regression, TW with a history of forced sex were 4.83 (95% CI, 1.59-14.61) times as likely to be HIV positive than those with a history of forced sex.

Conclusion: Understanding the pathways through which history of forced sex influences mental health and sexual risk behaviors can provide evidence for integration of mental health services in HIV-prevention efforts among MSM and TW in Haiti.

859 SEXUAL HEALTH OF RURAL AND URBAN YOUNG MALE COUPLES IN THE UNITED STATES

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Background: Young men who have sex with men (YMSM) are disproportionally affected by HIV, and main partnerships account for a large proportion of new HIV infections among YMSM (35-68%). The number of YMSM living with HIV

is highest in urban areas; thus, HIV prevention is largely focused on urban YMSM and less is known about sexual health of rural YMSM in relationships. Rural YMSM are less likely to be tested for HIV/STIs than urban YMSM, and inconsistent condom use is common. The present study used baseline data from a randomized controlled trial of a relationship education and HIV prevention program for male couples to test associations of rurality with HIV risk and prevention behaviors among YMSM. We hypothesized that higher rurality would be associated with fewer HIV risk and prevention behaviors.

Methods: Participants were 430 YMSM in relationships. Participants' average age was 28.70 years (SD = 7.34). Participants' HIV status was negative (75.3%), positive (10.7%), or unknown (14.0%). Couples were eligible based HIV risk criteria (i.e., at least one member reports having condomless anal sex with a known serodiscordant serious partner or with any casual sexual partner). Participants completed measures of HIV/STI testing history, PrEP use, number of sex partners outside of their main relationship, and condomless anal sex (CAS) acts with those partners. Rurality was measured using the Index of Relative Rurality, a continuous and threshold-free measure of rurality. Data were analyzed using multilevel mixed models. Analyses controlled for age and race.

Results: Results are summarized in Table 1. YMSM in more rural areas (i.e., higher rurality) were less likely to have been tested for HIV/STIs, and to have used PrEP, compared to urban YMSM. Higher rurality was also associated with fewer outside partners and fewer CAS acts; however, rates of CAS in the past three months were high for YMSM in both the top (i.e., most rural; M = 4.05, SD = 4.26) and bottom (M = 4.72, SD = 4.96) quartiles of rurality.

Conclusion: Rural YMSM lack access to sexual health-related services and face stigma associated with same-sex sexual behavior and HIV, which may act as barriers to HIV/STI testing and PrEP use. Although rural YMSM had fewer sex partners outside their relationship and fewer CAS acts than urban YMSM, CAS was not infrequent, highlighting the need for increased HIV prevention geared toward young male couples living in more rural, less resourced areas.

Table 1. Multi-Level Mixed Model Results

Model Term	N	Coefficient	Std. Error	t	Sig.	Exp.	Lower 95%	Upper 95%
HIV Testing Lifetime[a]	430	-3.69	1.24	-2.97	0.003	0.03	0.00	0.29
HIV Testing Past 3 Months[ac]	363	-1.80	0.85	-2.12	0.035	0.17	0.03	0.88
STI Testing Lifetime[a]	416	-5.15	1.46	-3.53	0.000	0.01	0.00	0.10
STI Testing Past 3 Months[a]	415	-2.70	0.81	-3.33	0.001	0.07	0.01	0.33
PrEP Use Lifetime[a]	384	-3.57	0.87	-4.13	0.000	0.03	0.01	0.15
PrEP Use Past 3 Months[a]	384	-3.57	0.91	-3.91	0.000	0.03	0.01	0.17
# Sex Partners Past 3 Months[b]	430	-1.50	0.42	-3.59	0.000	0.22	0.10	0.51
# CAS Acts Past 3 Months[b]	231	-1.21	0.53	-2.29	0.023	0.30	0.11	0.85

[a] *Probability distribution: binomial; link function: logit*

[b] *Probability distibution: negative binomial; link function: log*

[c] *HIV positive participants diagnosed more than 3 months ago excluded from analyses*

860 BURDEN OF HIV AMONG MEN ATTENDING EMERGENCY DEPARTMENTS IN SOUTH AFRICA

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Background: We sought to identify factors associated with HIV infection, HIV diagnosis, and lack of antiretroviral treatment (ART) among men attending emergency departments (EDs) in the Eastern Cape region of South Africa.

Methods: Men aged ≥18 years were approached in three EDs, between June 2017 and July 2018. Study staff offered HIV testing, completed testing and collected demographic data on participants. HIV positive patients were consented for a blood sample, which was tested for the presence of antiretrovirals (ARVs) and quantification of HIV viral load. Log-binomial models were used to characterize male's engagement in ART and care cascade and to determine factors associated with HIV prevalence.

Results: Overall, 21% (302/1458) of men tested positive for HIV, of which 41% (124/302) were unaware of their status. Of the HIV positive males that underwent further testing only 47% (104/222) tested positive for the presence of ARVs, and 43% (101/236) were virally suppressed (defined as a viral load <1000 copies/ml). HIV prevalence increased with age, with 4% of men aged <20 years testing positive to a peak of 35% of those aged between 36-45 years. Factors significantly associated with being HIV+ include presenting with generalized weakness (adjusted prevalence ratio [adjPR] 1.49, 95% CI 1.16,1.92), signs of tuberculosis (adjPR 1.95, 95% CI 1.55,2.44), and being admitted to the hospital (adjPR 1.26, 95% CI 1.03,1.54) relative to males with no weakness, tuberculosis or admissions, respectively. Men diagnosed with HIV in the ED were more likely to be younger (>50% were less than <35 years of age), trauma patients (vs. medical) (adjPR 1.69, 95% CI 1.11,2.57), or presenting with fever (vs. no fever) (adjPR 1.90, 95% CI 1.18,3.08). Less than 30% of men under the age of 35 years had evidence of ART and none of the 19 HIV+ men <25 years of age were virally suppressed. Furthermore, those with concurrent alcohol problems had lower frequency of being virally suppressed (38%, 36/96).

Conclusion: There is a high burden of HIV among men visiting EDs in the Eastern Cape, with almost half unaware of their HIV status. Furthermore, none of the youngest men were virally suppressed. The ED is a critical venue to identify HIV infected men not on treatment. HIV service providers, program implementers and policy makers, should consider how to leverage the ED as a venue to provide HIV services to young men in order to meet the 90-90-90 targets particularly in South Africa.

861 ROLE OF KEY POPULATIONS AND PAST INTERVENTIONS ON HIV TRANSMISSION IN CAMEROON

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Background: Key populations (KP) such as men who have sex with men (MSM), female sex workers (FSW) and their clients are at high risk of HIV. We estimated the impact of past interventions and the contribution of risks stemming from unmet HIV prevention/treatment needs of KP and lower-risk groups to HIV transmission in Yaoundé, Cameroon.

Methods: We developed and calibrated a deterministic model of HIV transmission within a Bayesian framework to reproduce the HIV epidemic in Yaoundé over time, based on a comprehensive review of site-specific demographic, behavioural, HIV and intervention coverage data. We estimated the fraction of incident HIV infections averted by condoms and antiretroviral therapy (ART) and the fraction of all transmitted infections over 10-year periods attributable to sex within different partnerships.

Results: Condoms and ART together averted 33% (95% uncertainty interval: 21-47) of infections over 1980-2018. Rising condom use among FSW had the largest historical impact (18% (9-37) of infections averted from 1980-2018); recent ART scale-up averted 36% (31-41) over 2009-2018. With increasing condom use during paid sex, the contribution of sex between FSW and their partners fell from 37% (17-61) of all transmitted infections over 1989-1998 to 22% (8-36) over 2009-2018 (Table). In the last decade, sex between clients (7% of all people living with HIV (PLHIV)) and their partners; MSM (8% of PLHIV) and their male and female partners; and between lower-risk individuals (82% of PLHIV) contributed to 39% (26-56), 42% (17-52), and 43% (31-60) respectively. By 2018, ART coverage was estimated to be highest among FSW (86% (79-91)), followed by lower-risk groups (51% (46-56)), MSM (47% (40-52)), and clients (44% (34-48)). Consequences of unmet HIV prevention/treatment needs of MSM are predicted to contribute to 44% (17-57) of new transmissions occurring in the coming decade (Table).

Conclusion: Increases in condom use among FSW, and recent ART scale-up have had a large transmission impact in Yaoundé and changed the relative contribution of different partnerships to onward transmission over time. Findings highlight the need to prioritize HIV prevention and treatment interventions to MSM and clients of FSW whose unmet needs are now contributing the most to onward transmission, while maintaining achievements in reducing HIV transmission in the context of sex work.

Estimated contribution of sex between Key populations and lower-risk groups with their partners on all incident HIV infections occurring in Yaoundé over successive decades.

Sex between	1989-1998	1999-2008	2009-2018	2019-2028
1 - MSM and all partners	**58% (31-72)**	**42% (18-56)**	**42% (17-52)**	**44% (17-57)**
• MSM and MSM	39% (19-50)	28% (12-37)	28% (12-36)	32% (12-41)
• MSM and female partners	51% (26-63)	35% (15-48)	32% (14-44)	31% (13-45)
2 - Clients and all partners	**46% (30-71)**	**43% (28-63)**	**39% (26-56)**	**36% (22-53)**
• Client and commercial sex partners	29% (13-54)	22% (8-37)	14% (5-27)	12% (5-23)
• Clients and non-commercial sex partners	38% (25-59)	36% (24-54)	33% (21-50)	31% (18-49)
3 - FSW and all partners	**37% (17-61)**	**29% (13-46)**	**22% (8-36)**	**19% (7-32)**
• FSW and commercial sex partners	29% (13-54)	22% (8-37)	14% (5-27)	12% (5-23)
• FSW and non-commercial sex partners	21% (9-43)	15% (6-29)	12% (5-24)	11% (4-23)
4 - FSW & clients and non-commercial partners	**47% (34-68)**	**44% (32-62)**	**40% (29-56)**	**38% (25-54)**
5 - Lower risk individuals	**35% (22-52)**	**41% (28-57)**	**43% (31-60)**	**41% (28-60)**

862 SEX-SPECIFIC ANALYSES IN ORAL ABSTRACTS FROM CROI 2019

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Background: Globally, women account for more than half of persons living with HIV (PWLH), yet remain underrepresented in research. Starting in 2018, CROI guidelines specifically recommended reporting of sex distribution and sex-adjusted analyses, but formal review showed rates of such reporting among CROI 2018 oral abstracts were low. Members of the Women's Health Inter-Network Scientific Committee (WHISC) of the ACTG and IMPAACT networks reviewed adherence to these guidelines among oral presentations from CROI 2019.

Methods: Each CROI 2019 webcast of oral abstract presentations was reviewed by at least 2 WHISC members. For presentations of research relevant to both sexes, reviewers assessed whether sex distribution and sex-adjusted analyses were presented.

Results: Overall, 85 oral abstracts (79 clinical studies and 6 pre-clinical studies) addressed a scientific question relevant to both sexes. 85% (67 of 79) of clinical studies included sex distribution compared to 76% at CROI 2018. In 10% of these (7 out of 67), sex was incorrectly referred to as gender, which was similar to CROI 2018. 51% (34 of 67) of clinical studies included ≤25% women; 7 included no women and 3 included no men, but only 5 of these 10 communicated this restriction in the abstract title. Reporting of sex of animals in pre-clinical studies remained low (0 of 6 in 2019 and 1 of 13 in 2018). Finally, 49% (39 of 79) of clinical studies at CROI 2019 included sex-adjusted results, which was slightly higher than the 30% reporting at CROI 2018. Sex-adjusted analyses were higher among observational studies (64%, 29 of 45) than in clinical trials (29%, 10 of 34); see Table.

Presentation of Sex-Adjusted Analyses By Study Size	Observational studies Overall: 29 of 45 (64%)	Clinical trials Overall: 10 of 34 (29%)
< 25 participants	2 of 4 (50%)	0 of 6 (0%)
26-100 participants	1 of 6 (17%)	1 of 14 (7%)
101-1000 participants	5 of 12 (42%)	4 of 8 (50%)
> 1000 participants	17 of 18 (94%)	5 of 6 (83%)
Unknown size	4 of 5 (80%)	NA
Presentation of Sex-Adjusted analyses by % female participation (10 single sex studies excluded)	**Observational studies Overall: 22 of 38 (58%)**	**Clinical trials Overall: 8 of 31 (26%)**
> 0-10% women	4 of 6 (67%)	1 of 5 (20%)
11-25% women	5 of 10 (50%)	2 of 6 (33%)
26-50% women	3 of 6 (50%)	1 of 8 (13%)
51-99% women	6 of 8 (75%)	4 of 8 (50%)
% women not presented	4 of 8 (50%)	0 of 4 (0%)

Conclusion: While there was some improvement in reporting sex-specific analyses among oral presentations at CROI 2019 compared to 2018, there is still much room for improvement. Consistent failure to report sex distribution in pre-clinical studies needs to be addressed. Reporting of sex distribution in clinical studies needs more emphasis since 15% of oral presentations failed to include this. Education regarding the difference between sex and gender is necessary and titles should indicate whether findings are restricted to one sex. Finally, enrolling adequate numbers of women to perform meaningful sex-stratified analyses and performing such analyses require additional guidance and even mandates given that over half of PLWH worldwide are women.

863 HIGH PROBABILITY OF SURVIVAL IN PATIENTS WHO MAINTAIN VIRAL LOADS <200 COPIES/ML

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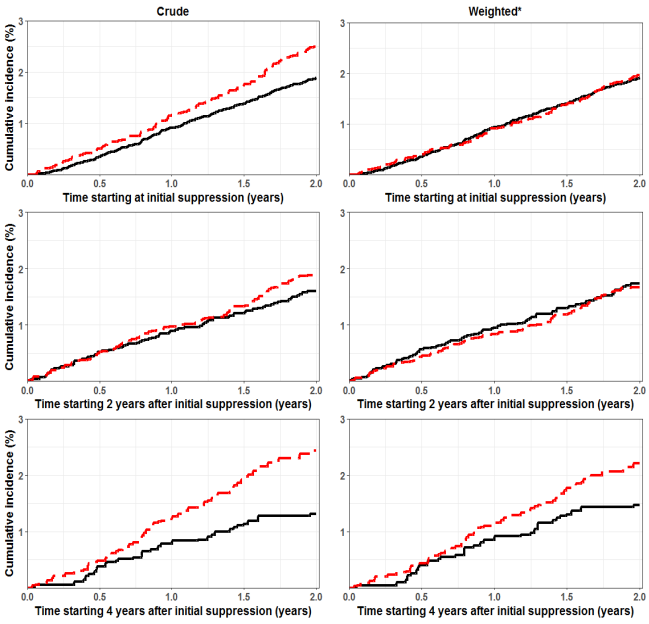
Background: It is unclear whether low, detectable viral load (VL), observed as viral blips and low-level viremia, impacts risk of death. Our objective was to estimate mortality risk after initial suppression in patients who maintained VLs <200 copies/mL while in care at NA-ACCORD clinical sites in 2007–2016.

Methods: We followed adults who newly initiated ART and achieved initial suppression (first VL under assay limit of detection [LOD]) under observation. Patients were followed from initial suppression until death, loss to follow-up (no VL for 15 months), or administrative censoring. Nearly 80% of VLs after initial suppression fell under varying LODs (LOD range: 20–500 copies/mL); multiple imputation based on demographic and clinical factors was used to address VLs <LOD. We estimated cumulative incidence (risk) of 2-year all-cause mortality at 0, 2, and 4 years after initial suppression. At each time point, analysis was restricted to patients who remained under observation and maintained all VLs <200 copies/mL up to that time. Patients were categorized as: a) those with all VLs <20 copies/mL; and b) those with ≥1 VL 20–199 copies/mL. Inverse probability weighting was used to account for confounders (see fig.).

Results: At initial suppression, 2-year crude mortality risks for 19463 patients with VL <20 copies/mL and those with VL 20–199 copies/mL were 1.9% and 2.5%, and weighted risks were 1.9% and 2.0%, respectively. Of the 11444 patients under observation with a VL measurement 2 years after initial suppression, 77% had maintained all VLs <200 copies/mL. Among those patients, 2-year crude risks for those with all VLs <20 copies/mL and those with ≥1 VL 20–199 copies/mL were 1.6% and 1.9%, and weighted risks were 1.7% and 1.7%, respectively. Of the 6100 patients under observation with a VL measurement 4 years after initial suppression, 69% had maintained all VLs <200 copies/mL. Among those patients, 2-year crude risks for those with all VLs <20 copies/mL and those with ≥1 VL 20–199 copies/mL were 1.3% and 2.4%, and weighted risks were 1.5% and 2.2%, respectively.

Conclusion: Patients in care who maintained all VLs <200 copies/mL experienced a 2-year survival probability that exceeded 97% up to 4 years after initial suppression. After accounting for confounders, patients with ≥1 VL 20–199 copies/mL had a similar 2-year risk of death as patients who maintained all VLs <20 copies/mL, which suggests that estimated VLs 20–199 copies/mL did not have a notable impact on near-term risk of death.

Two-year risk of all-cause mortality at 0, 2, and 4 years after initial suppression, stratified by viral load history. Solid black line, all viral loads <20 copies/mL; dashed red line, at least one viral load 20-199 copies/mL.



* Inverse probability weights included age, sex, race/ethnicity, HIV risk group, CD4 count, pre-ART viral load, ART regimen, year of ART initiation, time on ART, time to initial suppression, AIDS diagnosis, hepatitis B coinfection, hepatitis C coinfection, BMI, statin use, and study site.

864 FIRST HIV VIRAL LOAD REMAINS STRONG PREDICTOR OF TREATMENT SUCCESS IN SOUTH AFRICA

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Background: In the Simplifying HIV Treatment and Monitoring (STREAM) trial, point-of-care (POC) HIV viral load (VL) testing and task shifting significantly improved retention in care and viral suppression in South Africa. We sought to determine risk factors for poor retention and HIV viremia among trial participants.

Methods: STREAM was a randomized controlled trial in Durban, South Africa among people living with HIV (PLHIV) who were clinically stable and on antiretroviral therapy (ART) for six months. Participants (N=390) were randomized to receive either POC VL testing (Xpert® HIV-1 VL, Cepheid) and task shifting to an enrolled nurse or standard laboratory VL testing. A composite primary outcome of retention in care and viral suppression (<200 copies/mL) was assessed 12 months after enrolment. We estimated relative risks using modified Poisson models with robust standard errors to evaluate the association between participant baseline characteristics and 1) not achieving the composite primary outcome and 2) 18-month HIV VL ≥50 copies/mL.

Results: Among 390 participants, median age was 32 years (interquartile range [IQR] 27-38), 60.3% were female, and 93.1% had VL <200 copies/mL at study baseline. After 18 months on ART, 67 participants (17.2%) failed to achieve the composite primary outcome of retention and viral suppression. Baseline VL ≥200 copies/mL (RR=3.55, p<.01) and younger age (in 5-year increments, RR=1.15, p=.06) were associated with poor outcomes at study exit in univariate analyses and remained significant (aRR=3.82 p<0.01 and aRR=1.18, p=.04, respectively) when adjusted for distance traveled to the clinic, study arm, and CD4 count at six months. Among those with an 18-month VL, 280 (76.3%) were suppressed at <50 copies/mL. Six-month VL ≥200 copies/mL (aRR=2.51, p<.01) and lower CD4 counts (100 cells/mL increments, aRR=1.12, p<.01) were associated with 18-month VL ≥50 copies/mL, after adjusting for gender. We found no significant associations between failing to achieve the composite outcome or 18-month VL ≥50 copies/mL and education, having a primary partner, alcohol use, current smoking status, drug use, depression, time since HIV diagnosis, or self-reported ART adherence.

Conclusion: In the era of universal test and treat, the 6-month VL after ART initiation strongly predicts poor HIV outcomes. Identifying PLHIV with high VL early and focusing on VL suppression should be a priority to improve HIV outcomes in South Africa.

Table. Baseline characteristics associated with failure to achieve the composite primary outcome of retention in care and viral suppression (<200 copies/mL) after 12 months of follow-up in the STREAM Study, n=390

	Did not achieve primary outcome N (%)	RR (95% CI)	p-value	aRR [a] (95% CI)	p-value
Total cohort	67 (17.2%)				
Younger age in years- median [IQR]	31 [26-35]	1.15 (0.99-1.33) [b]	0.06	1.18 (1.01-1.38) [b]	**0.04**
Female gender	42 (17.9%)	1.11 (0.71-1.74)	0.66		
Traveled ≤5 kilometers to study clinic	18 (20.9%)	1.30 (0.80-2.11)	0.29	1.28 (0.80-2.05)	0.31
≥1 missed ART dose in past 4 days [c]	15 (20.3%)	1.23 (0.74-2.06)	0.43		
HIV viral load ≥200 copies/mL at study baseline [d]	14 (51.9%)	3.55 (2.29-5.52)	<0.01	3.82 (2.42-6.02)	**<0.01**
Lower CD4 count at study baseline- median [IQR] cells/mL [e]	436 [286-633]	1.05 (0.96-1.15) [f]	0.29	1.02 (0.94-1.11) [f]	0.64

CI denotes confidence interval, IQR interquartile range, HIV human immunodeficiency virus, ART antiretroviral therapy

a. Variables with p-value ≤0.3 in univariate analyses were included in the adjusted model. Final model was adjusted for age, distance traveled to the study clinic, HIV viral load at study baseline, CD4 count at study baseline, and study arm.
b. Age in the univariate and multivariate analyses is defined in 5-year increments.
c. Four-day ART adherence is self-reported.
d. Viral loads at enrolment measured per protocol by study arm. Laboratory viral load measured via Abbott m2000 RealTime, and point-of-care viral load measured via Cepheid Xpert® HIV-1 viral load assay.
e. Missing 1 observation of CD4 count at study baseline.
f. CD4 count at study baseline in the univariate and multivariate analyses defined in 100 cells/mL increments.

865 POPULATION-LEVEL HIV VIRAL LOAD VARIES BY GENDER, AGE, AND LOCATION IN RAKAI, UGANDA

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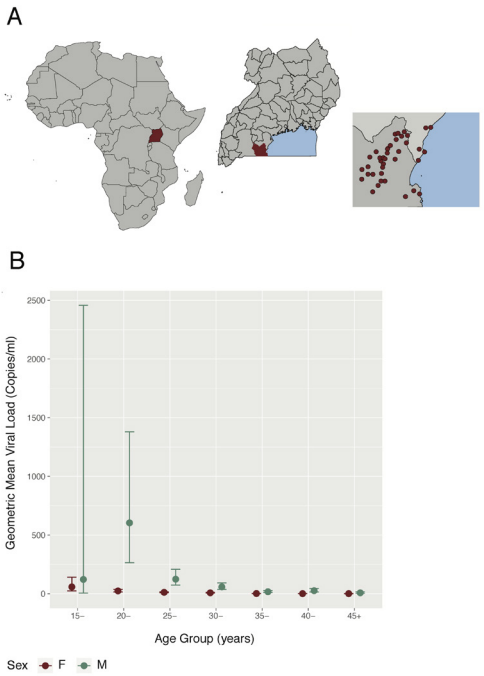
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Background: In the ART era, population HIV viral load (PVL) quantifies gaps in the HIV care cascade, as well as the residual transmission potential from population subgroups.

Methods: Between January 2015 and September 2016, we measured HIV viral load among HIV+ individuals aged 15-49 years in 40 communities of the Rakai Community Cohort Study, Uganda (Figure 1A). To measure PVL and viral suppression, we respectively quantified the proportion of individuals in the total population with detectable viral load above 1000 copies/ml plasma blood (PDVL) and the geometric mean viral load (PMVL), assigning a VL measurement of zero to HIV uninfected individuals. Sub-analyses were conducted among HIV infected individuals, and infected individuals with detectable viral load. Spatial heterogeneity in PVL measures was assessed with Gaussian kernel maps and spatial scan statistics.

Results: Of 18,656 participants, 3,467 (18.6%) were HIV-positive, of whom 3,454 (99.6%) had VL measured. Despite higher HIV prevalence among women (21.8% [21.0%-22.6%]) than men (15.0% [14.2%-15.7%]), PMVL was 1.4 [1.2-1.7] times higher among men than women. This reflected higher PDVL among men (5.8% [5.3%-6.3%] compared to women (4.8% [4.4%-5.2%]), and 7 (5-10) times higher geometric mean VL among infected men with detectable viral load compared to their female counterparts. PMVL peaked at age 20-24 in men and at age 15-19 in women (Figure 1B). In contrast PDVL peaked later, at age 30-34 in men and at age 25-29 in women. Spatial foci of high PMVL coincided with fishing communities along Lake Victoria.

Conclusion: Population-viral load analysis revealed marked differences in viral load suppression across demographic sub-groups and geography, with viral load burden greater in men than women, and concentrated in young age groups. Intensified interventions to improve health and reduce future infections are warranted especially among men and women aged <25 years, and geographic areas with excess detectable viral loads.



866 DISPARITIES IN VIRAL SUPPRESSION AMONG US ADULTS WITH RECENTLY DIAGNOSED HIV

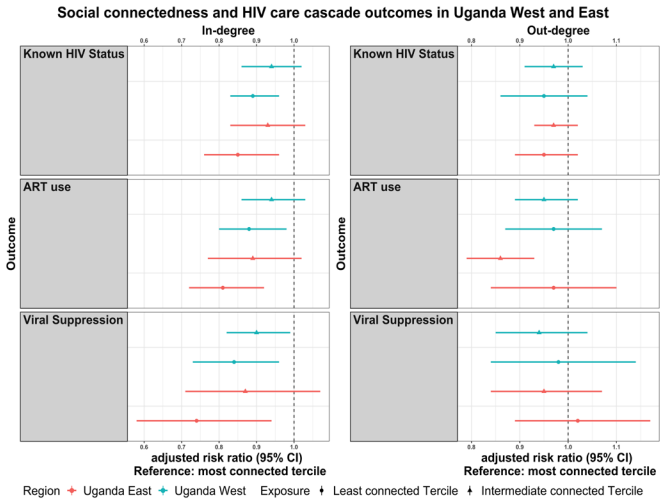
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Background: The Ending the HIV Epidemic (EHE) initiative focuses on rapid & effective treatment of people with HIV to achieve viral suppression, which is associated with improved health outcomes & reduced HIV transmission risk. Assessing disparities in viral suppression among persons with recent HIV diagnoses has the potential to guide practice and research. Using nationally representative data from the Medical Monitoring Project (MMP), we explored characteristics associated with viral suppression among adults with recent HIV diagnoses.
Methods: During 2015-2018, MMP conducted interviews among adults with diagnosed HIV. Viral load test results were abstracted from medical records. Viral suppression was defined as <200 copies/mL or undetectable based on the most recent viral load. Generalized anxiety disorder (GAD) in the past 2 weeks was assessed using a validated scale and categorized based on clinically meaningful cutpoints. Persons who reported needing but not receiving services had unmet needs for these services. All characteristics were based on the past 1 year unless otherwise indicated. Among persons with HIV diagnosed in the 5 years prior to interview (N=1,869), we assessed differences in viral suppression by selected characteristics using Rao-Scott $\chi 2$ tests ($p<0.05$).
Results: Of persons with recent HIV diagnoses, 31% were not virally suppressed, and 5% reported not currently taking ART. The proportion not virally suppressed varied by race/ethnicity (blacks: 37%, whites: 27%, Hispanics/Latinos: 26%) and age (18-24 years: 50%, 25-34 years: 35%, 35-44 years: 26%, 45-54 years: 23%, and ≥55 years: 22%). Persons who had a history of homelessness (40% vs. 30%), used non-injectable drugs (37% vs. 27%), had GAD (38% vs. 29%), and had unmet needs for HIV medicine (63% vs 29%), HIV case management (55% vs. 28%), and patient navigation services (67% vs. 28%) were less likely to be virally suppressed.
Conclusion: More than a quarter of persons with newly diagnosed HIV were not virally suppressed. Providers should ensure all persons with HIV are virally suppressed, including those newly diagnosed. Focusing efforts on programs, including comprehensive engagement, adherence support, & peer navigation, may result in improved health outcomes and reduced number of new HIV infections and supports the EHE initiative.

867 HIV+ PERSONS IN RURAL UGANDA WITH FEWER SOCIAL CONNECTIONS HAVE LOWER HIV SUPPRESSION

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Background: The social networks of HIV+ persons may facilitate access to HIV testing and care. We constructed community-wide social networks and assessed association between social connectedness and knowledge of HIV status, ART use, and HIV viral suppression among baseline HIV+ residents of rural Ugandan communities in the SEARCH Study (NCT01864603).
Methods: From 2013-2014, adults (≥15 yrs) in 10 communities in Uganda West and 10 in Uganda East were enumerated using a census and named social contacts in five domains: health, money, emotional support, food, and free time. Social networks were constructed by matching named contacts to other enumerated residents; 90% of residents were tested for HIV. We evaluated whether HIV+ persons in the lowest tercile of connectedness, based on in-degree (number of persons who named an individual as a contact) and out-degree (number of contacts an individual named), would be less likely to know their HIV status, have initiated ART, and be virally suppressed (HIV RNA<500 cps/ml) than their more connected counterparts. We used generalized estimating equations to adjust for sociodemographic risk factors including mobility and for clustering by community.
Results: A total of 57% of named within-community contacts in Uganda West and 63% in Uganda East were matched to enumerated residents, resulting in 20 networks with 108,521 nodes (enumerated persons) and 216,213 edges (social connections). Among 4,587 HIV+ persons who named ≥1 contact, 39% were not aware of their HIV status, 50% had not initiated ART, and 55% had viral non-suppression. HIV+ persons in the lowest tercile of in-degree (<1-2 contacts, depending on community) were less likely to know their status (Uganda West aRR:0.89 (95%CI:0.83, 0.96); Uganda East aRR:0.85 (0.76, 0.96)); to have initiated ART (Uganda West aRR:0.88 (0.80, 0.98); Uganda East aRR:0.81 (0.72, 0.92)), and to have viral suppression (Uganda West aRR:0.84 (0.73, 0.96); Uganda East aRR:0.74 (0.58, 0.94)) than those in the highest tercile (>3-7 contacts) (Figure). Out-degree was not associated with known HIV status or suppression in either region; persons in Uganda East with intermediate out-degree were less likely to have initiated ART.
Conclusion: HIV+ persons with fewer people naming them as contacts were less likely to know their HIV status, have initiated ART, or have a suppressed viral load. Interventions targeting HIV+ persons with fewer social connections may contribute to improved clinical outcomes.



868 LIFE EXPECTANCY GAINS WITH ART IN LATIN AMERICA, 2003-2017

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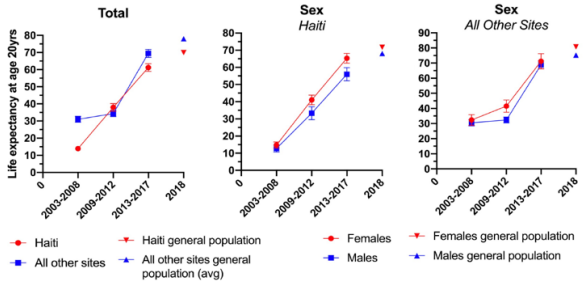
Background: Increased survival among persons living with HIV (PLWH) receiving antiretroviral therapy (ART) has been documented in the United States, Canada, and Europe. However, sparse data exist on life expectancy in low- and middle-income settings where ART is increasingly available. We therefore calculated life expectancy gains among PLWH initiated ART within the Caribbean, Central and South America network for HIV epidemiology (CCASAnet).

Methods: We included PLWH started on ART and ≥20 years old between 2003-2017 from CCASAnet sites in Haiti, Mexico, Honduras, Peru, Argentina, Chile, and Brazil. PLWH contributed person-time until the first of death, last cohort contact, database closure, or December 2017. Due to differences in general population life expectancies and clinical sites, we stratified analyses by Haiti vs. all other sites. We used the Chiang method for abridged life tables to calculate life expectancy at age 20 for three eras (2003-2008, 2009-2012, and 2013-2017) overall and by demographic and clinical characteristics at ART initiation. As mortality ascertainment varies by country, mortality rates were weighted for probability of loss to follow-up (LTFU) using adjusted Poisson regression models.

Results: Among 30,688 PLWH included, 17,491 (57%) were from Haiti, of whom 57% were female, 23% initiated ART in 2003-2008, 32% in 2009-2012, and 45% in 2013-2017. Of those from other sites, 23% were female, and 7% initiated ART before 2003, 29% in 2003-2008, 26% in 2009-2012, and 38% in 2013-2017. At ART initiation, 36% of PLWH from Haiti and 46% from all other sites had CD4+ count <200 cells/μL (17% missing). There were 1,470 deaths and 7,154 LTFU among PLWH from Haiti and 1,167 deaths and 3,174 LTFU at other sites. Crude and weighted mortality rates markedly decreased among all age groups over calendar eras. There were accompanying significant improvements in life expectancy, approaching that of the general population (61 years in Haiti and 69 years at other sites, in 2013-2017), though disparities by sex were significant in Haiti (Figure). While life expectancy improved over time, disparities by CD4+ count, education, and tuberculosis at or prior to ART persisted.

Conclusion: Life expectancy among PLWH on ART has significantly improved in Latin America and approaches that of the general population. Persistent disparities in life expectancy by sex, CD4+ count, education, and history of tuberculosis highlight vulnerable populations in the region.

Figure. Changes in estimated life expectancy among PLWH started on ART by calendar period within CCASAnet, weighted by inverse probability of censoring weights to account for differential losses-to-follow-up, and stratified by sex and site (Haiti vs. all other sites)



869 EXCESS MORTALITY AMONG PLWH WITH MULTIMORBIDITY COMPARED TO HIV-NEGATIVE CONTROLS

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Background: Antiretroviral therapy (ART) and gains in life expectancy have increased the likelihood of people living with HIV (PLWH) developing comorbidities. We examined which chronic comorbidities, experienced in isolation or in combination, led to higher mortality rates among PLWH compared to HIV-negative controls. Secondarily, we assessed the impact of multimorbidity on all-cause mortality among PLWH.

Methods: This population-based cohort study used longitudinal individual-level data on all treated PLWH and 1:5 age-sex-matched HIV-negative controls in British Columbia (BC), Canada. Eligible participants were ≥19 years old and enrolled in the Comparative Outcomes and Service Utilization Trends Study between 2001 and 2012 for ≥1 year. Comorbidities were identified from provincial administrative health databases (i.e., hospitalizations, outpatient physician, and pharmacy records). Selected comorbidities included liver, cardiovascular (CVD), renal, non-AIDS-defining cancers (NADC), hypertension, diabetes, and chronic obstructive pulmonary disease. Marginal structural models estimated the risk of all-cause mortality among PLWH with 1, 2 and ≥3 comorbidities (versus none).

Results: Overall, 51% of 8,405 PLWH, and 30% of 42,025 HIV-negative individuals developed ≥1 comorbidity by the end of follow-up. With the exception of the CVD-NADC combination, PLWH had higher all-cause mortality rates for all singular and combinations of diseases (see Figure). The largest disparity in mortality rate was related to renal disease (in isolation), where PLWH had a rate >30 times higher than that of HIV-negative controls. Among PLWH and the HIV-negative controls, a liver-NADC combination was associated with the highest mortality rate per 1000 person-years: 106.6 (95% confidence interval: 73.57-139.64) and 78.2 (46.24-110.16), respectively. After adjustment for demographic and time-dependent treatment-related confounders, PLWH with 1, 2 and ≥3 comorbidities were, respectively, 3.15 (2.57-3.86), 5.95 (4.65-7.61) and 12.96 (15.59-40.80) times more likely to die than PLWH without comorbidities.

Conclusion: Compared to HIV-negative controls, after adjusting for similar morbidities, PLWH experienced substantial excess in mortality rates. Additionally, we observed a strong positive dose-response between the number of morbidities and the risk of mortality among PLWH. These results highlight the critical role that additional morbidities continue to pose as drivers of mortality among PLWH within a publicly funded province-wide ART program.

(A) PLWH

	Liver	Cancer	Hypertension	CVD	Renal	Diabetes	COPD
Liver	965 27.44 (23.88-30.99)						
Cancer	55 106.6 (73.57-139.64)	153 51.96 (39.33-64.59)					
Hypertension	107 19.8 (11.12-28.47)	28 40.91 (16.73-65.08)	481 7.05 (4.61-9.49)				
CVD	63 62.53 (40.52-84.55)	10 21 (0.00-50.10)	86 12.05 (4.58-19.52)	113 38.06 (25.45-50.67)			
Renal	277 59.45 (49.35-69.56)	26 96.08 (51.69-140.47)	73 27.4 (15.08-39.73)	39 54.16 (27.62-80.69)	279 49.55 (39.98-59.12)		
Diabetes	52 15.65 (4.81-26.5)	9 37.87 (0.00-80.73)	125 3.88 (0.48-7.28)	17 71.08 (24.64-117.51)	44 30.98 (13.45-48.51)	251 6.18 (3.05-9.3)	
COPD	78 25.39 (13.66-37.12)	17 100.66 (43.70-157.61)	29 19.27 (2.38-36.17)	22 35.31 (9.15-61.47)	16 29.42 (0.59-58.25)	18 12.85 (0.00-30.65)	113 23.81 (14.48-33.15)

(B) HIV-Negative

	Liver	Cancer	Hypertension	CVD	Renal	Diabetes	COPD
Liver	457 9.58 (6.68-12.48)						
Cancer	39 78.2 (46.24-110.16)	587 27.84 (23.4-32.28)					
Hypertension	109 6.89 (2.12-11.67)	224 22.39 (16.25-28.54)	4533 1.51 (1.15-1.87)				
CVD	15 43.46 (8.68-78.24)	24 63.69 (29.07-98.31)	570 7.58 (5.31-9.85)	444 6.87 (4.41-9.33)			
Renal	20 49.29 (17.09-81.5)	13 53.81 (10.75-96.87)	138 5.88 (1.81-9.96)	16 18.13 (-2.39-38.65)	123 1.63 (0.00-3.90)		
Diabetes	53 9.45 (1.17-17.74)	59 24.3 (11.57-37.04)	1233 1.42 (0.77-2.08)	106 10.49 (4.29-16.69)	24 8.98 (-3.47-21.43)	1518 2.12 (1.38-2.87)	
COPD	24 24.54 (4.90-44.17)	31 55.97 (27.64-84.29)	136 6.51 (2.26-10.75)	21 15.29 (-2.01-32.60)	6 <0.001 (<0.001-<0.001)	48 7.73 (0.15-15.30)	271 5.06 (2.41-7.71)

870 EXCESS MORTALITY AFTER CANCER DIAGNOSIS IN PERSONS WITH HIV

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Background: Persons with HIV (PWH) may have reduced survival after a cancer diagnosis compared with uninfected persons, yet prior studies are limited by insufficient control for confounding from access to care and other comorbidities, and do not often account for the increased background mortality rate of PWH.

Methods: We conducted a cohort study during 2000-2016 of adult PWH who were members of Kaiser Permanente in Northern California, Southern California, or Mid-Atlantic States, which provide comprehensive cancer and HIV care. Uninfected adults were matched 10:1 to PWH by age, sex, race/ethnicity, medical center, and year. The primary outcome was all-cause mortality per 1,000 person-years (py), and the predictors were HIV status, and cancer grouped as: any cancer; AIDS-defining cancers (ADC); non-AIDS-defining cancers (NADC); virus-unrelated NADCs; virus-related NADCs; and HPV-related NADCs (see Table footnote). We first computed mortality rate differences (RD), separately by HIV status, to measure the increased mortality rates after cancer (RD>0 denotes higher mortality rates after cancer). Next, we modeled mortality rates using additive Poisson regression, including terms for HIV status, cancer, and an HIV*cancer interaction term. The interaction term represents the excess mortality rate associated with cancer among PWH as compared with uninfected persons. Adjusted models included terms for demographics, smoking, body

mass index>25 kg/m$_2$, alcohol/drug use disorders, and common comorbidities (see Table footnote).

Results: The study included 39,000 PWH (with 697 cancers) and 387,767 uninfected adults (with 2,876 cancers). Any cancer increased mortality for PWH with an RD of 62.2 deaths per 1,000 py, and for uninfected persons with an RD of 45.5 deaths per 1,000 py. This difference by HIV status persisted with adjustment for confounders with an adjusted excess mortality rate for any cancer of 20.5 per 1,000 py (P<0.001) for PWH compared with uninfected persons. Excess mortality rates for PWH with cancer varied by cancer group (Table) with the lowest for ADCs (11.8) and the highest for NADCs (30.3), virus-unrelated NADCs (30.6), and HPV-related NADC (24.7).

Conclusion: Even with access to comprehensive HIV and cancer care, PWH have excess mortality after cancer, especially NADCs. Additional research is needed to understand this disparity, including studies evaluating effectiveness and tolerability of cancer treatments in PWH.

Table. Increases in mortality rates after a cancer diagnosis among PWH and uninfected persons

	PWH	Uninfected	Excess mortality rate (P-value)[3] for PWH following cancer diagnosis	
Cancer group[1]	Rate difference[2]	Rate difference[2]	Unadjusted	Adjusted
Any cancer	62.2	45.5	16.7 (<0.001)	20.5 (<0.001)
ADC	47.7	43.6	4.1 (0.45)	11.8 (0.027)
NADC	73.1	46.0	27.1 (<0.001)	30.3 (<0.001)
Virus-unrelated NADC	68.9	41.3	27.7 (<0.001)	30.6 (<0.001)
Virus-related NADC	82.1	71.6	10.5 (0.27)	16.9 (0.076)
HPV-related NADC	60.2	38.2	22.0 (0.030)	24.7 (0.013)

[1]ADCs: Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer; NADCs: all cancers not classified as ADCs; HPV-related NADCs: anal, vulvar, vaginal, penile, and HPV-related oropharyngeal cancers; virus-related NADCs: HPV-related NADCs, liver, and Hodgkin lymphoma; virus-unrelated NADCs: all NADCs not classified as virus-related.

[2]Mortality rate (per 1,000 person-years) after cancer diagnosis minus mortality rate before cancer.

[3]Excess mortality rate from additive Poisson regression models, computed as rate difference in PWH minus rate difference in uninfected. Unadjusted models include terms for HIV, cancer, and HIV*cancer interaction. Adjusted models also include terms for age, sex, race/ethnicity, KP region, smoking, BMI>25, alcohol/drug use disorders, cardiovascular disease, diabetes, liver disease, and renal disease.

871 GAINS AND REMAINING CHALLENGES IN MORTALITY AMONG INDIVIDUALS WITH HIV, 1999-2017

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Background: Improvements in HIV care have resulted in people living with HIV reaching older ages. An increased risk of non-AIDS comorbid conditions may pre-date HIV infection, complicating efforts to close the gap in life expectancy compared to uninfected people. This study assessed trends in, and causes of, deaths in a state with high health insurance coverage.

Methods: We analyzed records of deaths in Massachusetts from 1999-2017 excluding non-residents. Using ICD-9 and -10 codes, we dichotomized deaths as with HIV or AIDS (ICD-9: 42, 43, 44; ICD-10: B20) or without HIV. We aggregated causes of death into broader system groupings (e.g. circulatory, digestive, respiratory, etc.) using WHO and CDC standards. We calculated the difference in the mean age at death for specific comorbidities during the earliest three-year period (1999-2001) with the most recent period (2015-2017) to assess improvements in longevity among individuals with HIV infection.

Results: There were 1,018,132 deaths in Massachusetts from 1999-2017; of these, 3,384 (0.3%) were among HIV infected individuals. The number of deaths among infected individuals declined from 1319 deaths in 1999-2003 to 565 deaths in 2013-2017; deaths among uninfected individuals increased from 274,625 to 275,744. Mean age of death increased from 42.5 years in 1999 to 60.0 years in 2017 among infected individuals but was unchanged among the uninfected (76.1 and 76.2 years, respectively). In both groups, diseases of the circulatory system ranked first; diseases of the respiratory system ranked third among infected individuals and second among uninfected. The second cause (31.2% of recent deaths) among infected individuals were infectious diseases; these ranked 9th (23,946 deaths or 8.7% of deaths) among uninfected individuals. Increases in age at death varied by cause of death and ranged from 5.2 to 17.7 years among infected individuals. Areas with the least improvement were hypertension (5.2 years), lower respiratory tract diseases (5.6 years), and diabetes (8.6 years). Areas with the most improvement were renal failure (17.7 years) and heart failure (16.9 years).

Conclusion: A gap in longevity remains.

872 A DETAILED LOOK AT HIV MORTALITY IN KING COUNTY, 2016-2018

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Background: While mortality among people living with HIV (PLWH) has declined 43% over the past decade in King County, death rates have remained stable over the past 5 years, from 1.0 to 1.1 deaths per 100 PLWH. Though some deaths among PLWH can be directly attributed to HIV, an increasing proportion of deaths are due to other factors, including the aging of PLWH. We compared a population based cohort of all PLWH 2016-2018 to decedents with HIV over those years, and conducted in depth investigations of causes of death, comorbidities, and social determinants of health for 2017 deaths.

Methods: Data were collected by provider interviews, medical record abstractions, and analysis of the CDC's HIV/AIDS surveillance system (NHSS). 268 deaths occurred among King County PLWH 2016-2018 relative to 7,922 PLWH. Of 98 deaths in 2017 82% had a local death certificate and of these 85% had a local medical record available for review; medical providers completed surveys for 56% of these.

Results: One third (34%) of decedents had CD4 counts <200 relative to 5% of PLWH; 44% of decedents were 60+ years relative to 18% of PLWH; and 57% of decedents were diagnosed with HIV in 2000 or earlier relative to 33% of PLWH (Table). Decedents were roughly twice as likely to have a history of injection drug use. Of the 68 patients whose medical records were abstracted, 10 (15%) had causes of death related to HIV; half had an AIDS-defining Opportunistic Illnesses (OI; 7%). Non-AIDS cancers were associated with death for 26%, heart disease for 18%, self-harm for 12%, and liver disease for 6%. An additional 10 had an AIDS OI within a year of death (making 22% total). More than half, 65% had a mental health diagnoses (mostly depression/anxiety), and 86% had some treatment of their mental illness. One quarter had HCV and one quarter of these had been treated, all of whom had sustained viral response. Provider interviews suggest roughly 1/3 of decedents had some social isolation. Those experiencing stigma (24%) had 9-fold higher odds of an HIV-related death relative to decedents without known stigma.

Conclusion: Expectedly, decedents were older, had been diagnosed with HIV longer, had lower CD4 counts, and were more likely to have used injection drugs than PLWH. The deaths of the majority of PLWH in King County are from non-HIV/AIDS related causes though AIDS-OIs contributed to 7% of deaths and were present for 22%. Data suggest stigma may be associated with HIV-related deaths but a larger study is needed to validate this finding.

Table: Demographics of PLWH relative to decedents 2016-2018, King County Washington

		Deaths (N=268)		People Living with HIV (N=7,922)		X^2 or X^2_{LT}
		N/Median	% (IQR)	N/Median	% (IQR)	P-Value
Sex at birth	Female	24	9%	986	12%	$\chi2$ P = 0.087
	Male	244	91%	6,936	88%	
Year of HIV diagnosis	Median year (IQR)	1998	(1993-2008)	2005	(1998-2012)	X^2_{LT} P < 0.001
Mode of HIV transmission	**MSM**	**158**	**59%**	**5,312**	**67%**	**$\chi2$ P= 0.006**
	PWID	**31**	**12%**	**319**	**4%**	**$\chi2$ P < 0.001**
	MSM-PWID	31	12%	726	9%	$\chi2$ P =0.182
	Heterosexual	17	6%	787	10%	$\chi2$ P = 0.052
Last CD4 (prior to death)	**<200**	**90**	**34%**	**426**	**5%**	
	200-499	**108**	**41%**	**2,214**	**28%**	**X^2_{LT} P < 0.001**
	500+	**66**	**25%**	**5,198**	**66%**	
Last Viral Load	**Suppressed (< 200)**	**208**	**78%**	**7,241**	**92%**	**$\chi2$ P < 0.001**
	Unsuppressed, 200+	**57**	**22%**	**634**	**8%**	
Age in years	Median (IQR)	56	(50-64)	48	(38-56)	X^2_{LT} P = <0.001

Bold designates statistical significance at the p<0.05 level; MSM = men who have sex with men PWID = people who inject drugs LT = Linear Trend; IQR = Interquartile Range

873 USING MULTISTATE MODELS TO DISENTANGLE MORTALITY & LOSS TO FOLLOW-UP IN HIV+ PATIENTS

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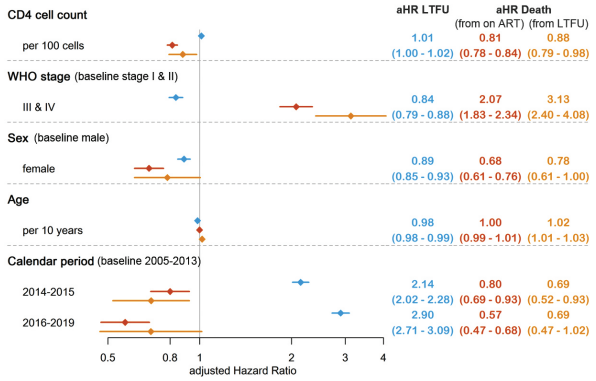
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Background: Estimating mortality in HIV-positive patients starting antiretroviral therapy (ART) is challenging, as clinics often face substantial loss to follow-up (LTFU). Many studies ignore LTFU, leading to biased estimates. Others correct for LTFU, but conventional methods give pooled estimates, which makes it impossible to asses risk factors and mortality estimates separately for those LTFU and remaining in care. We examined the use of multistate models to overcome this problem, using data from rural northern Mozambique, where patients LTFU are routinely traced.

Methods: We used clinical and tracing data from Ancuabe District, Mozambique. We used a multistate illness-death model without recovery to describe progression of patients from the initial state "on ART" through the intermediate state "LTFU" to the final absorbing state "Death". We used Nelson-Aalen and Aalen-Johansen estimators to estimate crude cumulative transition hazards and probabilities, respectively. We fitted Cox proportional hazards models to examine associations between patient characteristics and transition hazards.

Results: Analyses included 17342 patients; 1403 (8.1%) had died and 8817 (50.8%) were LTFU. 1342 of patients LTFU were traced, of whom 46 (3.4%) were found to have died. At 5 years after ART start, estimated cumulative hazard (risk) of dying was 0.26 (95%-CI 0.17-0.39) out of the "LTFU" state and 0.19 (0.18-0.20) out of the "on ART" state, indicating an increased risk of dying for patients LTFU. Male sex, less advanced clinical stages, and starting ART in more recent calendar periods were associated with a greater hazard of LTFU (Figure). Higher mortality was associated with male sex, lower CD4 counts, more advanced clinical stages, and starting ART in earlier calendar periods. These associations were apparent for both patients on ART and LTFU, but differed in their magnitude (Figure).
Conclusion: Multistate models are an attractive alternative to common approaches for dealing with LTFU when estimating program-level mortality in ART facilities. They allow us to distinguish between patients LTFU and those remaining in care, while still providing pooled estimates combining the two groups. Progression of patients from starting ART to LTFU and death can thus be described in more detail to inform the design of appropriate models of differentiated care.

Figure: Adjusted hazard ratios (aHR) for loss to follow-up (LTFU) and death



874 INCREASED MORTALITY AMONG PEOPLE AT HIGH RISK FOR HIV IN THE UNITED STATES

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Background: People with and at risk for HIV have competing risks of mortality independent of their HIV status, such as smoking, injection drug use (IDU), and serious mental illness. We sought to quantify the non-HIV-associated mortality rates among people from the major HIV transmission categories compared to those without the relevant risk factor: men who have sex with men (MSM); high-risk heterosexuals; and people who inject drugs (PWID).
Methods: We used the National Health and Nutrition Examination Survey (NHANES) (cycles 2001-14) and the National Health Interview Survey (NHIS 1991) with linked mortality data (through 2015) to examine independent associations of mortality with sexual orientation, low socio-economic status (SES), and IDU among adults (>18y). We considered male respondents to be MSM if they reported a history of male sexual partner or self-identified as gay or bisexual and compared them to heterosexuals (in NHANES). We considered low socio-economic status (SES) as a proxy for the mortality risk experienced by high-risk heterosexuals and characterized low/high SES as poverty income ratio (PIR) <1 or ≥1 to examine associations between SES and mortality (in NHANES). We categorized individuals as ever PWID if they reported ever using heroin and compared them to never IDU (in NHIS). We included all major causes of death but excluded the "other" category to avoid double-counting HIV-associated causes of mortality. We used Cox proportional hazard models to estimate age- and race-adjusted mortality rates and hazard ratios (HR) with 95% confidence intervals (CI). Analyses were stratified by age at risk (≤55y vs >55y).
Results: MSM older than 55y had a non-significant higher risk of mortality compared to male heterosexuals (HR, 1.62) (Table). For females of low SES, mortality was higher for both ≤55y and >55y compared to females of high SES (HR, 2.93/3.34), whereas mortality was increased only among males of low SES older than 55y compared to males of high SES (HR, 2.47). Mortality was higher among ever PWID compared to never PWID. This was significant among ever PWID ≤55y (M/F HR, 2.75/4.09).
Conclusion: People from many of the major HIV transmission categories had a higher risk of non-HIV-associated mortality compared to those without the relevant risk factor. Interventions for people with HIV should also focus on reducing non-HIV-related causes of death to achieve maximum impact.

Table. Mortality rates among people in the major HIV transmission categories compared to those without the relevant risk factor

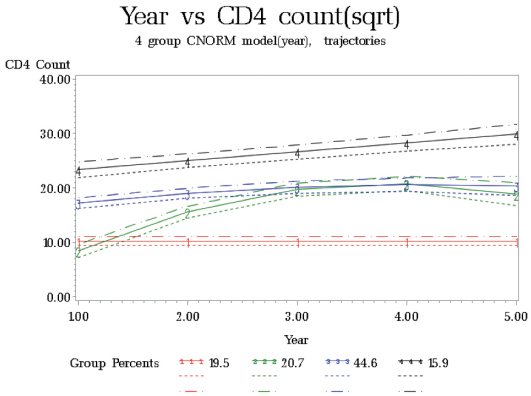
Sex	Transmission Category	All-cause Mortality Rate (per 100 PYs)	Non-AIDS Mortality*,# HR (95% CI) Age ≤55y	Non-AIDS Mortality*,# HR (95% CI) Age >55y
Male	Heterosexual	0.61	--	--
	MSM	0.96	1.00 (0.39, 2.56)	1.62 (0.73, 3.61)
	High SES	0.54	--	--
	Low SES	0.95	1.04 (0.63, 1.72)	**2.47 (1.57, 3.88)**
	Never PWID	0.53	--	--
	Ever PWID	1.23	**2.75 (1.50, 5.04)**	1.84 (0.94, 3.58)
Female	High SES	0.30	--	--
	Low SES	0.83	**2.93 (1.63, 5.26)**	**3.34 (1.57, 7.07)**
	Never PWID	0.33	--	--
	Ever PWID	0.98	**4.09 (2.02, 8.29)**	1.93 (0.55, 6.75)

We used SES as a proxy for the risk of non-HIV-associated mortality among high-risk heterosexuals. Statistically significant results are in bold.
*Analyses were restricted to known causes of mortality that do not include HIV
#Cox models included age, sex, race, transmission category, and age*sex* transmission category interaction
Abbreviations: PY: person-year; HR: hazard ratio; CI: confidence interval; SES: socio-economic status; PWID: people who inject drugs

875 CD4 COUNT PATTERNS OVER TIME IDENTIFY LONG-TERM HIV CARE TRAJECTORIES IN SOUTH AFRICA

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Background: Predicting long-term care engagement at HIV diagnosis would allow targeted interventions for those at high risk of poor outcomes. Our objective was to uncover distinct CD4-based trajectories and determine baseline contextual, clinical and sociobehavioral factors associated with higher risk of being in a worse CD4 trajectory.
Methods: We used data from the Sizanani trial (NCT01188941) in which adults (≥18y) were enrolled prior to HIV testing at 4 Durban outpatient sites from Aug 2010-Jan 2013. We ascertained longitudinal CD4 count data over 5y follow up using probabilistic matching with data from the National Health Laboratory Service. We used group-based statistical modeling to identify groups with similar CD4 count trajectories over time and Bayesian information criteria to determine distinct CD4 trajectories. We then evaluated baseline risk factors that predict membership in a specific (worse) trajectory using multinomial logistic regression. We examined year of enrollment, age, gender, whether people lived alone, TB positivity at enrollment, and number of domains of self-identified barriers to care (related to service delivery, financial, personal health perception, logistical, and structural) and accounted for ART initiation within 3 months of diagnosis and mortality.
Results: 688 participants had longitudinal data available by NHLS crossmatch; 555 (81%) were women and median baseline CD4 count was 218 (IQR 94-368). Group-based trajectory modeling identified 4 distinct trajectories (Figure); Group 1 (19.5% of sample), with a consistent very low CD4 count that did not increase (red); Group 2 (20.7%), with a very low at baseline but increasing over time CD4 count (green), Group 3 (44.6%) with a medium-low but increasing CD4 count (blue), and Group 4 (15.9%) with a high baseline CD4 count that increased steadily overtime (black). Earlier year of enrollment, younger age, failure to start ART within 3 months, male sex, TB positivity and a greater number of self-identified barriers to care domains predicted membership in groups with poorer outcomes (Groups 1 and 2) compared to Group 4 (reference).
Conclusion: One-fifth of people newly-diagnosed with HIV presented with low CD4 counts that failed to rise over time. Factors available in early clinical encounters, including potentially modifiable healthcare barriers, can predict long-term outcomes. Identifying those at high risk for poor care engagement can inform design of differentiated interventions to improve long-term clinical outcomes.



876 PREDICTIVE VALUE OF THE CD8 COUNTS AND CD4/CD8 RATIO AT 2 YEARS OF SUCCESSFUL ART

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Background: While increased CD8+ T cell counts and low CD4/CD8 ratio during treated HIV CD4/CD8 ratio correlate with immunosenescence, cohort studies have yielded conflicting results on its additional predictive value to identify HIV-infected individuals at higher risk of clinical events.
Methods: We selected treatment-naive individuals initiating ART from ACTG studies 384, 385, A5095, A5142, A5202 and A5257 who had achieved viral suppression at year 2. We examined the effect of CD4/CD8 at year 2 on the probability of AIDS and serious non-AIDS events in years 3-7, using A5001 long-term follow-up. We examined different CD8+ T cells and CD4/CD8 ratio categorizations. We used inverse probability weighting methods to address informative censoring, combined with multivariable logistic regression models.
Results: Among 5133 participants who met our inclusion criteria, 961 reached year 7 while on suppressive ART, and 3787 (74%) were censored due to treatment failure, ART discontinuation or drop-off. 385 had a clinical event during years 3-7. At ART initiation, the median age was 38 years, 959 (19%) were female, 2168 (42%) were white, 407 (8%) reported current or previous IDU; year 2 median CD4 counts 503 cells/uL (348-668), CD8 counts 772 cells/uL(578-1022), CD4/CD8 ratio 0.65 (0.41-0.95). Adjusted odds ratios indicated that CD8+ T cell counts had the clearest stepwise effect across the full range of values for the association with clinical events at the different cut-offs. CD4/CD8 ratio was also predictive of greater risk of events through year 7 at extremely low values (Table 1). The estimated probability of an event in years 3-7 was 30% among participants with CD4/CD8 ratio <0.15 and 15% among those ≥0.15 (P=0.001). Sensitivity analyses did not reveal major differences when restricting to infectious vs. non-infectious events or AIDS vs. non-AIDS events.
Conclusion: The results of this analysis with pooled data from clinical trials support the value of the CD8+ T cell count as a predictor of clinical progression. People with very high CD8 counts during suppressive ART might benefit from closer monitoring and may be a target population for novel interventions.

Table 1. Adjusted odd ratios and 95 percent confidence intervals for the first event at years 3-7 and the association with CD4 and CD8 counts at year 2.

Variables	Odds Ratio (95% CI)	P-value
CD4 count at year 2*		
≤200 vs >200	0.94 (0.7, 1.26)	0.67
CD8 count at year 2*		
≥1500 vs 500-1499	1.79 (1.33,2.41)	<0.001
CD4:CD8 ratio at year 2**		
<0.15 vs >0.3	2.81 (1.61,4.9)	<0.001

**Model 1: Adjusted for race/ethnicity, injection drug use, age at entry, initial ART regimen, pre-ART HIV RNA, and history of a clinical event on or before year 2.*
***Model 2: Adjusted for CD4 counts at year 2. Adjusted OR when adjusted as in model 1: 1.34 (0.76, 2.39), p=0.31*

877 EFFECT OF ERECTILE DYSFUNCTION DRUGS ON T CELLS AND IMMUNE MARKERS IN MEN

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Background: Erectile dysfunction (ED) drugs are frequently used in men who have sex with men (MSM). Although commonly associated with increased vasodilation, there is evidence of beneficial immunomodulatory effects of these drugs in animal studies. However, studies on the effect of ED drugs on immune capacity and function in MSM are limited.
Methods: A total of 1,391 HIV positive men and 307 HIV negative men were included from the Multicenter AIDS Cohort Study (MACS), an ongoing prospective HIV/AIDS cohort study in the U.S., from 1998 onwards, with ages ranging from 19 to 70 years. We used marginal structural models in the form of g-computation in complex longitudinal setting to assess the causal mean differences (MD) in CD4 and CD8 T cells for 10 years, as well as other immune biomarkers up to 4 observations.
Results: ED drug use over time was associated with an increase in the number of CD4 cells in HIV positive men. After controlling for important confounding variables such as age, viral load and ART, the causal MD in CD4 cell counts in HIV positive men after 1 year of ED drug use was 57.6 cells/μL and increased to 117.7 cells/μL after 10 years. CD8 cell counts were higher among ED drug users over a 10-year period compared to non-users in the HIV positive group but showed almost no significant differences in HIV negative group. HIV positive ED drug users also showed reduced levels of pro-inflammatory markers, IL-6 (MD: -1.98, 95% CI = -2.22 – -1.75) and TNF-α (MD: -2.31, 95% CI: -2.48 – -2.14) after one year of observation. An anti-inflammatory cytokine, IL-10, was higher in ED drug users compared to non-users. HIV negative subjects showed similar effects with ED drug use over time with respect to inflammatory markers.
Conclusion: ED drug use was associated with a significantly higher CD4 T cell outcome in HIV positive MSM. Furthermore, analyses of immune biomarkers showed ED drug use to have been associated with lower pro-inflammatory and higher anti-inflammatory markers over time. This observation suggests a favorable immunomodulatory effect of ED drugs in MSM.

878 PREEXPOSURE PROPHYLAXIS ADHERENCE AND PERSISTENCE IN KENYAN TRANSGENDER WOMEN AND MSM

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Background: Transgender women (TGW) and men who have sex with men (MSM) in sub-Saharan Africa have high HIV acquisition risks and can benefit from daily pre-exposure prophylaxis (PrEP) if taken regularly. We set out to assess PrEP adherence by measuring tenofovir-diphosphate (TFV-DP) levels and explore motives for PrEP persistence in a sample of TGW and MSM in coastal Kenya.
Methods: Participants enrolled in a one-year PrEP programme and made quarterly visits irrespective of whether they were still using PrEP. At their month 6 visit, participants provided a dried blood spot to be tested for TFV-DP levels; protective levels were defined as those compatible with ≥4 pills per week (700-1249 fmol/punch). Before TFV-DP levels were available, sub-set of these participants completed in-depth interviews (IDIs). All TGW and purposively selected MSM participated in the IDIs. We used semi-structured topic guides to explore motives to start and adhere to PrEP, and reasons to stop it. IDI data were analyzed thematically.
Results: Fifty-three participants (42 MSM and 11 TGW) were enrolled. At month 6, 12 (22.6%) participants (9 MSM and 3 TGW) were lost to follow up. Any TFV-DP was detected in 62.5% (5/8) of TGW vs. 15.2% of MSM (5/33, p=0.004). Protective levels were detected in 37.5% of TGW (3/8) but not in any MSM. Nineteen IDIs were conducted, with 7 TGW and 8 MSM on PrEP, and 1 TGW and 3 MSM off PrEP. Unplanned or frequent risky sexual risk behaviour, including condomless anal intercourse, were the main motives for PrEP uptake. Among TGW, the notion that PrEP reinforced their female gender identity seemed to aid adherence. Inconsistent PrEP use was attributed to situational factors and included illness, concomitant drug use, travel, and less sexual satisfaction. Motives to discontinue PrEP included negative reactions from partners, experience of side-effects, and change in risk taking behaviour.
Conclusion: Although 1 in 5 participants were lost to follow up, almost 40% of TGW were protected by PrEP. MSM appear to have greater challenges adhering to PrEP. TGW appeared to have had more agency to take PrEP. Personal and

contextual factors determining PrEP adherence call for a more supportive TGW and MSM-centred approach. MSM may require additional adherence support.

879 HIV PREVALENCE AND RISK IN MALE, TRANSMALE, AND TRANSFEMALE SEX WORKERS IN ZIMBABWE

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Background: National epidemics in sub-Saharan Africa become increasingly concentrated among high risk populations. In Zimbabwe, HIV prevalence is 13.3% in the general population compared to 56.5% amongst female sex workers. HIV services have been successfully set up for female sex workers (FSW) and reached over 45.000 women. However, male and transgender sex workers remain hidden and disconnected from services. Little is known about them, while their HIV risk is expected to be high. We determined HIV prevalence and risk among male and transgender sex workers in Zimbabwe.
Methods: By July 2018, the Centre for Sexual Health and HIV/AIDS Research (CeSHHAR) Zimbabwe has integrated an outreach intervention for male and transgender sex workers within the existing program for female sex workers. Participants were recruited through peer educator referral at multiple sex work hotspots throughout the country. From July 2018 to June 2019 in total 603 male and transgender sex workers enrolled the program. Trained staff administered a sociodemographic and behavioral survey and performed HIV voluntary counselling and testing. Determinants of HIV risk were analyzed through univariate and multivariate logistic regression analysis and compared to program data from 12,315 female sex workers.
Results: In total 221 male sex workers (MSW), 233 transfemale sex workers (TFSW) and 149 transmale sex workers (TMSW) were included in the study. Crude HIV prevalence estimates were 28.2% in MSW, 37.6% in TFSW and 38.1% in TMSW, compared to 36.5% in FSW. Reported risk behavior appeared high in all groups, in particular high rates of condomless vaginal sex for all groups, and high rates of condomless anal sex amongst MSW and TFSW. High rates of female clients were reported by all groups. PrEP was significantly more commonly used amongst MSW and TFSW and appeared protective for HIV.
Conclusion: To our knowledge this is the first study conducted in sub-Saharan Africa specifically focused at male, transfemale and transmale sex workers. HIV prevalence among Zimbabwean male and transgender sex workers was as high as for female sex workers. High numbers of transmale sex workers and female clients give a new insight into the diversity of people participating in sex work. HIV research and interventions focused on sex work should be made inclusive for all genders.

880 FACTORS ASSOCIATED WITH HIV, HCV, AND HSV-2 SEROSTATUS AMONG US TRANSGENDER WOMEN

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Background: Transgender women (TW) bear a disproportional burden of disease in the United States. The Leading Innovation for Transgender Women's Health and Empowerment (LITE) study recruited subjects from six eastern and southern cities in the US. We identified factors associated with the infection of HIV, HSV-2 and HCV among TW at enrollment.
Methods: Serum samples were collected from 562 TW residing in Boston (n=110), New York (n=86), Baltimore (n=108), Washington DC (n=95), Atlanta (n=67) and Miami (n=96) from March 2018 to March 2019. Sociodemographic, behavioral, and socioeconomic information were obtained and log-binomial models were used to assess the prevalence ratios of factors associated with infection.
Results: Of the 562 individuals, 254 (44%) were sero-negative for all three infections. The prevalence of HIV, HSV-2, and HCV were 29%, 48%, and 5% respectively. 130 (23%) had laboratory-confirmed HSV-2 only, 5% were HIV only, and 1% HCV only. 21% (119/562) were co-infected with HIV and HSV-2 and 2% were infected with all three. Compared to Boston, the prevalence of having one or more infections was higher in New York (adjPR 1.88, 95%CI 1.36, 2.6), Baltimore (adjPR 1.51, 95%CI 1.12, 2.04), Atlanta (adjPR 1.38, 95%CI 1.02, 1.88), and Miami (adjPR 1.49, 95%CI 1.10, 2.01). The frequency of disease burden increased with age, as having any one or more infections increased from 27% for those <26 to 81% for those older than 45 years of age. Compared to white TW, Black, Hispanic and mixed race TW had a higher burden of disease (adjPR 3.21 95%CI 2.25, 4.59; 2.46 95%CI 1.68, 3.61; 2.28 95%CI 1.74, 3.54, respectively). Though those who ever experienced unstable housing or were without full–time employment had higher burdens of disease, these associations were attenuated in the full model. Of note, family support was associated with a higher burden of disease (adjPR 1.29, 95%CI 1.08, 1.55). This finding can be partially explained by the greater level of family support for Black TW (69%) vs. White TW (52%).
Conclusion: We found a high burden of disease among TW. Difference in disease burden were found geographically, by race and ethnicity, family support studies and with age. Surprisingly, employment status and lifetime unstable housing status were not associated with an increased risk of infection. Findings highlight the need for prospective research to further evaluate TW vulnerabilities, including for incident infections.

881 HIV PREVALENCE AMONG TRANSGENDER MEN AT AN NYC COMMUNITY HEALTH CENTER

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Background: There have been multiple studies demonstrating elevated incidence and prevalence of HIV among transgender women (TW) especially African-American TW, however few studies have been conducted among transgender men (TM). HIV prevalence among TM in the US is estimated to be between 0-4%. There have not been any studies examining prevalence that stratify by HIV risk factor, e.g., TM who have sex with MSM or use injection drugs. Callen-Lorde Community Health Center is a NYC-based clinic that predominately serves the LGBT communities and people living with HIV. It has the largest transgender patient population in the USA, serving nearly 5000 transgender and gender non-binary (TGNB) patients. The aim of this study was to examine HIV screening behaviors, prevalence and risk factors among TM.
Methods: The Transgender Data Project was an IRB-approved retrospective chart review of all TGNB patients at the clinic, ages 18+. Charts were reviewed manually. Data retrieved included birth sex, gender identity, race/ethnicity, education, employment, housing, insurance status, sex work, receipt of gender-affirming care (hormones, surgeries), STI history, HIV screening and HIV status. Multivariable logistic regression models were used to assess associations with HIV screening and HIV status.
Results: 577 TM, mean age 32.15 (18.3-70.5, SD 9.31) were included in this analysis. The majority were white (55% white, 13.9% black, 11.7% Hispanic, 5.8% Asian/Pacific Islander,13.5% mixed race). 78.9% had received testosterone and 41.6% had received at least one gender-affirming surgery. Fewer than half (242, 41.9%) had undergone HIV screening. HIV prevalence was 2.9% (7/242) and highest among African Americans(African American 6.8%, hispanic 3.2%, white 2.1%) and among TM who had sex exclusively with cisgender men (11.1%). HIV screening was associated with gender-affirming surgery (aOR 1.67, 95% CI=1.08, 2.58), substance use (aOR 5.18, 95%CI=1.41-18.99) and non-white race (aOR 2.56, 95% CI=1.69-3.85). Having a high school diploma reduced the odds of HIV infection (aOR 0.10, 95% CI= 0.10-0.69).
Conclusion: HIV prevalence is thought to be low among TM however this analysis found an HIV seroprevalence >10% among TM who exclusively have sex with cisgender men. These results underscore the need to account for sexual risk (sexual behaviors and sexual orientation identity) among TM when interpreting HIV prevalence data. TM who have sex with cisgender men should be prioritized for inclusion in HIV prevention efforts.

882 PROGRESSION THROUGH THE HIV CARE CONTINUUM FOR TRANSGENDER WOMEN IN THE NA-ACCORD

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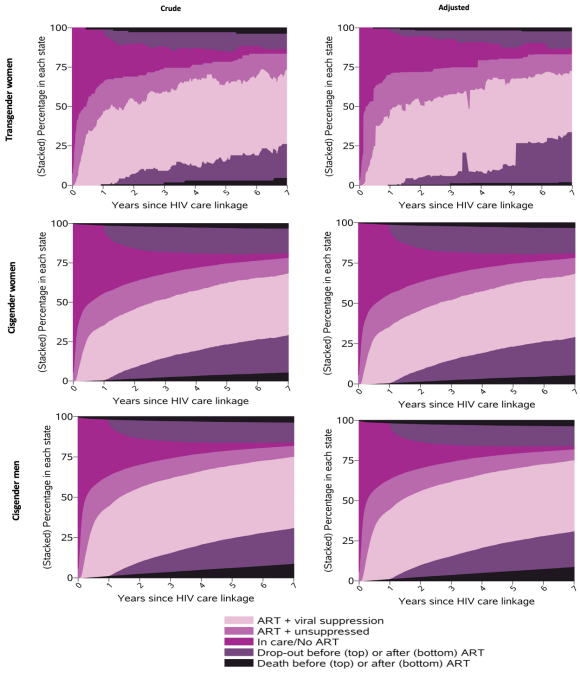
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Background: Transwomen (TW) are uniquely vulnerable to poor HIV control due to gender identity-related stigma and discrimination. Standard HIV care continuum estimates ignore how long people spend in each stage and may artificially inflate positive outcomes by excluding people who die.

Methods: We included antiretroviral therapy (ART)-naïve TW, ciswomen (CW) and cismen (CM) who engaged in care between 2000-2016 in 15 United States (US)-based NA-ACCORD cohorts that contributed data on transgender patients. We estimated the proportion of the cohort alive, engaged-in or lost-to-clinic, ART-initiated, and virally suppressed or not over the first 7 years in care. We summarized over time by reporting the average years over 7 years that each gender identity group spent in each stage. To do this, we added and subtracted series of cumulative incidence functions for death (from registry or medical record data); loss-to-clinic (12 months without a clinic visit, CD4 cell count, or viral load) and subsequent return-to-clinic; ART initiation; and viral suppression or loss of suppression after ART initiation. We report crude estimates and also adjusted for age, race/ethnicity, and calendar year. We report 95% confidence intervals (CI) around these estimates from 1000 non-parametric bootstrap resamples.

Results: We included 123 TW, 6979 CW, and 35751 CM. TW were younger (median age=30 years, vs. 39 and 40 years for CW and CM) and enrolled into care later during the study period (2009 vs. 2007 and 2007). Over the first 7 years in care, TW spent an average of 3.2 (95% CI: 2.7, 3.7) years virally suppressed after ART initiation, 1.1 (0.8, 1.4) years not virally suppressed after ART initiation (includes gaps in treatment, poor adherence, and virologic failure), 1.2 (0.9, 1.6) years in care prior to ART initiation, and 1.3 (0.7, 1.8) years lost-to-clinic, and they lost 0.3 (0.0, 0.6) years to death (figure). Compared with CW and CM, respectively, TW spent 0.7 (95% CI: 0.2, 1.2) and 0.2 (-0.3, 0.8) more years virally suppressed. After adjustment, differences between TW and CW and CM were generally smaller.

Conclusion: In several US clinics, longitudinal engagement in HIV care among TW was similar to that seen for CW and CM. Many of the HIV clinics in this analysis provide gender-affirming care; these results may not generalize to other contexts. Given the small sample of TW, further studies are recommended to explore other care outcomes in this highly vulnerable population.



883 HIV CARE AMONG TRANSGENDER WOMEN IN NORTHERN AND WESTERN PARIS: 2008-2018

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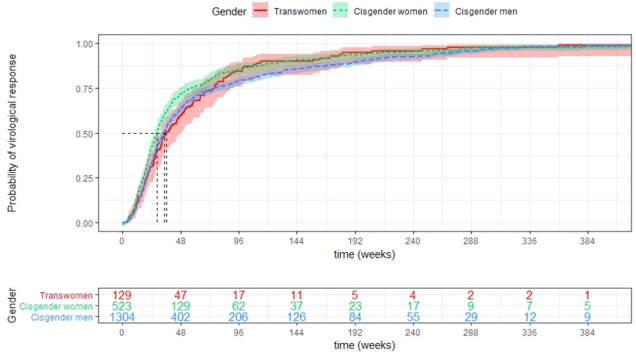
Background: HIV prevalence in Transwomen (TW) has been estimated at 19.1% worldwide with a risk of HIV infection 48.8- fold higher than adults of reproductive age (Confidence Interval 95% [21,2-76,3]). Few studies are however available on HIV care continuum in this population, with in addition discordant results. The objective of this study is to describe characteristics of this population and compare to cisgender men (CM) and cisgender women (CW) living with HIV.

Methods: This study was conducted in HIV-infected adults who began their follow-up between 2008 and 2018 in two HIV clinical cohorts, namely Ambroise Paré and Bichat-Claude Bernard Hospitals, in which sociodemographic, clinical, and immunovirological data were prospectively collected at each patient visit. We compared TW characteristics with CM and CW; in patients recently diagnosed (<6 months), we in addition compared, adherence to care and virological response (VR) defined by a viral load less than 50 copies/ml. Individuals were considered loss of follow-up when they did not attend clinical visits for 24 months. We estimated time of loss of follow-up and time of VR using survival analysis (survival curves with Kaplan Meier's method, Logrank method, and Cox's model).

Results: From 2008 to 2018, 456 TW began their follow-up for an HIV infection in the two Hospitals, 93.4% were from South-America (44% Peru, 34% Brazil). Age at diagnosis was lower in TW than CM (n = 2960) and CW (n = 1481) (mean 29.3 y vs 35.3 y and 33.6 y, respectively, p <0.01). Tuberculosis was responsible for 62.5% of AIDS cases among TW vs 25.5% and 35.5% for CM and CW, respectively. Patients recently diagnosed represented 28.9% of TW (132/456), 46.5% of CM (1375/2960) and 38.2% of CW (566/1481). Median baseline CD4 cell count was 399/mm$_3$, 390/mm$_3$ (p = 0.30) and 340/mm$_3$ (p = 0.01) in recently diagnosed TW, CM and CW. Median Time of VR was 35 weeks in TW (InterQuartile Range (IQR) [19-68]), 31 weeks in CM (IQR [19-57]; p= 0.32), and 27 weeks in CW (IQR [16-47]; p = 0.01) (Figure). Median time of loss of follow-up was 6 months in TW (IQR [2.3-31]), 10.5 months in CM (IQR [1.6-33.4]; p = 0.61), and 10 months in CW (IQR [1.6-29.5]; p = 0.73). Being a TW was not found to be independently associated with time of loss of follow-up or time of VR.

Conclusion: Our study highlights that TW are infected younger than other gender groups, but without lower CD4 cell count at initiation of care. They are not an increased risk of loss of follow-up or later VR than other groups.

Figure: probability of virological response over time stratified by gender (cumulative event curves by Kaplan Meier's method)



884 IMPROVING DATA ON THE NYC HIV EPIDEMIC BY IDENTIFYING TRANSGENDER PEOPLE ON MEDICAID

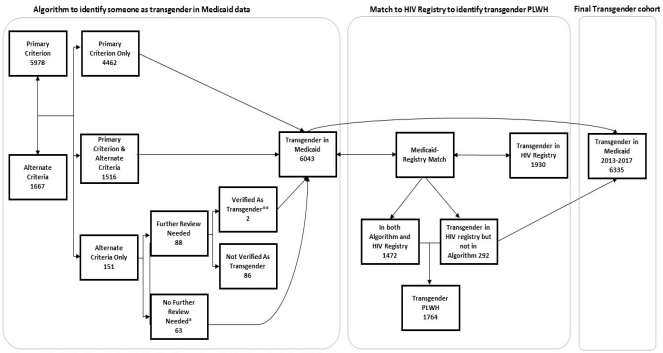
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Background: Since 2005, the New York City Department of Health and Mental Hygiene HIV Surveillance Program has ascertained transgender status among people living with HIV (PLWH) using data on sex assigned at birth and gender identity. Due to challenges in data availability, undercounting of transgender PLWH in NYC remains prevalent. In order to improve our ability to accurately enumerate transgender PLWH and address their needs for gender-affirming HIV care, we used claims data to identify transgender Medicaid enrollees and match these persons to the HIV registry.

Methods: Medicaid claims do not specify gender identity inclusive of transgender status. In consultation with clinical experts on HIV and gender-affirming care, we developed an algorithm to identify transgender enrollees using diagnoses, prescriptions and sex at birth from claims records in 2013-2017. In order to identify those living with HIV, we matched Medicaid enrollees to individuals diagnosed with HIV before 2018 in the registry.
Results: Our algorithm identified 6,043 unique transgender persons who accessed Medicaid in 2013-2017, with 1,472 (24%) reported to the HIV registry, 1,168 (79%) of whom were identified as transgender in the registry. We found an additional 292 transgender individuals in the registry that had accessed Medicaid during this period but were not identified by our algorithm, for a total of 6,335 transgender individuals accessing Medicaid during this period (0.1% of the NYC Medicaid population) and 1,764 transgender PLWH (28% of transgender individuals accessing Medicaid). From 2013 to 2017, there was a 35% increase in transgender individuals accessing Medicaid.
Conclusion: Using a novel method we identified a large sample of transgender individuals in Medicaid, many of whom were PLWH. We were able to calculate the prevalence of HIV among transgender Medicaid beneficiaries and to improve ascertainment of transgender persons in the HIV registry. We also saw a sizeable increase in transgender individuals accessing Medicaid over the five-year period, likely due in part to expansion of Medicaid policy to cover transgender-related healthcare. Given the high coverage among transgender PLWH, Medicaid is a valuable source of health information for the transgender population, a group that is often difficult to identify due to issues of stigma, reduced access to appropriate care, and misgendering by healthcare personnel.

Figure 1. Steps in an algorithm to identify transgender individuals in Medicaid claims data and a match with the HIV registry, New York City 2013-2017.



Primary criteria=Medicaid beneficiaries with at least one transgender-related ICD diagnosis code from 2013 to 2017.
Alternate Criteria=From 2013-2017, met at least 1 of 12 possible combinations of diagnoses, sex, and hormone therapy.
*Individuals did not need further review either because they met more than 1 alternate criterion or their combination of prescriptions was specific to therapy for transgender individuals.
**Individual review included a review of diagnoses and procedures to confirm that the person was transgender.
PLWH= people living with HIV

885 BUPRENORPHINE TREATMENT IS RELATED TO DECREASED HIV RNA LEVELS AMONG PEOPLE WITH HIV

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Background: Initiation of buprenorphine (BUP) for people with HIV (PWH) and opioid use disorder (OUD) may improve HIV clinical outcomes. We examined level of HIV RNA among PWH initiating BUP in an urban HIV clinic.
Methods: In the Johns Hopkins Hospital HIV Clinic Cohort (JHHCC), we identified 207 PWH who started buprenorphine treatment between 2002 and 2018. We allowed multiple number of treatment episodes (defined as continuous buprenorphine prescription with gaps less than 30 days). A quantile linear model was used to assess the relationship between buprenorphine (BUP) and viral load considering skewed distribution and the large proportion of individuals who were suppressed. We estimated quantiles with cluster bootstraps to account for repeated observations within participants. We included CD4 counts, sex, race, age, injection drug use, and men who have sex with men as covariates. Each individual contributed viral loads one year before and one year after their BUP initiation. We present difference in the 25th, 50th, and 75th percentiles comparing prior and subsequent to any episode of BUP treatment.
Results: The 207 PWH were primarily male (69%), black (88%), with median age of 49 (IQR: 44-53) at their initial BUP treatment. Individuals contributed a median of 1 (IQR:1-2) treatment episodes. HIV viral loads before and after initial treatment were a median of 80 (IQR: 50-6690) and 50 (IQR: 50-1721) copies/mL respectively. The figure shows a scatterplot and the unadjusted quantiles of HIV RNA as time prior to and subsequent to initial BUP treatment. In the model in which we considered time-varying treatment status, the estimated difference in the four quantiles comparing before and after treatment were 25th: 0 [95% CI: -4.675, 3.889], 50th: -43.94 [95% CI: -156.7, 1.208], and 75th: -4360 [95% CI: -10930, -195.8]. Approximately 74% of viral loads were below 1500 copies/mL (a meaningful cutoff for the risk of HIV transmissibility) after the BUP treatment compared to 69% before treatment. Restriction to individuals who started BUP treatment after 2011 similarly suggested difference of viral loads in higher quantiles, but was limited in sample size (61).
Conclusion: These data suggest that BUP treatment for OUD among PWH is likely to have beneficial effects on HIV RNA. By increasing the proportion of PWH below 1500 copies/mL, it would lower the overall risk for HIV transmission.

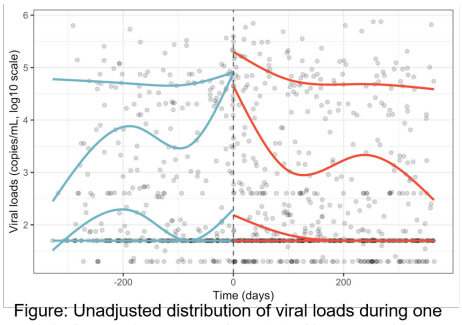


Figure: Unadjusted distribution of viral loads during one year before and one year after start of buprenorphine treatment. The four lines of each color represent 90, 75, 50, and 25th percentiles estimated by quantile regression

886 AFFORDABLE CARE ACT'S IMPACT ON SUBSTANCE-USE TREATMENT IN PEOPLE WHO INJECT DRUGS

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Background: Substance use treatment (SUT) for Persons Who Inject Drugs (PWID) can reduce the risk of HIV and HCV transmission, yet the lack of health insurance or insurance plans that cover these services is a major barrier to PWID entering SUT. Provisions in the U.S. Patient Protection and Affordable Care Act (ACA) were expected to increase the use of SUT in PWID by increasing access to health insurance and including these services as an essential health benefit.
Methods: We analyzed SUT use before and after the implementation of the ACA in California on January 1, 2014 among participants enrolled in STAHR-II (2012-2016)—a longitudinal cohort study of PWID in San Diego, California that included a baseline and up to 4 semi-annual follow-up interviews. We examined changes in self-reported SUT within participants pre- and post-ACA implementation. We included participants who had both a baseline visit and a follow-up visit before and after the implementation of the ACA in California. We excluded visits with referent time periods that overlapped with the ACA implementation date.
In bivariate analysis, we used McNemar's test for paired comparisons to determine the association between the ACA and SUT, as well as potential confounders. We used multivariable logistic regression analysis with Generalized Estimation Equations (GEE) for repeated measures to assess the association between the ACA and SUT, adjusting for baseline covariates: age, sex, race, education, HIV, HCV, chronic disease, prior SUT use, past 6-month daily injection, past 6-month homelessness, perceived need for SUT. Insurance status was a time-updated covariate.
Results: Of 170 participants who had both baseline visit and a follow-up visits before and after the implementation of the ACA in California, 71% were male, 50% were White and mean age was 45 years. There was an 11.8% increase in SUT use after the ACA, compared to before (52.4% vs. 40.6%, p=0.01) and a 10.6% increase in the proportion who had insurance after the ACA compared to before (81.2% vs. 70.6%, p<0.01). The positive impact of the ACA on SUT remained after adjusting for age, race, ever using SUT, perceived need for SUT, and insurance status (AOR: 1.85, 95%CI: 1.25-2.76).
Conclusion: Implementation of the ACA in California was associated with an increase in SUT use among PWID in San Diego, suggesting that the ACA successfully achieved the objective of increasing access to SUT.

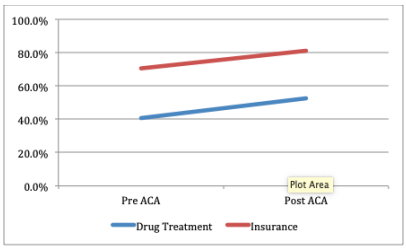


Figure 1. Proportion of PWID in a San Diego, California cohort who reported drug treatment use in the past 6 months and who had insurance in the past 6 months, prior to and after the implementation of the Affordable Care Act.

887 UNMET NEED FOR MEDICATION-ASSISTED TREATMENT AMONG PERSONS WHO INJECT DRUGS

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Background: Persons who inject drugs (PWID) are at increased risk of HIV and hepatitis C virus (HCV) infections and premature mortality due to drug overdose. Medication-assisted treatment (MAT) reduces high-risk injecting behaviors, HIV and HCV transmission, and mortality from opioid overdose among PWID with opioid use disorder. Using data from National HIV Behavioral Surveillance (NHBS), we evaluated self-reported unmet need for MAT among PWID in 23 US cities in 2018.

Methods: PWID were recruited by respondent-driven sampling in 2018 and interviewed. This analysis includes PWID who reported injecting drugs in the past 12 months, were 18 years or older and reported opioid use (including heroin) in the past 12 months. Unmet need for MAT was measured by asking participants if they tried to get methadone or buprenorphine to treat drug use but were unable to in the past 12 months. We used log-linked Poisson regression with generalized estimating equations to examine the association between self-reported unmet need for MAT and high-risk injecting practices and nonfatal opioid overdose. Models were adjusted for complex survey design and for confounding for age, race/ethnicity, city of residence, peer network size, current homelessness, having health insurance and being enrolled in MAT in the past year; we obtained adjusted prevalence ratios (aPR) and 95% confidence intervals (CI).

Results: Of 10,965 PWID who reported opioid use in the past 12 months, 30% were female, and the median age was 44 years. In total, 28% of PWID reported unmet need for MAT in the past 12 months, and 82% of those reported visiting a health care provider in the previous year. After adjusting for confounding, PWID who reported unmet need for MAT were more likely to report injecting more than once a day (aPR 1.09, 95% CI: 1.07-1.12), receptive sharing of syringes (aPR 1.11, 95% CI: 1.04-1.19) and opioid overdose (aPR 1.33, 95% CI: 1.24-1.43) in the past 12 months.

Conclusion: More than 1 in 4 PWID reported unmet need for MAT and more than 80% of those had seen a health care provider in the past 12 months. PWID with reported unmet need for MAT were more likely to report high-risk injecting behaviors and experiencing opioid overdose. These findings highlight a missed opportunity for enrolling PWID on MAT as part of a comprehensive prevention approach to reduce the risk of HIV and HCV transmission and opioid overdose among PWID. Health care providers engaging with PWID could be an important source for linkage to MAT.

888 UNMET NEEDS AND BARRIERS TO CARE SERVICES AMONG HIV-POSITIVE PERSONS WHO INJECT DRUGS

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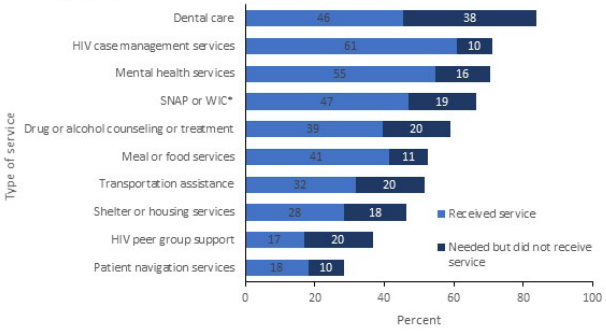
Background: HIV-positive persons who inject drugs (PWID) have poorer clinical outcomes compared with other persons, and limited access to medical care services may be a contributing factor. Data on use of and barriers to services can inform interventions intended to improve access to care but estimates are lacking. We report nationally representative estimates on use of, need for, and barriers to services among HIV-positive PWID.

Methods: We used data from the Medical Monitoring Project, a national surveillance system that reports representative estimates of characteristics among adults with diagnosed HIV. During 6/2015–5/2018, interviews were conducted to assess injection drug use, use of and need for services, and barriers to care in the past 12 months. Among persons who injected drugs during the prior 12 months (n=340), we reported the percent who received certain services and percent of persons who needed, but did not receive those services during the past 12 months (i.e., experienced unmet need). Of those with unmet needs, we reported barriers to care for each service. We reported weighted percents to account for complex survey design.

Results: Of adults with diagnosed HIV, 3% injected drugs in the past 12 months. Almost all (99%) HIV-positive PWID received ≥1 service; most commonly used services included those for HIV case management (61%) and mental health (55%) (Figure). Forty percent received drug/alcohol treatment. Overall, 79% had an unmet need for ≥1 service. The services with the highest unmet need were for dental care (38%), drug/alcohol treatment (20%), transportation assistance (20%), and HIV peer group support (20%). Of those with unmet needs, 46% of persons needing dental care did not seek services because they could not pay for services; 79% of those needing drug/alcohol treatment did not seek services due to personal reasons, such as fear or embarrassment; 53% of those needing transportation assistance did not have information on services; 57% of those needing HIV peer group support also did not seek services due to personal reasons.

Conclusion: Almost all HIV-positive PWID received ≥1 medical service, but a substantial proportion had unmet needs, including for drug/alcohol treatment. Barriers to care varied by service type. Addressing barriers to receiving services, including for drug/alcohol treatment, may help improve ART adherence and viral suppression among HIV-positive PWID.

Figure. Use of, and need for, medical care services among HIV-positive persons who inject drugs—Medical Monitoring Project, 2015–2018.



*Supplemental Nutrition Assistance Program or the Special Supplemental Nutrition Program for Women, Infants, and Children

889 ESTIMATING HIV INCIDENCE AMONG PWID: POPULATION- AND FACILITY-BASED APPROACHES

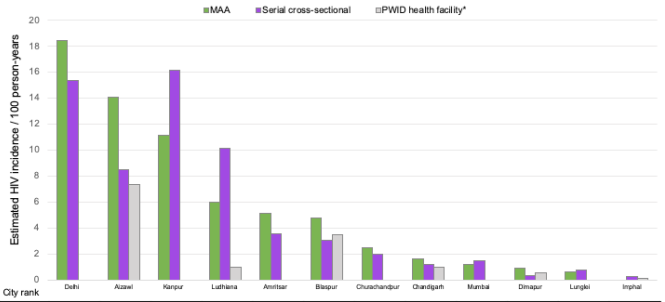
Allison M. McFall[1], Sunil S. Solomon[2], Oliver Laeyendecker[3], Syed Iqbal[4], Shanmugam Saravanan[4], Nandagopal Paneerselvam[4], Pachamuthu Balakrishnan[4], Aylur K. Srikrishnan[4], David D. Celentano[1], Gregory M. Lucas[2], Shruti H. Mehta[1]
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Background: Monitoring HIV incidence is vital for characterizing the epidemiology and trajectory of HIV epidemics and impacts of prevention efforts. Standard methods for measuring incidence such as cohort studies take considerable time and cost and are often not feasible in settings, leading to a reliance on new HIV diagnoses, inherently a biased measurement. We compare HIV incidence estimation using 3 different methods/data sources which might leverage available program data in a variety of settings.

Methods: We used data derived from a cluster-randomized trial among people who inject drugs from 12 Indian cities to estimate HIV incidence. First, we used a validated multi-assay algorithm (MAA) to define recent HIV infection within the trial's follow-up cross-sectional samples (Aug 2016-Apr 2017) accrued using respondent-driven sampling (RDS). Second, we estimated incidence from PWID that participated in two (confirmed via biometrics) cross-sectional RDS samples - baseline (Jan-Dec 2013) and follow-up (Aug 2016-Apr 2017) - and were serologically HIV negative at baseline. Third, we estimated incidence from initially HIV-negative PWID clients who received one or more repeat HIV tests at integrated care centers (ICCs) (Jun 2014-Feb 2017) in 6 of the 12 cities. The goal was to test clients every 6 months. ICCs also provided opioid agonist therapy and other PWID services (e.g., needle exchange).

Results: Across all cities, MAA-estimated incidence was generally highest, followed by the serial cross-sectional, with ICC estimates being substantially lower. MAA annual incidence ranged from 18.5% (New Delhi) to zero (Imphal), serial cross-sectional incidence from 16.1% (Kanpur) to 0.3% (Imphal), and ICC incidence from 7.3% (Aizawl) to 0.1% (Imphal). On average, the serial cross-sectional estimate was 19% lower than the MAA (range: -60% to +190%) and 20% higher than the ICC (range: -32% to +953%). While estimates were variable, rank order generally stayed the same across the estimates (Figure). Spearman rank correlation was 0.94 for the MAA-serial cross-sectional estimates, 0.83 for MAA-ICC, and 0.66 for serial cross-sectional-ICC estimates.
Conclusion: While HIV incidence estimates within a given city were variable by method, the rank order by incidence was consistent. While use of facility-based data will generally underestimate population incidence, using cross-sectional population-based data to estimate HIV incidence can prioritize where resources may optimally be directed.

Figure Estimated HIV incidence among PWID in 12 Indian cities by estimation approach



MAA	1	2	3	4	5	6	7	8	9	10	11	12
Serial CS	2	4	1	3	5	6	7	9	8	11	10	12
Facility*	-	1	-	4	-	2	-	3	-	5	-	6

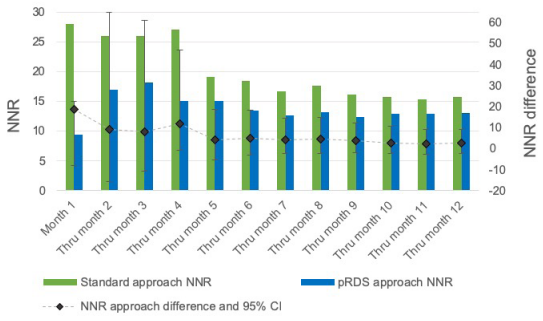
*Facilities in 6 of the 12 cities
PWID: people who inject drugs; MAA : multi-assay algorithm

890 OPTIMIZING SOCIAL-NETWORK SAMPLING TO FIND UNDIAGNOSED HIV-INFECTED PWID

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Background: People who inject drugs (PWID) experience high HIV burden and lag behind in UNAIDS 95-95-95 targets, particularly at diagnosis. We evaluated whether identification of undiagnosed HIV-infected PWID via respondent-driven sampling (RDS), a chain referral approach that leverages social networks, can be enhanced through a precision RDS (pRDS) approach.
Methods: We identified characteristics that predicted recruitment of an undiagnosed HIV-infected PWID using previously collected RDS data from PWID in north India. We developed a multivariable prediction algorithm comprised of factors identified by the area under the receiver operator curve from logistic regression models and a random forest. pRDS was tested in Morinda, Punjab where participants were randomly assigned (1:1) to standard or pRDS. In the standard approach, all participants received 2 coupons. For pRDS, an individual's probability of recruiting an undiagnosed PWID was determined by the algorithm and they received 2 (if low probability) or 5 (if high probability) coupons. The identification rate and number needed to recruit (NNR) - average number recruited in order to find one undiagnosed PWID - of each approach were compared.
Results: Predictors of recruiting an undiagnosed HIV-infected PWID included HIV/HCV infection, network size, use of syringe services, and the injection environment. Among 1631 PWID recruited in Morinda, HIV prevalence was 10%, of whom 70% were undiagnosed. From the standard approach, 615 were recruited including 39 who were undiagnosed; from pRDS, 1012 were recruited including 77 who were undiagnosed. pRDS had a significantly higher identification rate of undiagnosed PWID (1.5/week) compared to the standard (0.8/week; difference: 0.7, 95% CI: 0.3, 1.1). However, the NNR for pRDS (13.1) was not significantly lower than the standard coupon system (15.8; difference=2.6, 95% CI: -2.6, 10.0). NNR differences were more substantial in the first four months but decreased over time (test for trend p-value=0.002) (Figure). Cost to identify one undiagnosed PWID was ~10 USD lower in the pRDS approach vs. the standard.
Conclusion: A precision RDS approach identified nearly twice as many undiagnosed PWID significantly faster than the standard. While the NNR was not lower in pRDS, given the importance of timely identification and linkage to antiretroviral therapy, pRDS may be particularly useful in outbreaks when rapidly reaching undiagnosed people living with HIV is needed.

Figure NNR over months of recruitment, by recruiter's coupon system



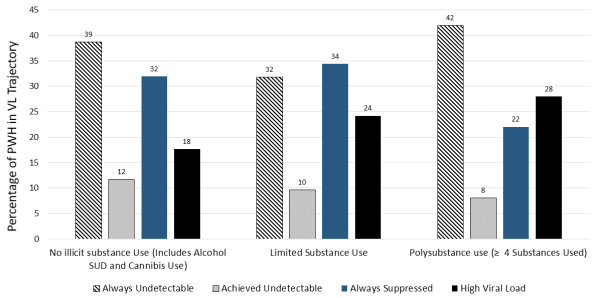
NNR: number needed to recruit one undiagnosed HIV-infected person who injects drugs; CI: confidence interval

891 LATENT CLASS ANALYSIS OF SUBSTANCE USE AND HIV VL TRAJECTORY PATTERNS AMONG PWH IN DC

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Background: People with HIV (PWH) with substance use disorders (SUD) have worse health outcomes than PWH without SUD. Our objective was to characterize substance use (SU) patterns and their impact on Viral Load (VL) trajectories among PWH.
Methods: Data from PWH aged >18 years enrolled Jan 2011-Mar 2018 in the DC Cohort, a longitudinal observational study of PWH in care at 14 clinics in Washington, DC, were analyzed. Data were abstracted from participants' electronic medical records. SU was defined as documented SU at DC Cohort enrollment and/or the presence of SU-related ICD9/10 codes during study follow-up. Treatments for alcohol and opioid use were also used to identify PWH receiving care for SU. Participants with least 3 VL were included in analysis. Latent class analysis (LCA) was used to determine classes with similar patterns of SU. HIV RNA values were examined using discrete mixture models to determine classes of group-based logVL trajectories and constructed using 3 VL measures. The number of classes for both SU patterns and VL trajectory were chosen using Bayesian Information Criterion, MLE, and maximized model fit. Differences in demographic and clinical characteristics between the SU classes were evaluated using a multivariable-adjusted multinomial model. The relationship between classes of SU patterns and classes of VL trajectories was examined using χ^2 test.
Results: 6,301 participants were assigned to one of three LCA SU classes based on posterior probability: (1) No illicit SU;(2) limited SU and (3) polysubstance use. There were 4 VL trajectory classes: (a) always undetectable; (b) achieved undetectable VL; (c) always VS; and (d) high VL. In multivariable models, individuals in both the polysubstance or limited SU classes were less likely to have private insurance (P<0.05), more likely to be current smokers (P<0.001,) and homeless (P<0.01) compared to the no illicit SU class after adjusting for cohort demographics. Polysubstance use participants were most likely to be categorized in the trajectory that did not achieve VS, followed by participants in the limited SU class (28% and 24% respectively; p-value <0.001). Proportions of participants in each trajectory are shown given membership in SU classes (Fig).
Conclusion: LCA identified distinct patterns of SU among PWH, with limited and polysubstance users having higher proportions of high VL trajectories. These results may guide planning of SU treatment especially for newly diagnosed PWH to improve their ability to achieve and sustain VS.

Fig. Conditional Probability of HIV RNA Trajectory, given Substance Use Class among PWH



892 MORTALITY AMONG PERSONS WITH HIV WITH A HISTORY OF INJECTION DRUG USE, NEW YORK CITY

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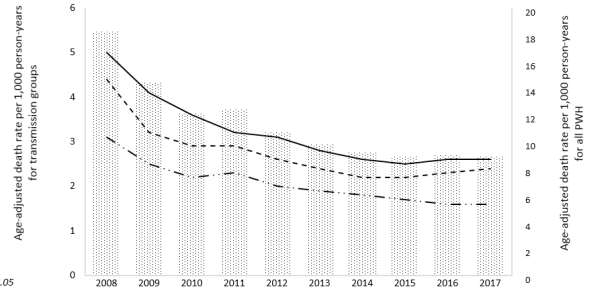
Background: Persons with HIV (PWH) who reported a history of injection drug use (IDU) have disproportionately higher mortality than those who did not report a history of IDU despite decreasing trends in all-cause mortality as well as new HIV diagnoses.

Methods: We used New York City (NYC) Surveillance data for PWH age ≥20 years and alive at end of 2017 or who died during 2008-2017, and data on underlying cause of death for decedents from the Vital Statistics Registry or National Death Index, to examine the characteristics, cause of death and age-standardized mortality rates of PWH with a history of IDU.

Results: There were 145,799 PWH included in the analysis, representing 1,192,752 person-years. Of these, 25,144 (17%) reported a history of IDU, of whom 6,733 (27%) died by the end of 2017. Although mortality rates decreased substantially among NYC PWH overall and among all transmission risk groups during 2008-2017, the mortality rate was persistently higher among PWH with IDU history compared to PWH in other HIV transmission risk groups (Figure 1). Of decedents with IDU history, nearly nine out of ten were either non-Hispanic Black or Hispanic (88%), nearly half were age 50-59 years (44%; median age 55 (Interquartile range: 47-61)), and nearly two-thirds lived in high or very high poverty neighborhoods (62%). Of IDU PWH decedents, nearly two-thirds (60%) died from a non-HIV-related cause and 39% died from an HIV-related cause. The top causes of non-HIV-related deaths were cancer (n=976, 24%; liver and lung most common) and cardiovascular diseases (CVD) (n=946, 24%; ischemic heart disease and hypertensive heart disease most common). After adjusting for demographic factors, PWH with IDU history age 50-59 (hazard ratio (HR) 1.6, 95% CI 1.5-1.8), Hispanics (HR 1.5, 95% CI 1.4-1.7) and those living in high or very high poverty neighborhoods (HR 1.4, 95% CI 1.3-1.5) had higher risk of death.

Conclusion: Although it declined, mortality among NYC PWH with IDU history remained high during 2008-2017. Older IDU PWH, Hispanic IDU PWH and IDU PWH living in high poverty neighborhoods had elevated mortality risk. Since over a third of deaths were due to HIV, improvement in HIV outcomes in this population should reduce HIV-related mortality. Additionally, interventions are needed for IDU PWH to reduce the prevalence of factors such as smoking, high-risk sexual behaviors, and co-infections such as hepatitis C given their role in CVD- and cancer-related mortality.

Age-adjsuted death rates per 1,000 person-years among persons with HIV by trasnmission risk, NYC, 2008-2017



*p for trend <.05	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
PWH-All p=0.004*	18.2	14.4	12.1	12.4	10.7	9.8	9.2	8.9	9.0	8.9
PWH-IDU p<.0001*	5.0	4.1	3.6	3.2	3.1	2.8	2.6	2.5	2.6	2.6
PWH-Hetero p<.0001*	4.4	3.2	2.9	2.9	2.6	2.4	2.2	2.2	2.3	2.4
PWH-MSM p<.0001*	3.1	2.5	2.2	2.3	2.0	1.9	1.8	1.7	1.6	1.6

HIV - human immunodeficiency virus, PWH - persons with HIV, IDU - injection drug use, Hetero - heterosexual contact, MSM - men having sex with men.

893 HCV, AIDS, LIVING IN US SOUTH ARE RISK FACTORS FOR MORTALITY IN HIV+ SUBSTANCE USERS

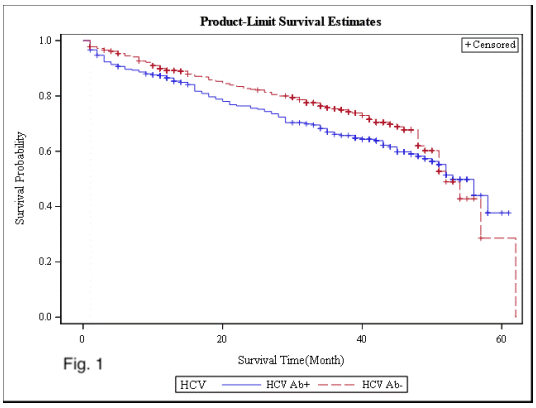
Mamta K. Jain[1], Mark A. Vasquez[1], Lauren Gooden[2], Rui Duan[3], C. Mindy Nelson[3], Daniel J. Feaster[3], Ank E. Nijhawan[1], Jonathan Colasanti[4], Meg Sullivan[5], Allan Rodriguez[3], Gerogina Osorio[6], Robrina Walker[1], Petra Jacobs[7], Carlos del Rio[4], Lisa R. Metsch[2]
[1]University of Texas Southwestern, Dallas, TX, USA, [2]Columbia University, New York, NY, USA, [3]University of Miami, Miami, FL, USA, [4]Emory University, Atlanta, GA, USA, [5]Boston University, Boston, MA, USA, [6]Icahn School of Medicine at Mt Sinai, New York, NY, USA, [7]NIH, Bethesda, MD, USA

Background: Hospitalized HIV substance users were enrolled into Project HOPE to evaluate the effect of patient navigation (PN) vs. PN with financial incentives vs. usual care on HIV viral suppression. Those who provided consent for future contact were invited to participate in a follow-up study to evaluate hepatitis C virus (HCV) infection and the impact of care facilitation vs. usual care on progression along the HCV care continuum. We examined overall mortality and predictors of death which occurred during the primary study and through the end of the follow-up study.

Methods: Retrospective cohort study conducted among 801 HIV-infected participants enrolled in Project HOPE between July 2012 and January 2014; they were followed for a maximum of 62 months. Kaplan-Meier estimates with a Renyi type test were used for the survival curves and an Accelerated Failure Time (AFT) model assuming a log logistic distribution was used to examine predictors of all-cause mortality.

Results: Participants were 33% women, 73% black, 59% lived in the South, 40% had <high school education, average age was 44.6±10 years, and 38% were HCV coinfected. Overall, 243 (30%) died during follow-up. Estimated median survival time was 54 months (95%CI 52-58). Participants with HCV had worse survival time with a slight reversal at the end of the survival curves (Fig.1; Renyi test statistic=3.58, p=<.001). In the multivariate AFT model, Project HOPE randomization group, baseline age, race, gender, education, HCV, low CD4 count (CD4 <200), active drug use, homelessness, health insurance and living in the South were included. Participants with HCV, low CD4 count and living in the South had worse survival time. Average survival time for participants with HCV was 27% lower than those without (p=0.049), with low CD4 count was 40% lower than those with higher CD4 count (p=0.002), and for those located in the South was 38% lower than those not in the South (p=0.002).

Conclusion: One out of three HIV substance users died over a 5-year follow-up. HCV, having AIDS, and living in the South significantly increased the risk of death. Inadequate access and fragmented care, often seen in the South, may decrease survival in HIV substance users. To achieve End the Epidemic goals, new strategies are needed to improve the care process for this population.



894 HIGH MORTALITY RATE AMONGST HIV INFECTED PEOPLE WHO INJECT DRUGS (PWID) IN SCOTLAND

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Background: Globally almost 18% of people who inject drugs (PWID) are living with HIV and HIV related mortality has decreased over time, with availability of antiretroviral therapy (ART). Non-AIDS mortality in high income settings is estimated at 2.34 per 100 person years (1.80-2.89) and drug-related death

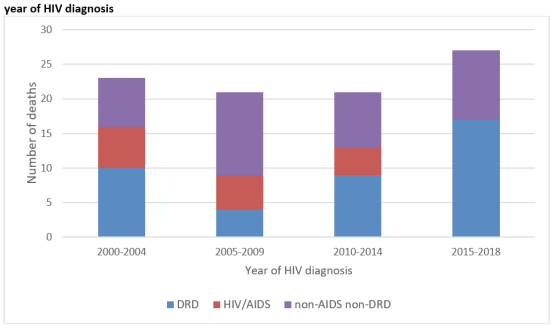
(DRD) is the leading cause of death amongst PWID. DRD in Scotland, a high income country, were reported at the highest on record in 2018. Amongst PWID in Scotland, the HIV prevalence is estimated at 2.3%, a recent increase explained by an outbreak in Glasgow. We sought to retrospectively evaluate the non-AIDS crude mortality rate (CMR), amongst PWID diagnosed with HIV in Scotland, and examine causes of death, over time.

Methods: A retrospective cohort review of all patients diagnosed with HIV, with injecting drug use identified as the transmission risk factor, between 1st January 2000 and 31st December 2018, with follow up until 30th June 2019, identifying those who died. Data was collated on basic demographics, virological markers, cause of death and time from HIV diagnosis to death. The main outcome measure was the all-cause crude mortality rate (CMR) and primary cause of death over time. Drug-related mortality was defined as per the National Records of Scotland definition.

Results: 413 PWID were diagnosed with HIV in the study period. 32% (133/413) were female. Mean age at diagnosis increased over time from 33 years (diagnosed 2000-04) to 39 years (diagnosed 2015-18). Until 30th June 2019, 22% (92/413) of these had died. Mean age of death was 42 years with no change over time. The non-AIDS CMR (per 100 PYFU) was 6.96 in those diagnosed from 2015-2018. The cause of death by year of HIV diagnosis are shown in figure 1; death from HIV/AIDs decreased from 61% (14/23) in those diagnosed 2000-2004 to 0% in those diagnosed from 2015-2018. DRD increased from 43% (10/23) to 63% (17/27) for the same groups.

Conclusion: Mortality amongst PWID living with HIV in Scotland is increasing over time and non-AIDS CMR is now higher than previously reported PWID living with HIV. HIV/AIDS is no longer a cause of death in this cohort and DRD are increasing, despite extensive, free to access, addiction and recovery services. To tackle the rising mortality rate, alongside high quality HIV care this cohort require novel interventions including heroin assisted treatment and highlight the case for safer drug consumption facilities.

Figure 1. Primary cause of death (AIDS related, drug related death and Non-AIDS non-drug related death) by year of HIV diagnosis



895 ASSOCIATIONS OF ALCOHOL CONSUMPTION WITH VIRAL SUPPRESSION AND ALL-CAUSE MORTALITY

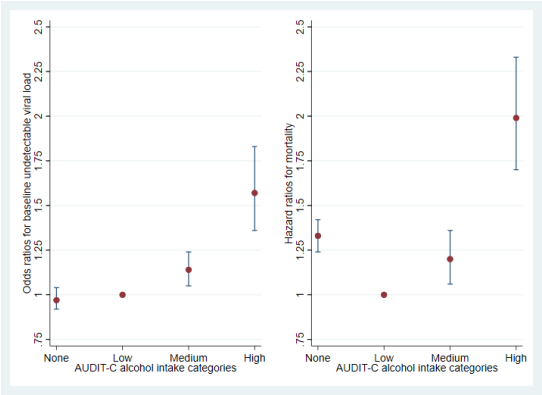
Adam Trickey[1], Suzanne Ingle[1], Lei Zhang[1], Mario Sarcletti[2], Matthias Cavassini[3], Michael Saag[4], Heidi M. Crane[5], Derek Satre[6], Michael J. Silverberg[6], Amy C. Justice[7], Jonathan Sterne[1], for the ART-CC and the COMpAAS consortium
[1]University of Bristol, Bristol, UK, [2]Innsbruck Medical University, Innsbrusk, Austria, [3]Lausanne University Hospital, Lausanne, Switzerland, [4]University of Alabama at Birmingham, Birmingham, AL, USA, [5]University of Washington, Seattle, WA, USA, [6]Kaiser Permanente Division of Research, Oakland, CA, USA, [7]Yale University, New Haven, CT, USA

Background: Unhealthy alcohol use may lead to higher morbidity and mortality among people living with HIV (PLHIV), either directly or by influencing the success of antiretroviral therapy (ART). We investigated associations of alcohol intake with viral suppression and all-cause mortality.

Methods: We assembled data from 5 cohorts participating in the Antiretroviral Therapy Cohort Collaboration that provided AUDIT-C alcohol measures (categorised as no drinking and low [reference group], medium and high intake). Eligible PLHIV were aged ≥16 years and started ART 1996-2018. The date of AUDIT-C measure after ART start was taken as baseline, with follow up censored at the first of loss to follow-up or death. We used logistic regression to estimate adjusted odds ratios (aOR) for detectable viral load at baseline and Cox models (stratified by cohort) to estimate adjusted hazard ratios (aHR) for virological failure among those with undetectable baseline viral load (censoring at 3 years after ART start) and for all-cause mortality. Models were adjusted for baseline CD4 count, age, gender and transmission risk group with mortality analyses additionally adjusted for baseline viral load.

Results: Of 33206 PLHIV, 4056 died during 183,683 person-years follow-up. 9,623 (28.7%) of PLHIV were non-drinkers, whilst 19,738 (58.9%), 3,320 (9.9%), and 857 (2.6%) had low, medium, and high alcohol intake, respectively. PLHIV with medium and high alcohol intake had higher odds of detectable viral load at baseline (aORs 1.14 [95%CI 1.05, 1.24] and 1.57 [1.36, 1.83], respectively) compared with low intake (figure). Medium- and high-drinkers had faster time to detectable viral load than those with low intake, aHRs 1.13 (1.02, 1.26) and 1.60 (1.35, 1.90), respectively. For mortality, aHRs compared with low intake were 1.33 (1.24, 1.42) for non-drinkers, 1.20 (1.06, 1.36) for medium intake, and 1.99 (1.70, 2.33) for high intake.

Conclusion: Among PLHIV, high or medium alcohol intake is associated with higher mortality than low intake. Higher mortality risk for non-drinkers is likely due to a "sick-quitter" effect. PLHIV with medium or high alcohol intake were more likely than those with low intake to have a detectable viral load at baseline. Interventions to reduce unhealthy alcohol use among PLHIV should be considered.



896 DEPRESSION AND VIROLOGIC REBOUND AMONG PATIENTS WITH HIV IN THE UNITED STATES

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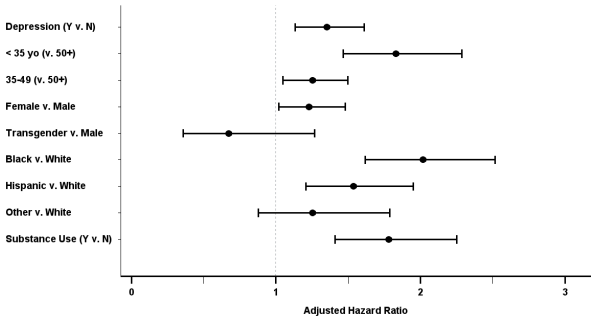
Background: The relationship between depression and HIV virologic rebound among persons with HIV has not been characterized. We analyzed nationally representative data from the Medical Monitoring Project (MMP) to examine the association between depression and virologic rebound among adults with diagnosed HIV in the United States.

Methods: We used data collected during 6/2015-5/2018 from MMP, a surveillance system that produces nationally representative estimates of behavioral and clinical characteristics among adults with diagnosed HIV. Demographic characteristics were collected through interview. Data on viral loads and diagnoses including clinical depression and substance use disorder were abstracted from medical records during the two years prior to interview. A total of 7133 patients who were prescribed antiretroviral therapy (ART), had an initial HIV RNA viral load [VL] level <50 copies/mL, and had at least 1 subsequent VL measure during 2 years of follow-up were included in the analysis (9232 person-years). We estimated weighted incidence rates of virologic rebound (defined as having a VL ≥200 copies/mL following viral suppression during follow-up) and used Cox proportional hazards modeling to estimate the association between depression and the time to first virologic rebound, adjusting for selected covariates and accounting for sample weights and design.

Results: Overall, 27% of patients had depression. The weighted incidence rate of virologic rebound was 9.2 per 100 person-years (95% confidence interval [CI] = 9.1-9.4) among patients with depression, and was 6.8 per 100 person-years (95% CI = 6.7-6.9) among patients without depression. In a multivariable Cox proportional hazards model that accounted for sample weights and design, and controlled for age group, gender, race/ethnicity, and diagnosis of substance use disorder, factors known to be associated with viral rebound, patients with depression had a significantly higher hazard of virologic rebound during follow-up, compared with patients without depression (adjusted hazard ratio = 1.35, 95% CI = 1.13-1.61, p <0.001; Figure).

Conclusion: Among US patients with HIV who achieved viral suppression to <50 copies/mL, those with depression had a 35% higher risk of virologic rebound compared with patients who had similar demographic and substance use characteristics without depression. Patients with HIV and depression may need closer monitoring and support to avoid virologic rebound.

Figure. Predictors of HIV virologic rebound* among adults with HIV who achieved viral suppression, United States, 2015-2018.



* Cox proportional hazards regression model included all variables in the figure and accounted for sample weights and design.

897 PREVALENCE AND FACTORS RELATED TO TRAUMA SYMPTOMS AMONG PEOPLE WITH HIV

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[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: Among persons with HIV (PWH), trauma symptoms (TS) are a barrier to achieving HIV control. We sought to determine factors associated with TS among PWH and the association of TS with viral suppression.
Methods: In the Johns Hopkins HIV Clinical Cohort (JHHCC) between 2013-2018, we measured trauma symptoms using the Primary Care Post Traumatic Stress Disorder Screen (PC-PTSD). We categorized TS as a PC-PTSD score ≥3. Prevalence of TS was examined by model based recursive partitioning allowing for repeated measures. Factors hypothesized to be associated with TS included age, race, depressive (PHQ-8≥5), anxiety symptoms (GAD-7≥5), cocaine, heroin, and hazardous alcohol. Logistic regression with generalized estimating equations was used to examine the association of TS with viral suppression. Models were stratified by gender.
Results: Our analytic sample included 666 cis-gender women (89% African American (AA), 30% IDU as risk factor for HIV acquisition, 65%<55 years old), and 1154 cis-gender men (78% AA, 33% IDU, 59%<55 years old). At baseline, prevalence of TS was 10.4% among women and 8% among men. PWH with TS at baseline had lower ART adherence (visual analogue scale<90 35 vs 17%, p<0.001), less viral suppression (56 vs. 76% p=0.1), more depression (88 vs. 39%, p<0.001), and anxiety (85 vs. 16%, p<0.001), and greater substance use (hazardous alcohol: 31 vs 17%; cocaine: 13 vs 4.4%; heroin: 20 vs. 8.3%, all p<0.001) compared to PWH without TS. Among women, the co-occurrence of anxiety and depressive symptoms was associated with an increased prevalence of TS reaching 41% (figure, node 5) TS compared to 1% (node 2) among those without anxiety irrespective of depressive symptoms. For men, the prevalence of TS among those with anxiety and depressive symptoms was 38% (node 9), followed by those without anxiety, but with co-occurring depressive symptoms and hazardous alcohol use (20%, node 6). Among both women and men, those with TS were had similar risk of being virally suppressed as compared to those without TS (women: risk difference= -11%, 95%CI: -27, 5; men: RD= -2%, 95%CI: -13, 7).
Conclusion: Overall prevalence of TS is high and related to other psychiatric comorbidities among PWH. Adding TS screening would significantly increase identification of overall psychiatric morbidity. While TS by itself was not related to non-suppression, it is likely that treatment of overall psychiatric morbidity together may potentially decrease the risk of viral non-suppression.

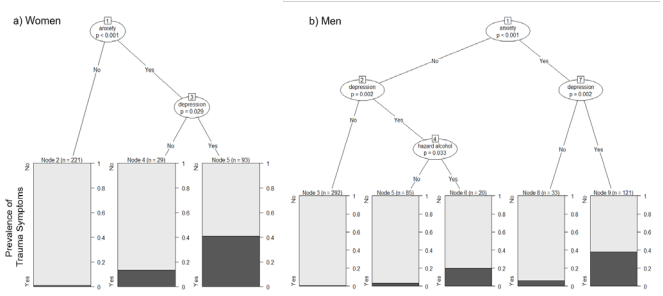
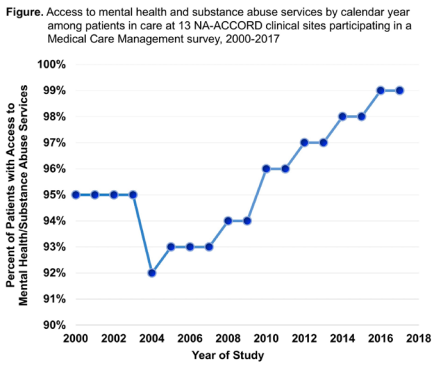


Figure: Prevalence of trauma symptoms among women and men according to model based recursive partitioning examining age, anxiety, depression, race, and substance use

898 MENTAL HEALTH AND SUBSTANCE ABUSE SERVICES AND RETENTION IN HIV CARE IN NORTH AMERICA

Cassandra Oliver[1], Bryan Lau[2], Keri N. Althoff[2], Kate Buchacz[3], Heidi M. Crane[4], Michael John Gill[5], Michael A. Horberg[6], Kenneth H. Mayer[7], Angel M. Mayor[8], Richard D. Moore[2], Asher Schranz[9], Timothy R. Sterling[1], April Pettit[1], Peter Rebeiro[1], for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA
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Background: Retention in care (RIC) is associated with reduced HIV transmission and mortality. Mental health and substance abuse services are associated with better RIC and uptake differs by sex, but few studies include diverse clinics or assess sex as an effect modifier. We quantified the association between availability of mental health and substance abuse services on-site or by referral and individual RIC within the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), assessing sex as an effect modifier.
Methods: Adults (≥18 years) with HIV who had ≥1 clinic visit at 13 NA-ACCORD sites in the US and Canada from 2000-2017 were included. Availability of mental health and substance abuse services were assessed by site survey in 2000, 2005, and 2010 and carried forward in other years. RIC was defined as ≥2 encounters per year, ≥90 days apart, recorded until death, administrative censoring (December 31, 2017), or loss to follow-up (no visit for >12 months with no future visits). Modified Poisson regression stratified by sex, clustered by site using generalized estimating equations, and adjusting for calendar year, age, race, and HIV risk factor, was used to estimate risk ratios (RR) with 95% confidence intervals (CI) for the association between clinic services and RIC. A Wald homogeneity test assessed sex as an effect modifier with α=0.20.
Results: Among 28,831 individuals contributing 205,937 person-years (p-y), 67% of p-y were spent in care. The median age was 44 years and males contributed 76% of p-y. Almost half were white (46%),44%black, non-Hispanic, and 4% Hispanic. The most common HIV transmission risk was MSM (52%), though 11% reported injection drug use as a risk factor. Overall, 97% of patients had access to mental health and substance abuse services for ≥1 year; availability increased over time, and 99% had access at these sites by 2017 (Figure). There was heterogeneity of effects by sex (p=0.05). Available mental health and substance abuse services were associated with better RIC among both males (RR=1.11; 95% CI: 1.07-1.14) and females (RR=1.05; 95% CI: 1.01-1.10).
Conclusion: Among patients receiving HIV care at NA-ACCORD clinical sites between 2000 and 2017, mental health and substance abuse services were associated with better individual RIC. These results may imply that mental health and substance abuse services themselves, or other services for which they are proxies, may enhance RIC in diverse settings, and males may benefit slightly more than females.



899 MORTALITY IN PEOPLE LIVING WITH HIV AND MENTAL HEALTH DISORDERS IN SOUTH AFRICA

Andreas D. Haas[1], Yann Ruffieux[1], Ernest Mokotoane[2], Johannes P. Mouton[2], Mpho Tlali[2], Mary-Ann Davies[2], Matthias Egger[1], Gary Maartens[2], for the IeDEA Southern Africa Collaboration

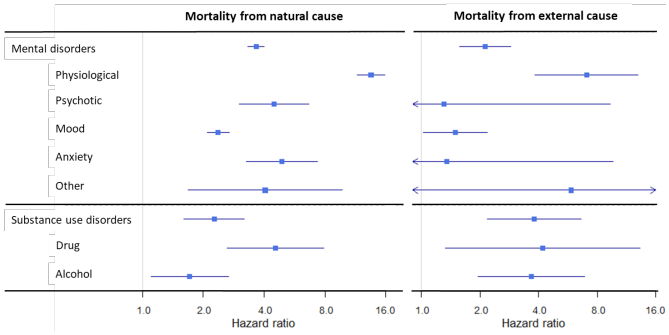
[1]University of Bern, Bern, Switzerland, [2]University of Cape Town, Cape Town, South Africa

Background: People with mental and substance use disorders (MSD) often die prematurely from suicide, accidents or chronic comorbidities. We quantified mortality from natural and external causes in people living with HIV and MSD enrolled in the Aid for AIDS (AfA) program in South Africa.

Methods: AfA is a large South African private sector HIV management program. AfA collects demographic, clinical and laboratory data. We linked the AfA data with mortality and cause of death information (natural vs. external cause) from the South African national population registry and with ICD-10 diagnoses from hospitalization records covering the period 2011-2018. We left-truncated ART records in 2011. HIV+ children and adults who initiated cART from 2001-2018 were followed for up to 15 years on ART. We estimated cumulative mortality using the Kaplan-Meier method. We calculated adjusted hazard ratios (aHR) for associations between MSD and mortality using Cox regression. HR were adjusted for age, gender, CD4 count at ART initiation and year of ART initiation.

Results: Out of 219,686 individuals who initiated ART, 9,527 (4.3%) were admitted for an MSD for a median duration of 7 days (IQR 4-14). The cumulative mortality from natural and external causes 15 year after ART initiation was 15.5% (95%CI 14.9-16.1) and 2.3% (CI 2.1-2.6), respectively. The Figure shows aHRs and 95% CIs comparing mortality in ART patients with and without MSD. AHRs for mortality from natural causes were 3.65 (CI 3.33-4.01) for people with mental disorders and 2.27 (CI 1.61-3.20) for people with substance use disorders. AHRs for mortality from external causes were 2.13 (CI 1.57-2.89) for people with mental disorders and 3.79 (CI 2.18-6.59) for people with substance use disorders. Individuals with mental disorders due to organic causes (e.g. dementia) had the largest increase in risk of mortality from natural 13.52 (CI 11.57-15.80) and external 7.04 (CI 3.83-12.94) cause. The risk of mortality from natural causes was about four times higher for people with psychotic, anxiety, other psychiatric disorder, or drug use disorder, and about double for people with mood or alcohol use disorders, compared to people without those disorders.

Conclusion: Excess mortality of people with MSD is a major public health concern that warrants action. Differentiated care models that account for the special needs of people living with HIV and MSD might be a promising approach to reduce excess mortality in this vulnerable population.



900 COMPARING METHODS FOR ESTIMATING SEXUAL TRANSMISSION RISK AMONG US ADULTS WITH HIV

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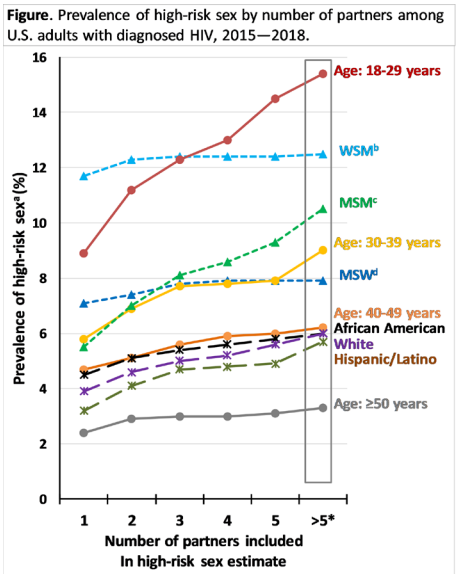
[1]CDC, Atlanta, GA, USA

Background: An accurate assessment of sexual risk behaviors associated with HIV transmission is important for informing the Ending the HIV Epidemic (EHE) initiative. The Medical Monitoring Project (MMP) produces nationally representative estimates for high-risk sex using information from all past year partnerships. To potentially reduce data collection burden, we explored whether most recent sexual partner data was enough to accurately assess high-risk sex among adults with diagnosed HIV.

Methods: MMP staff interviewed adults with diagnosed HIV to collect information on demographic characteristics and sexual behaviors with the last 5 partnerships during the past 12 months (P12M); for those with >5 partners, aggregated information on sexual behaviors with additional partners was also collected. Viral load results were abstracted from medical records. Using weighted data collected 6/2015—5/2018 (n=11,914), we estimated the prevalence of high-risk sex, defined as 1) having ≥1 detectable viral load (≥200 copies/mL) over P12M and 2) having condomless anal or vaginal sex with an HIV-negative or HIV-unknown partner not reported to be using pre-exposure prophylaxis (PrEP). We reported the incremental contributions of each sexual partner to the measure, and compared prevalence of high-risk sex overall and by age, race/ethnicity, and sexual behaviors using data from the most recent partner compared with all partners.

Results: Of adults with diagnosed HIV, 58% had anal or vaginal sex in P12M, of whom 44% reported >1 partner and 12% reported >5 partners. A higher percentage of men who had sex with men (MSM), whites, and people aged 18-29 reported having multiple partners. The prevalence of high-risk sex was 6% overall, 11% among MSM, 13% among women who had sex with men, and 15% among persons aged 18-29. Estimates of high-risk sex were lower when information of the last partner only vs. all partners was assessed (4% using last partner vs. 6% using all partners), particularly for MSM (6% vs. 11%), persons aged 18-29 (9% vs. 15%), and Hispanics/Latinos (3% vs. 6%) (Figure).

Conclusion: Estimates of high-risk sex using last partnership were not adequate to accurately describe the prevalence of HIV transmission risk—particularly for groups highly affected by HIV, such as MSM and young adults. Using information on all sexual partners may be helpful to identify key populations in need of additional support for HIV prevention and can help inform EHE initiative activities.



901 USING SURVEILLANCE DATA TO MEASURE TRIAL HIV INCIDENCE OUTCOMES: A MODELLING STUDY

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Background: Cluster-randomized trials (C-RCTs) are expensive to conduct. Using surveillance data on new HIV diagnoses instead of measuring incidence in the trial could reduce costs. We used mathematical models to evaluate when surveillance data can be used to estimate impact in HIV intervention C-RCTs.
Methods: We used a model of HIV transmission among men who have sex with men in Baltimore, US, to simulate C-RCTs scaling up antiretroviral therapy (ART), pre-exposure prophylaxis (PrEP) and HIV testing in combination or alone. We tested whether modelled reductions in total cumulative HIV diagnoses predict model cumulative HIV incidence reduction over a 2-year trial. We also tested if reductions in diagnoses predict incidence reduction better over a longer trial duration (≤4 yrs) or when measured in later trial years. We explored if reductions in other surveillance measures – diagnoses with acute infection, diagnoses with early (CD4>500 cells/μl) infection, or diagnoses adjusted for testing volume – better predict incidence reduction. We used Pearson correlation to assess precision and report bias and sensitivity to detect a true incidence reduction.
Results: Over a 2-year trial expanding ART+PrEP+testing, model results suggest total diagnosis reductions correlate poorly with incidence reduction(r=0.386), underestimate incidence reduction (by 97%), and have 52% sensitivity (Table). Precision and sensitivity were better in trials expanding ART(r=0.878; sens 100%) or PrEP(r=0.960; sens 88%) alone, but bias remained (-52% for ART, -55% for PrEP). In trials expanding testing alone, diagnoses increased with decreasing incidence(r=-0.915). Measuring impact in longer trials or over later years improved correlations between diagnosis and incidence reductions for trials expanding ART+PrEP+testing, up to r=0.795 over the 4th year, and reduced bias. For ART+PrEP+testing trials, reductions in acute, early or adjusted diagnoses correlate poorly(r<0.51) with incidence reduction. Reductions in acute or early diagnoses correlate sufficiently with incidence reduction only when ART alone is expanded(r=0.993, r=0.953, respectively), but are biased (-18%, -41%).
Conclusion: Modelling results suggest that surveillance diagnoses data can only rarely be used to estimate C-RCT HIV incidence reductions. Reductions in acute/early or total diagnoses may be adequate predictors in C-RCTs expanding ART or PrEP alone if bias can be adjusted for. None of the diagnoses markers explored were appropriate for C-RCTs expanding HIV testing.

Table: Characteristics of the relationship between different surveillance markers and reductions in HIV incidence over a 2-year trial, across 1014 simulated intervention scenarios.

Intervention	Outcome measure	Correlation with incidence reduction[a]	Relative bias in estimate[b]: median	Sensitivity to detect incidence reduction[c]
ART+PrEP+HIV testing	Total diagnoses	0.386	-97%	52%
	Acute diagnoses	0.497	-84%	55%
	Early diagnoses	0.423	-92%	53%
	Adjusted diagnoses	0.506	12%	100%
ART	Total diagnoses	0.878	-52%	100%
	Acute diagnoses	0.993	-18%	100%
	Early diagnoses	0.953	-41%	100%
	Adjusted diagnoses	0.882	-52%	100%
PrEP	Total diagnoses	0.960	-55%	88%
	Acute diagnoses	0.814	-24%	76%
	Early diagnoses	0.927	-43%	85%
	Adjusted diagnoses	0.934	87%	100%

[a]Pearson's correlation coefficient. [b]Reduction in diagnoses subtracted from reduction in infections, then divided by reduction in infections. [c]Proportion of intervention scenarios where reduction in diagnoses seen.

902 PAST BEHAVIOR OUTPERFORMS DEMOGRAPHY AND GEOGRAPHY AS PREDICTOR OF MISSED HIV CARE

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Background: Missed HIV care provider visits are associated with increased mortality beyond the core indicators of retention in care and are an immediately actionable event. Previous prediction models for missed visits have not incorporated data beyond the individual level.
Methods: We developed prediction models for missed HIV care provider visits among adult people living with HIV (PLWH) with ≥1 visit in the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) from 2010-2016. Potential predictors were identified at the individual-, community-, and structural-levels. Individual-level data included demographics, patient-reported outcomes (tobacco use, AUDIT-C, patient health questionnaire-9, EuroQOL Health Related Quality of Life-5D, HIV symptom index), insurance type, and prior visit adherence. Community-level data were obtained from the American Community Survey using ZIP Code tabulation area of residence. Structural-level data included HIV criminalization laws, Medicaid expansion, and proportion of budget dedicated to AIDS Drug Assistance Programs by state of residence. Variables were selected and models fit using random forests and 10-fold cross-validation; candidate models with highest area under the curve (AUC) were identified.
Results: Data from 382,548 HIV care provider visits among 20,889 PLWH followed for a median of 3.7 years were included. Median age was 44 years, 81% were male, 37% were Black non-Hispanic, and 57% reported male-to-male sexual contact as HIV transmission risk factor. Prior visit adherence improved discrimination most in all models; AUC jumped from 0.68 to 0.75 with its addition alone in one candidate model. The highest AUC was 0.75 (Table); the strongest predictors in this model were prior visit adherence, follow-up time, age, and CD4+ count at the individual-level, along with proportion with Black race, proportion unemployed, and proportion living below the poverty line at the community-level.
Conclusion: Prediction models validated using multi-level data in a population representative of US PLWH had a similar AUC to previous models developed using only individual-level data. Strongest predictors were individual-level variables, particularly prior visit adherence, though community-level variables were also predictive. Absent additional behavioral, social, structural, or clinical data, PLWH with previous visits should be targeted by interventions to improve visit adherence.

Table. Candidate predictive models and discriminatory ability (area under the receiver operating characteristic curve, or AUC) for missed HIV care visits, constructed using random forests and 10-fold cross validation, among CNICS cohort participants, 2010-2016

Description of Variables Included in Model	AUC	Sample Size*
All data included	0.73	183,888
Patient-reported outcomes data excluded	0.75	382,548
Only patient-reported outcomes data included	0.55	183,888
Patient reported outcomes and prior adherence data excluded	0.68	382,548

*Patient-reported outcomes data were only available for 183,888 of 382,548 (48%) visits.

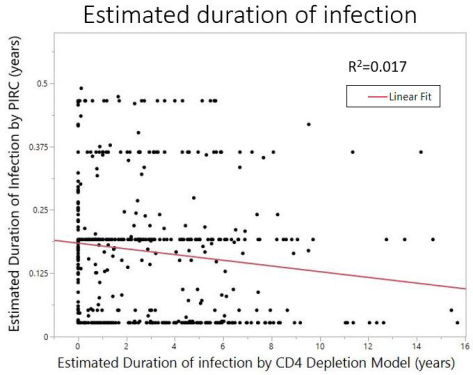
903 THE CD4 DEPLETION MODEL DOES NOT DIFFERENTIATE INCIDENT FROM CHRONIC INFECTION

Michael E. Tang[1], Sanjay R. Mehta[1], Susan J. Little[1], Christy M. Anderson[1]
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Background: The Ending the HIV Epidemic (EtHE) initiative targets a 75% decline in HIV incidence in 5 years and a 90% decline in 10 years. Available estimates for U.S. population incidence are derived from a CD4 depletion model developed by investigators at the Center for Disease Control. We evaluated this model in a cohort with well characterized estimated dates of incident infection.
Methods: We evaluated 702 antiretroviral (ART)-naïve, newly HIV-1 diagnosed individuals with acute and early HIV infection enrolled to the San Diego Primary Infection Resource Consortium (PIRC) between June 1996 and July 2019. Clinical data, including CD4 counts were collected at baseline (Day 0), weeks 4, 12, 24, and every 24 weeks thereafter. Persons with acute infection (antibody neg/HIV nucleic acid test pos) had additional CD4 and VL measures at weeks 2 and 8. We calculated an estimated date of infection (EDI) using previously characterized serologic and virologic criteria. We compared this PIRC EDI with the EDI generated by the CD4 model.
Results: Of the 702 newly HIV diagnosed individuals (age 16-71), 234 (33.3%) were diagnosed during acute infection, 468 (66.7%) during recent infection; 90.8% estimated by limiting-antigen (LAg) avidity assay in combination with viral load information (PIRC EDI model) and 9.2% by interval HIV seroconversion

(documented negative HIV serology in prior year). The PIRC EDI was weakly correlated with the CD4 model EDI (R2 = 0.017) (Figure). Among the 159 (23%) PIRC participants with follow-up CD4 data for ≥1 year prior to starting ART, we also used the pre-ART CD4 to calculate the CD4 model EDI (i.e., sampled during chronic infection). The pre-ART CD4 EDI also was weakly correlated with the PIRC EDI (R2=0.00058). When using the PIRC EDI as the gold standard, the sensitivity of the CD4 model was 51% (95% CI 47%-55%) and specificity was 60% (95% CI 52%-67%).

Conclusion: The CD4 depletion model did not correctly identify persons with incident infection and did not differentiate persons with incident and chronic infections. The CD4 depletion model is not an appropriate model for monitoring incidence trends among smaller sample sizes, such are likely to be represented within the highest burden EtHE jurisdictions. Alternative strategies are needed, including scale-up of objective measures of HIV incidence, to measure the primary outcome of the EtHE initiative.



904 ESTIMATING INCIDENCE AT A REGIONAL LEVEL WITH THE CD4 DEPLETION MODEL

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Background: The Ending the HIV Epidemic (EtHE) initiative targets a 75% decline in HIV incidence in 5 years and a 90% decline in 10 years. Currently HIV incidence in the U.S are derived from the Center for Disease Control's CD4 depletion model. The EtHE initiative requires an understanding of HIV incidence at a regional and local level to evaluate the impact of prevention interventions. Here we examine the accuracy of the CD4 depletion model for measuring incidence in sub-epidemics.

Methods: Using the San Diego Primary Infection Resource Consortium estimated date of infection (PIRC EDI) model as a gold standard (a model that estimates recency using the limiting-antigen [LAg] avidity assay in combination with viral load information which has an estimated false recency rate of 1%), we found that the sensitivity of the CD4 model was 51% (95% CI 47%-55%) and specificity was 60% (95% CI 52%-67%) (see abstract 1291). We used this to calculate the predictive values of CD4 recency testing in various epidemic scenarios.

Results: Using the above estimates, we calculated the positive predictive value (PPV), negative predictive value (NPV), and the posterior odds (PO), for various proportions of incident infections, ranging from 5% to 50%, in a setting of 1000 newly diagnosed infections. For a test on a single individual, PPV ranged from 6.3% to 56.0%, NPV ranged from 95.9% to 55.1%, and PO from 0.67 to 1.28. Using a fixed proportion of 25% incident infections among all new diagnoses, we varied the size of the sampled population from 250 to 10,000 to evaluate the accuracy of the CD4 model in predicting the number of incident cases in different size epidemics. The estimated values were approximately 1.7 fold greater, ranging from 106.8 (95% CI 105.5 to 135.3) incident infections (true value 62.5) for a population of 250, to 4275 (95% CI 3850 to 4775) incident infections for a population of 10000 (true value 2500).

Conclusion: Although the CD4 model is not designed to predict if an infection is incident at an individual test level, the uncertainty in this test also impacts population scale estimates. As interventions to prevent HIV transmission are scaled up as part of the EtHE effort, we need more accurate estimates of incidence that can be applied at smaller population scales, so that we will be able to measure the impact of our outcomes.

905 KEY POPULATION SIZE ESTIMATION IN NIGERIA: NOVEL APPROACHES TO SAMPLING AND ANALYSIS

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Background: Nigeria has the fourth largest HIV burden globally. Key populations (KP), including female sex workers (FSW), men who have sex with men (MSM), and people who inject drugs (PWID), are more vulnerable to HIV than the general population owing to stigma and discrimination, and often have poor social visibility. Previous population size estimates (PSE) in Nigeria were based on programmatic mapping of hotspots with enumeration of KP at venues. The results failed to account for KP who were not present at venues, resulting in underestimates of population sizes that also lacked precision. Reliable PSE are needed to guide focused and appropriately scaled HIV epidemic response efforts for KP. We used novel approaches for sampling and analysis to calculate PSE in Nigeria.

Methods: We used three-source capture-recapture (3S-CRC) to estimate the size of KPs in seven states in Nigeria (October–December 2018). Hotspots were mapped just before 3S-CRC sampling. We independently sampled FSW, MSM, and PWID 3 times approximately 1 week apart. During encounters at KP hotspots, distributors offered inexpensive and memorable objects to FSW, MSM, and PWID that were unique to each capture round and KP. In subsequent rounds, participants were offered an object and asked to describe those received during previous rounds; we tallied correct identifications of the object. Distributors recorded responses on tablets using REDCap™ software and uploaded data to a secure central server. Data were aggregated by KP and state for analysis. Median PSEs were derived using Bayesian nonparametric latent-class models with 80% highest density intervals (HDI) for precision.

Results: During three rounds of independent captures in each state, there were approximately 310,000 encounters in 13,899 hotspots. Table 1 summarizes median PSE by KP and state.

Conclusion: We are the first to implement 3S-CRC to calculate median PSE with 80% HDI in Nigeria. Overall, our PSEs were larger than previously documented for each KP in each state. Empirical methods and analysis using Bayesian models that account for factors (i.e., social visibility and stigma) that influence heterogeneous capture probabilities may produce more accurate PSE. The large estimates suggest a need for programmatic scale-up to reach these populations with high HIV risk. 3S-CRC methods, in similar epidemic settings, could help estimate critical population denominator data needed to inform HIV prevention and treatment programs.

Table 1: Median population size estimates* (80% Highest Density Intervals) for female sex workers, men who have sex with men, and people who inject drugs in seven U.S. President's Emergency Plan for AIDS Relief-funded states in Nigeria (October–December 2018)

State	Female Sex Workers PSE (HDI)	Men Who Have Sex with Men PSE (HDI)	People Who Inject Drugs PSE (HDI)
Federal Capital Territory (FCT)	45,700 (23,100–56,700)	8,200 (6,500–10,700)	3,400 (2,800–4,100)
Akwa Ibom	64,300 (44,100–84,900)	61,000 (16,200–82,000)	22,500 (15,100–30,900)
Benue	46,700 (27,500–113,900)	10,800 (8,000–13,100)	27,600 (22,900–35,600)
Cross River	15,300 (11,900–20,000)	3,200 (2,700–3,600)	20,100 (11,500–25,500)
Lagos	48,200 (30,900–76,100)	6,500 (4,900–8,400)	9,400 (7,100–13,400)
Nasarawa	55,600 (26,000–73,700)	5,000 (3,700–6,400)	6,900 (5,800–7,600)
Rivers	14,500 (14,100–15,200)	41,400 (8,400–61,800)	30,400 (7,600–44,600)

*Estimates were derived using Bayesian nonparametric latent class models; PSEs are rounded to the nearest hundred.
Abbreviations: PSE, population size estimate (median); HDI, 80% highest density interval;

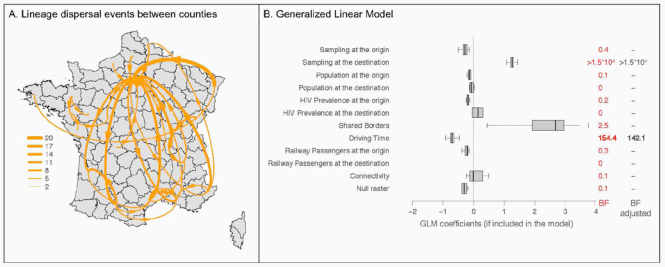
906 5GEOSPATIAL HIV DYNAMICS IN FRANCE: A GRAVITY EFFECT MODEL

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Background: HIV epidemiology is constantly evolving and regular surveillance studies are needed to monitor the HIV genetic diversity shifts or global transmission patterns. Individuals during the primary HIV infection contribute disproportionately to the spread of the HIV epidemic due both to at risk behaviors and to high viral loads. Thus, monitoring HIV epidemiology in this population is crucial in tracking the leading edge of HIV epidemics. We explored

the geospatial dynamics of the HIV epidemics across mainland France to identify factors associated with HIV dispersal for guiding prevention efforts.
Methods: We applied a multistep phylogenetic approach on a large set of HIV-1 pol sequences from PHI individuals diagnosed in mainland France in ANRS AC43 laboratories performing genotypic resistance tests between 2014-2017: (1) We first performed an overall maximum likelihood phylogenetic inference to identify well-supported monophyletic clades; (2) All clades of size≥3 were used to perform a discrete phylogeographic inference to evaluate the dispersal history across mainland France; (3) We then applied a generalized linear model (GLM) to test the association of demographic, geospatial factors and connectivity (i.e. geographic distances and the intensity of air traffic passenger flow) with lineage dispersal.
Results: A total of 1,545 pol sequences were collected. After combining these with 48,658 publicly available sequences, we identified 71 clusters from 37 counties. The discrete phylogeographic analysis revealed varying levels of virus exchange between counties (Fig.A). The GLM analysis revealed that viral migration was strongly associated with limited driving time (BF=142, Fig.B). These observations illustrate the HIV dynamics across mainland France with Paris and Lyon areas (the 2 largest cities) being major sources and recipients of viral dispersal. It suggests the role of local human migration and large urban area in sustaining the HIV epidemics.
Conclusion: The combined use of phylogeography and GLM provides deeper insights into geospatial transmission patterns and factors associated with viral flows. Phylogeographic analyses confirm that highly populated areas could have a gravity effect on the French epidemic. These results may help to more efficiently allocate prevention resources and will allow to evaluate the impact of changes in demographic trends and policies.

Figure. A Lineage Dispersal Between Counties in France Inferred by Discrete Phylogeographic Analysis. Only transition curves that represent ≥2 transition events are shown. **B. Summary of phylogenetic generalized linear model results.** Box plots of the GLM coefficients for all predictors. BF support for inclusion of each predictor in the model is indicated in red on the right.

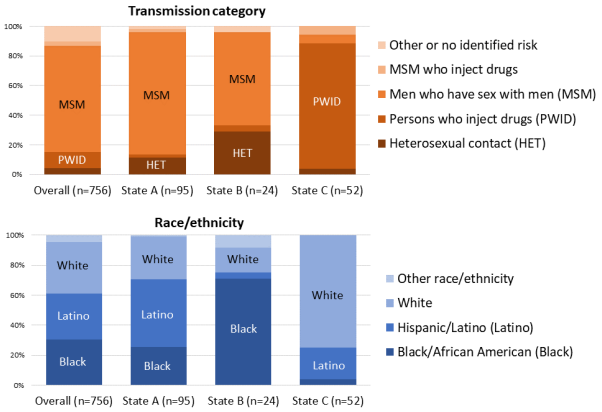


907 INCREASING CAPACITY FOR DETECTING CLUSTERS OF RAPID HIV TRANSMISSION: UNITED STATES

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Background: Responding to HIV clusters and outbreaks is a pillar of the U.S. Ending the HIV Epidemic (EHE) initiative, which will initially focus on 48 counties; Washington, D.C.; San Juan, Puerto Rico; and 7 states with substantial rural burden. Molecular cluster detection uses HIV sequence data and can identify rapid transmission for public health response; in 2015–2016, most persons involved in U.S. clusters were men who have sex with men (MSM)—only 1% were persons who inject drugs (PWID). In 2018, requirements to collect HIV sequence data expanded from 27 to all CDC-funded health departments. We described changes in molecular cluster detection capability in EHE and non-EHE areas and geographic variation in transmission dynamics.
Methods: We examined HIV-1 polymerase sequence completeness in the National HIV Surveillance System from December 2015 (first implementation of molecular cluster detection) to March 2019 for people with HIV diagnosed in the past 3 years. Clusters of rapid transmission were identified quarterly among people with HIV diagnosed in the past 3 years using HIV-TRACE with a pairwise genetic distance threshold of 0.5%. Priority clusters had ≥ 5 diagnoses in the past 12 months. We described people in clusters first detected in 2018–19 after expansion of reporting.
Results: Sequence completeness increased from 26% (December 2015) to 42% (March 2019); increases were seen in EHE areas (30% to 43%) and in areas not previously funded to collect sequences (3% to 27%). Of 194 priority clusters identified during December 2015–March 2019, 87 were first detected in 2018–19. Of 756 people in these 87 clusters, 71% were MSM and 11% were PWID; 53% resided in EHE areas at diagnosis. State-by-state analysis showed tremendous variation in risk and racial/ethnic groups included in clusters of rapid transmission (Figure).
Conclusion: Sequence completeness has increased nationwide. Molecular cluster analysis demonstrates ability to identify recent and rapid transmission in varied populations, including capacity for detecting the rapid transmission among PWID that has occurred in recent years. Molecular cluster detection offers an opportunity for a focused, local approach to identify populations experiencing rapid transmission and tailor response to scale up services for these populations. These results demonstrate great potential for public health response to clusters and outbreaks in jurisdictions identified for the EHE Initiative.

Figure. Characteristics of people involved in clusters of rapid transmission first detected in 2018–2019, overall and for three selected states.



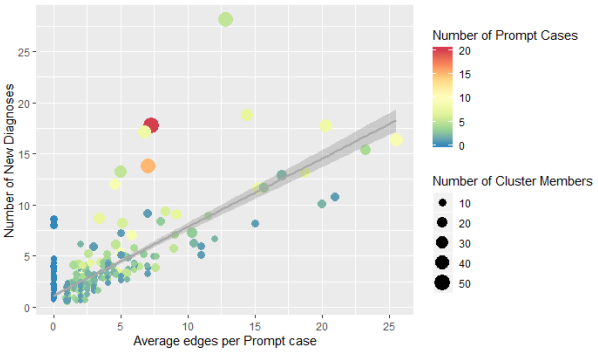
908 STATEWIDE HIV-1 TRANSMISSION CLUSTER DETECTION AND PRIORITIZATION FOR RESPONSE

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Background: New HIV diagnoses continue in the Southern US despite widespread prevention efforts, underscoring the need for innovative deployment of prevention tools. Detection and response to genetically clustered infections is a pillar to the Ending the Epidemic initiative. We combined viral load (VL) and surveillance data to prioritize genetic clusters where re-engagement to care activities could be intensified.
Methods: We developed automated cluster analyses to prospectively monitor clusters in North Carolina; the system is routinely updated with pol sequences (from clinical and public testing sites), demographic, and clinical data. Clusters were constructed from pairwise genetic distances (TN-93), connecting edges <1.5% difference. Prioritization metrics were assessed for clusters with recent diagnoses (2017-2019) and based on the adjacent nodes to recent diagnoses (edges <1.5%), including members potentially disengaged from care ("Prompt" cases). Prompt cases were defined as members without VLs or persistent/rising viremia (VL>200 c/mL) in the prior 12 months. Connectivity of Prompt cases in clusters was estimated by number of edges to all adjacent nodes (i.e. node degree) per prompt case.
Results: Of 15,558 persons with 25,509 sequences in the pipeline, 2195 had recent diagnoses; 59% (1294) of these were identified in 532 clusters. Clusters involved 2512 members: 1218 (48%) were past diagnoses (≤2016). Recent diagnoses in clusters were more likely to be MSM (65% vs. 46%), younger (33% vs. 15% 18-24 years), and have acute infection (9% vs. 5%) compared to non-clustered recent diagnoses (all p<0.01). Recent diagnoses tended to cluster with other recent diagnoses: 60% (775) clustered with ≥3 recent diagnoses (range 3-28). However, most clusters (65%) involved ≥1 Prompt case and the Prompt connectivity was associated with more recent diagnoses in clusters (Figure). A prioritization threshold of ≥5 recent diagnoses and connectivity ≥5 per cluster,

yielded 39 priority clusters (698 members) with 187 Prompt cases (4.8 vs. 1.6 Prompt cases/cluster in non-priority clusters).
Conclusion: We detected a high rate of clustering among recent diagnoses with frequent involvement of past diagnoses. Harnessing longitudinal VL and sequence data allows for timely detection and monitoring of such clusters. Clusters with rapid growth and high network connectivity with past diagnoses without viral suppression can be prioritized for intensified care re-engagement and retention support.

Figure: Clusters with HIV diagnoses 2017-2019



909 DO PARTNER SERVICES INITIATED FROM MOLECULAR CLUSTERS YIELD NEW OR VIREMIC HIV CASES?

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Background: Molecular HIV surveillance is increasingly utilized as an approach to identify new HIV diagnoses linked to clusters. Health departments employ partner services to interview people newly diagnosed with HIV—index clients— to elicit named sexual/injection drug-use partners. We examined whether the yield of new diagnoses or viremic named partners varied by molecular cluster (versus not in a cluster) when attempting to interview index clients with HIV pol sequences.
Methods: We matched and analyzed HIV surveillance (including HIV pol sequences) and partner services data from HIV diagnoses in Chicago from 2012 through 2016 from the Chicago Department of Public Health. We constructed molecular clusters using HIV-TRACE at a pairwise genetic distance threshold 0.5%. We compared the normalized proportion of partners reported by index clients who were a new HIV diagnosis or recently had detectable viremia ('yield' of partner services) in a molecular cluster vs. those whose HIV sequences did not cluster.
Results: Of 2,404 newly diagnosed index clients, 1,015 (42%) had HIV sequence data available and partner services initiated within 12 months of diagnosis. Of these, 336 (33%) had HIV pol sequences that clustered and 96 (29%) of them named at least one partner. The average age of index clients in clusters was 28, 47% were Black, 29% Latinx, 6% female and 89% men who have sex with men. Of the 539 named partners, 162 (36.6%) were linked to indexes in a cluster and of those 20% were either new diagnoses or viremic. There was no statistically significant difference in the yield of new diagnoses or viremic partners linked to index clients in a cluster versus not in a cluster (RR 1.54 (0.10-2.38); p=0.051).
Conclusion: Partner services that were initiated from the subset of index clients whose HIV sequences are in a molecular cluster yielded similar new HIV case finding or identification of those with viremia as index clients not in clusters. Future research should examine the yield among growing molecular clusters as well as partner services originating from molecular clusters that identify HIV clients co-infected with syphilis and other STIs, and by consideration of compositions by transmission categories in molecular clusters.

910 THE RELATIONSHIP BETWEEN THE HIV TRANSMISSION NETWORK AND CARE CONTINUUM IN LA COUNTY

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Background: Successful public health action combatting HIV relies on navigation through the HIV continuum of care: timely diagnosis of infection followed by linkage to care and initiation of antiretroviral therapy to achieve and maintain suppression of viral replication. Molecular epidemiology can identify rapidly growing HIV genetic transmission clusters. How these clusters relate to the care continuum has not been previously characterized.
Methods: We performed a population-based retrospective study on HIV/AIDS surveillance data from 5226 adult living with HIV, had a reported HIV pol sequence, resided in Los Angeles County, and were diagnosed between January 2010 through December 2014 with laboratory data reported through 2016. An HIV genetic transmission clusters was constructed using HIV-TRACE based on these pol sequences using a pairwise genetic distance threshold of 0.015 substitutions/site. We characterized cluster growth as the number of cases added to a cluster in the previous year divided by the number of cases in the cluster. Separate Cox proportional hazard models assessed the time to each event along the care continuum and gamma frailty models accounted for heterogeneity between genetic transmission clusters.
Results: Of the cases linked to care, 92% achieved viral suppression and 26% experienced post-suppression viral rebound. Median time from diagnosis to suppression was six months (IQR 4-13). Contrary to expectation, there were no differences in time to these events among individuals in clusters with different growth dynamics. However, upon achieving viral suppression, cases in high growth clusters were less likely to rebound (Hazard Ratio 0.83, p=0.011) compared with cases in low growth clusters. Heterogeneity due to cluster membership in the timing to each of event in the care continuum was highly significant (p<0.001), even after adjusting for transmission risk and demographics.
Conclusion: Combining molecular epidemiology and HIV surveillance approaches, we characterized the relationship between the HIV transmission network and the rates of linkage to care, viral suppression, and post-suppression viral rebound. Individuals within the same transmission cluster have similar trajectories through the HIV care continuum. These findings suggest molecular epidemiology can assist public health officials in identifying clusters of individuals who may benefit from assistance navigating the HIV care continuum.

911 SOCIODEMOGRAPHIC FACTORS ASSOCIATED WITH HIV CLUSTERING ACROSS BOTSWANA COMMUNITIES

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Background: Understanding HIV transmission networks is important for intervention programming. However, factors associated with molecular HIV clusters in southern Africa are not well-studied. We sought to identify independent predictors of being part of a molecular HIV cluster using data from HIV-positive persons enrolled in a large community-randomized HIV prevention trial in Botswana.
Methods: The Botswana Combination Prevention Project was conducted in 30 communities across Botswana in 2013-2018. At study enrollment, near-full length HIV-1 genome sequences were obtained (from RNA or DNA) from HIV-positive persons and analyzed for genetic relatedness. We defined an inferred molecular HIV cluster (transmission network) as a phylogenetically distinct viral lineage giving rise to a monophyletic subtree of the overall phylogeny with bootstrap support of splits >0.80. Multivariate logistic regression models (adjusted for clustering) were constructed using a backwards elimination procedure to select from pre-specified set of candidate socio-demographic and behavioral variables.
Results: Among the 6,536 HIV-positive BCPP participants, sequences were obtained from 4,009 (61%) and 1,904 (46% of 4,009) were in one or more of the 850 unique molecular HIV clusters identified. The majority of cluster members were female (73%) with a median (IQR) age of 40 years (33, 48). Factors associated with being in a cluster included: age 25-34 years (aOR:1.29; 95%CI:1.01–1.65), transactional sex (aOR:1.51; 95%CI:1.09-2.10), and viremia

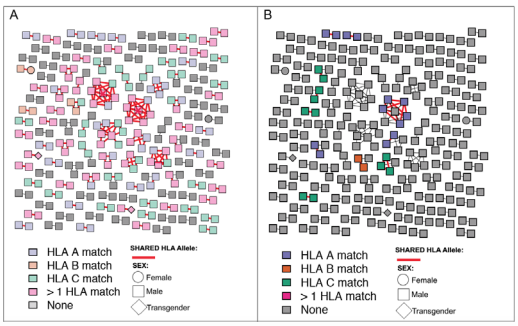
(aOR:1.37; 95%CI:1.16-1.61). In sensitivity analyses examining factors associated with membership in a cluster with a seroconverter also identified lack of religious affiliation as an independent predictor (aOR:1.56; 95%CI:1.02-2.41) in addition to age (P=0.03) and viremia (P=0.047).
Conclusion: Molecular epidemiology can be applied to characterize HIV transmission networks. Clustering was associated with younger age group, , and lack of viral suppression. These findings reinforce the importance of enhanced targeted HIV testing programs and scale-up of ART to increase viral suppression in persons living with HIV.

912 ASSOCIATIONS BETWEEN PHYLOGENETIC TRANSMISSION CLUSTERS AND HLA PROFILES IN MEXICO

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Background: Class I Human leukocyte antigen (HLA-I) is a major driver of HIV evolution, both at the individual and population level, promoting HIV adaptation to cellular immune responses. The extent to which HIV adaptation to HLA-I plays a role in transmission is not well understood. Here, we examined associations between HLA-I profiles and HIV transmission in the Mexico City HIV epidemic.
Methods: 1,049 HIV-1 subtype B pol sequences sampled between 2016 and 2018 from unique, HLA-I-typed individuals in Mexico City were analyzed. Genetic transmission networks were inferred using HIV-TRACE, establishing putative transmission linkage below a genetic distance threshold of 1.5%. High-resolution HLA profiles were determined using next-generation sequencing. Newman's assortativity coefficients were estimated using igraph. Fisher's exact tests were used to determine whether there was enrichment of specific HLA alleles in clustering vs. non-clustering individuals. P-groups, known to bind similar peptides, were used for HLA-match analyses.
Results: 286/1,049 (27%) individuals were genetically linked with at least one other person, forming 120 clusters (range: 2-8 individuals). All but 2 clustering individuals were male. Clustering and non-clustering individuals did not differ by age, baseline CD4 or HIV RNA level. HLA-C*02:02 was enriched in clustering individuals (p=0.02). Overall 30% (86/286) of clustering individuals shared ≥2 HLA-I P-groups/alleles in any of the three loci (Fig. 1A), and 26 had fully concordant (i.e. two matching alleles) HLA-A (13; 4.5%), HLA-B (2; 0.7%) or HLA-C (11; 3.8%) loci (Fig. 1B). Rates of HLA-I allelic concordance among clustering individuals were significantly higher than among the full cohort at all three loci (p<0.01).
Conclusion: HLA-I haplotypes were significantly more concordant than expected among clustering individuals in Mexico City. These findings suggest that viral adaptations may enhance transmissibility. However, further work is needed to determine if this increased concordance is due to viral factors (i.e. adaptation) or sociodemographic factors (i.e. ancestry, racial assortativity).

Figure 1. HIV Transmission Network and HLA Concordance. HIV transmission clusters. All edges represent a genetic distance of ≤1.5%. Lines in bold red indicate individuals who shared any HLA-I P-group. **A.** Nodes are colored according to locus of shared alleles in persons with at least 1 match. **B** individuals sharing both HLA-A, -B or -C alleles are shown.



913 HIV RISK INCREASES WITH POSITIVE TIES IN HIGHLY CONNECTED SOCIOSPATIAL PWID NETWORK

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Background: People who inject drugs (PWID) bear high HIV and hepatitis C virus (HCV) burden and account for some of the most explosive epidemics globally. While individual risk factors for infection are well understood, less is known about network and spatial factors. Moreover, network studies have been limited by focusing on immediate ties (egocentric network) rather than the broader sociometric/spatial networks.
Methods: 2,512 PWID were recruited via a chain referral method in 2017-19 in New Delhi, India. An index initiated sampling and was asked to recall who they injected with in the past month and was provided referrals for those partners (index's egocentric network). Similarly, each recruit named and recruited their recent injection network (recruit's egocentric network and index's sociometric network). Participant biometrics identified duplicates and cross-network linkages. All completed a survey, provided blood and information on injection locations; these data were used to generate spatial networks. Sociometric injection networks were created and analyzed using bespoke Python code. Individual and network-level factors were analyzed for associations with prevalent HIV infection; machine learning was used to nominate predictors.
Results: Median age was 26; 99.1% were male. HIV prevalence at baseline was 36.9% and 7.4% were virally suppressed; HCV antibody prevalence was 65.1%. The networks of 8 of 11 indexes merged into one network (Figure). Average degree (number of injection partners) was 2.1 (range: 0–47), network diameter was 39 and average path length was 14. Of 928 HIV-positive participants at baseline, 64.6% were directly connected with at least one other HIV-positive PWID. Of 1,634 HCV-positive participants at baseline, 86.8% were directly connected with at least one other HCV-positive PWID. The odds of HIV increased with each additional HIV-infected ego in a network (OR=1.21) and injecting at a specific hotspot (OR=1.86), factors that were independent of individual needle sharing (OR=1.89) and injection frequency (OR=1.36; all p<0.001).
Conclusion: These are among the first data to comprehensively characterize the complete sociometric injection network of PWID in an urban setting. We observed a highly connected network structure where HIV and HCV prevalence were associated with network connections and spatial overlap after adjusting for other predictors. These data have implications for the success of network-based prevention/treatment strategies.

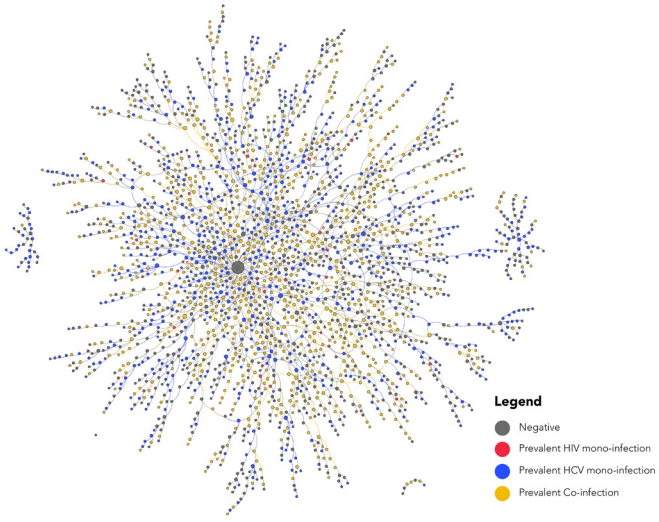


Figure. Complete sociometric injection network of 2,512 people who inject drugs in New Delhi, India. Nodes are colored by HIV and HCV status at baseline.

914 USING MOLECULAR EPIDEMIOLOGY TO CHARACTERIZE HIV TRANSMISSION NETWORKS OF TW AND MSM

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Background: Transgender women (TW) are highly vulnerable to HIV, yet little is known about their sexual networks. TW are often conflated with men who have sex with men (MSM), with the implicit assumption that the sexual networks of MSM and TW overlap, resulting in HIV transmission between the populations. However, sex partners of TW (PTW) are largely cisgender men who have sex with cis- and transgender women, suggesting that the sexual networks of MSM and TW/PTW may be separate. We examined the genetic similarity of HIV sequences from TW, male PTW, and MSM from research cohorts in Lima, Peru to determine whether the imputed transmission network, and therefore the sexual network, of TW/PTW overlaps with that of MSM.
Methods: We used HIV-1 pol sequences and epidemiologic data collected through 3 research studies conducted among primarily high-risk MSM, TW, and PTW in Lima from 2013–2017. A transmission network and phylogenetic tree were constructed using all study sequences (n=303 MSM, n=139 TW, n=25 PTW) as well as all South American sequences from the Los Alamos HIV Database (n=552). Molecular clusters were identified within the transmission network, with cluster membership defined as ≥2 sequences linked to each other based on a TN93 pairwise genetic distance threshold of 0.015 substitutions/site, and patterns in clustering were assessed with chi squared tests.
Results: 200 participants (43%) were found in 62 clusters (Fig 1), with no difference in probability of clustering by group. Both MSM and TW were more likely to cluster with members of their own group than would be expected based on chance alone. While only 28% of the sample were TW, 77% of TW found in a cluster were clustered with TW ($p<0.001$). Similarly, while 67% of the sample were MSM, 91% of clustered MSM were found in clusters with MSM ($p<0.001$). TW were less likely to be found in clusters with MSM than would be expected (57% observed vs 67% expected, $p=0.086$), but frequency of co-clustering of TW and MSM did suggest transmission occurring between the two populations. No characteristics were predictive of men clustering with TW, including reporting a TW sex partner.
Conclusion: Co-clustering of TW/MSM was less common than expected but still signified sizable overlap in transmission networks. This contrasts with reported sexual behavior among TW and their sex partners, and may indicate that a subset of high-risk men who have sex with both TW and men drive HIV transmission between these two populations.

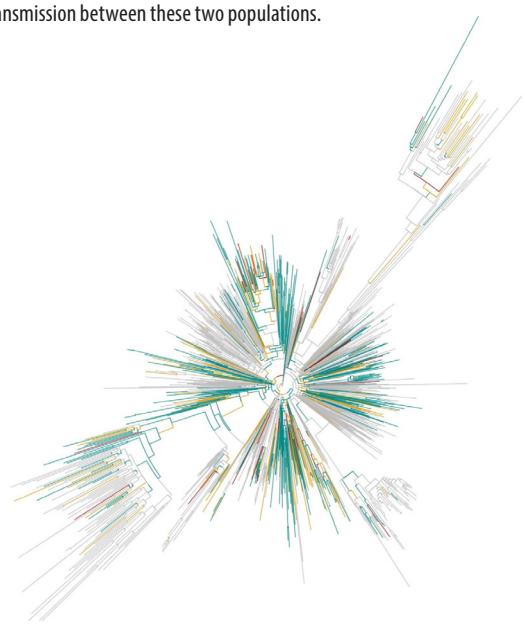
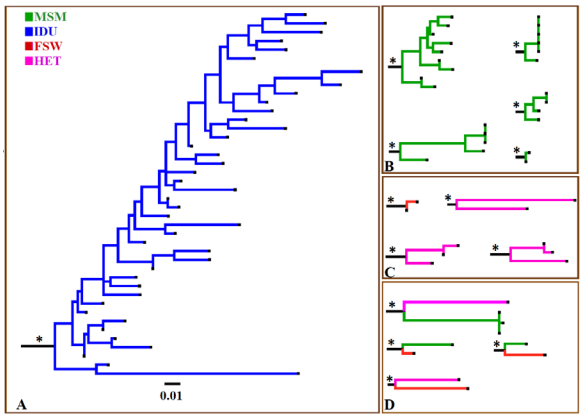


Figure 1: Phylogenetic tree of clustering of TW, their partners, and MSM against overall South American pol sequences from the Los Alamos National Database. Colors indicate group (Blue: MSM; Yellow: TW; Red: PTW; Gray: Los Alamos sequences, gender and sexual behavior unknown)

915 PHYLOGENETIC EVIDENCE OF HIV-1 MIXING BETWEEN KEY RISK GROUPS IN COASTAL KENYA

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Background: HIV-1 transmission patterns within and between populations at high-risk of HIV-1 acquisition in Kenya are not well understood. We investigated HIV-1 subtype distribution and transmission dynamics in men who have sex with men (MSM), injecting drug users (IDU), female sex workers (FSW) and heterosexuals (HET) in coastal Kenya.
Methods: We used maximum-likelihood and Bayesian phylogenetics to analyse new (N=163) and previously published (N=495) HIV-1 pol sequences collected 2005-2019 from treatment naïve individuals. To perform a subtype-specific cluster analysis of the coastal Kenyan sequences, we obtained reference sequences (N=1079) from GenBank based on similarity. Transmission networks were classified based on the number of sequences per cluster into dyads (2 sequences), networks (3-14 sequences) and large clusters (>14 sequences). Temporal and phylodynamic analyses were performed using a Bayesian Markov Chain Monte Carlo approach.
Results: Of 658 sequences, 131 (20%) were MSM, 58 (9%) IDU, 109 (17%) FSW, and 360 (55%) HET. The majority (66%) of the sequences were sub-subtype A1, with lower fractions of subtypes D (10%), C (7%), G (<1%), and recombinant forms (17%). Overall, 206 (31%) sequences formed 39 dyads, 21 networks, and one large cluster. Most clusters (85%) consisted of sequences from the same transmission group, indicating frequent within-group transmission. However, 15% of the clusters were mixed between MSM, FSW and HET sequences. One large IDU cluster was found, suggesting that HIV-1 was introduced from a single source followed by fast spread within the IDU population, distinguishing IDU transmission relative to other risk groups. Phylodynamic analysis of the sub-epidemic among IDU indicated a steady increase in HIV-1 infections from the origin of the cluster in 1987.
Conclusion: Our work suggests that in addition to frequent transmission within-risk-groups, HIV-1 transmission between MSM, FSW and HET is also common in coastal Kenya. Targeting HIV-1 prevention programmes to FSW, MSM and IDU will be necessary to reduce HIV-1 transmission in coastal Kenya.

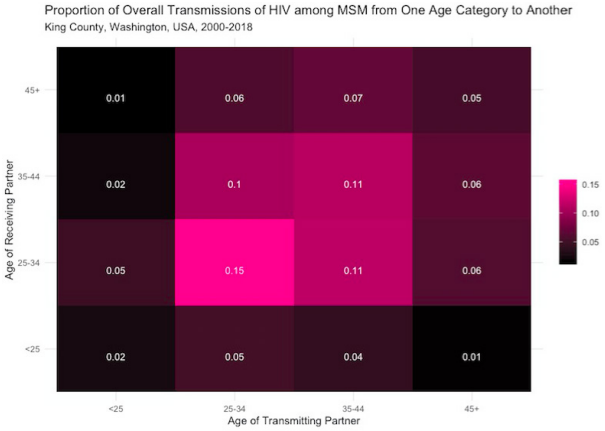


916 PHYLODYNAMIC EVIDENCE OF HIV TRANSMISSION BETWEEN AGE-DISCREPANT MSM IN KING COUNTY

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Background: Sexual mixing is typically age-assortative. Mathematical modeling studies conducted in the 1990s suggested an important role for age-disassortative mixing in HIV transmission dynamics among men who have sex with men (MSM), suggesting that young MSM (YMSM) may acquire HIV from older partners. We compared molecular epidemiology methods with phylodynamic methods to examine the frequency of HIV transmission between age discrepant MSM.

Methods: Using 2000-2018 HIV surveillance data from Public Health–Seattle & King County, HIV-1 pol gene sequences were linked to demographic, clinical, and epidemiological information. We identified genetic similarity clusters of 2+ individuals using TN93 pairwise genetic distance with a 0.015 threshold, and assessed correlates of clustering using multivariate logistic regression. We conducted probabilistic phylodynamic modeling to estimate transmission flows between YMSM (age <25) and older MSM (categorized for analyses as age 25-34, 35-44, and >45).
Results: From 2000-2018, 4597 MSM were diagnosed with HIV in King County, with 654 (14%) diagnoses among YMSM. Among 2851 (62%) of MSM with an available sequence, 1435 (50%) clustered in 277 genetically similar clusters: 9 clusters were comprised of only YMSM, 166 of only older MSM, 102 of both older and YMSM. YMSM had higher odds of clustering compared to those >25 years old (AOR 1.6; 95% CI: 1.3, 2.0). Older MSM were more likely to cluster with other MSM >25 years old (AOR 4.3; 95% CI: 2.3, 3.1) and less likely to cluster with YMSM (AOR 0.4; 95% CI: 0.3, 0.5), compared to YMSM. Phylodynamic modeling suggest that the majority (47%) of HIV transmissions occurs among MSM age 25-34 and 35-44 years old. The overall assortativity coefficient was 0.08. YMSM had the highest probability of acquiring HIV from MSM aged 25-34 years old (39%) and 35-44 years old (31%), with a 19% probability of acquiring HIV from other YMSM. Phylodynamic models estimated that YMSM acquire HIV from MSM with probability-weighted mean age difference of 11.2 years older (IQR 4 to 18 years).
Conclusion: Both molecular epidemiology and phylodynamic methods were suggestive of age-assortative mixing among older MSM, among whom the majority of HIV transmissions occurred. However, molecular cluster analyses were suggestive of high relative rates of transmission among YMSM. Phylodynamic models also found that YMSM frequently acquire HIV from older partners, suggesting that age-discrepant partnerships play an important role in HIV dynamics among YMSM.



917 HOMOPHILY IN THE SOCIOSEXUAL NETWORKS OF GAY AND BISEXUAL MEN

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Background: Kenyon & Delva (2018, "It's the network, stupid") argue that the elevated prevalence of sexually transmitted infections (STIs) in sub-populations is due to the structure of their socio-sexual networks. Homophily, which measures the degree to which individuals associate with those like themselves, has been regularly identified as a key determinant of socio-sexual network structure. Thus, we aim to describe patterns of homophily within the networks of gay and bisexual men (GBM).
Methods: Sexually-active GBM, aged 16+, were recruited between 2/2012 and 2/2015 using respondent-driven sampling. Participants recruited up to six participants in their social or sexual networks. Homophily estimates (h), based on recruitment patterns, were calculated in RDSAT and ranged from -1.00 (completely heterophilous) to +1.00 (completely homophilous).
Results: Among 774 GBM, high homophily (h>.50) was observed by HIV serostatus (Positive: h=.62; Negative: h=.31; unknown h=.03), gender (Cis-man: h=.59; Trans-man: h=.57), and age (Age < 30: h=.57; Age > 30: h=.55). Moderate homophily (h>.30) was observed for ethnicity (White: h=.39; Indigenous: h=.29; Asian: h=.33; Other: h=.11), residential neighborhood (Downtown Vancouver: h=.39; Vancouver: h=.37; Outside Vancouver: h=.31), education (High school or greater: h=.34; Less than high school: h=.09), patronage of gay bars and clubs (About once per month or more: h=0.33; Less than once per month: h=.19), and use of online sex seeking apps (About once per month or more: h=.32; Less than once per month: h=0.16), and use of GHB (Yes: h=.30; No: h=.25), LSD (Yes: h=.41; No: h=.14), crystal methamphetamine (Yes: h=.37; No: h=.29), and crack (Yes: h=.14; No: h=.40). Low homophily (h<.30) was observed for perceived HIV transmission risk (Low Risk: h=0.27; High risk: h=0.11), STI history (Ever Diagnosed: h=.27; Never Diagnosed: h=.09), and for patterns of condom use: (No anal sex: h=.07; No condomless anal sex (CAS): h=.04; CAS with only sero-concordant partners: h=.01; CAS with serodiscordant/unknown status partners: h=.11).
Conclusion: We observed moderate to high homophily across demographic characteristics, substance-use, and dating-venues, but low homophily of sexual behaviours.

918 PHYLOGENETIC INSIGHTS ON HIV-1 TRANSMISSION DYNAMICS AMONG MSM AND MIGRANTS IN QUEBEC

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Background: Phylogenetic analyses of the interrelationships of viral sequences, using novel statistical tools, provide molecular epidemiological frameworks to reconstruct HIV transmission networks. We applied these methods to gain novel insights on HIV transmission patterns in Quebec, uncover cryptic at-risk populations, and elucidate epidemic drivers that cannot be identified by traditional epidemiological approaches.
Methods: Genetic analyses were performed on subtype B pol sequences derived from newly-infected Men having Sex with Men (MSM, n=4800) and Heterosexuals subgroups, including People who Inject Drugs (PWID) and Migrants from Haiti and the Americas (n=1836). Phylogenetic analyses were also conducted on non-B viral subtypes originating from Migrants from Africa, Asia and Europe (n=1578). Growth trajectories of transmission networks (6+ members/cluster) were analyzed using Maximum-Likelihood in MEGA10 and/or HIV-TRACE (TRAnsmission Cluster Engine) platforms.
Results: Half of new infections (n=2328) among MSM segregated as solitary "dead-end" transmissions (n= 1478) or small transmission networks having 2–5 members/cluster (n=850). The remaining half of new infections (n=2371) were in large transmission networks (6–150 members, mean 42 members/cluster). Phylodynamics showed a marked decline in singleton transmissions and small cluster outbreaks post-2008, concomitant to advances in Treatment-as-Prevention paradigms. This was offset by an increase in large cluster transmissions rising from 37% of infections in 2004 to 65% of new infections among MSM in 2017. HIV-TRACE maps showed differential features of forty large cluster sub-epidemics (members' age, sex, sequence diversity). Heat maps of individual clusters distinguished "actively-growing" clusters and "newly emerging" clusters from older low-risk clusters. Phylogenetics uncovered the cryptic introduction and spread of subtype B and non-B subtype sub-epidemics in recent migrants to the province.
Conclusion: The ability to predict, identify and respond to emerging "active" HIV transmission clusters in close to real-time may inform public health interventions to avert transmission cascades and control the HIV epidemic.

919 NON-B SUBTYPE HIV INFECTIONS IN GERMANY BEFORE AND AFTER THE EUROPEAN MIGRANT CRISIS

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Background: The presence of HIV-1 non-B subtypes in Germany has been increasing in recent years and is commonly attributed to migration from non-European countries. We combined molecular epidemiology and geospatial data to explore dynamics of HIV-1 non-B subtypes in Germany, before and after the European migrant crisis 2015.

Methods: Sociodemographic, geographic and HIV-1 pol sequence data were obtained from individuals who accessed care at seven University Hospitals (Bonn, Cologne, Freiburg, Frankfurt, Hamburg, Hannover, Munich) in Germany, between 2001 and 2018. Phylogenetic and genetic network analyses were performed to infer putative transmission links (genetic distance ≤1.5%). Individuals' origins were grouped into six regions: Western Europe and other high resource countries; Eastern Europe; North Africa and the Middle East; sub-Saharan Africa; Latin America and the Caribbean; and Asia.

Results: We included data from 3,110 HIV-1 infected individuals. The overall proportion of the non-B subtypes increased from 27% (673/2,490) before January 2015 to 31.5% (195/620) after 2015 (subtype G 7.4%; 184/2,490 before 2015 vs. 9.5%; 59/620 after). This was particularly driven by the year 2017, where non-B subtypes made up 39.4% of new HIV diagnoses. The proportion of non-B infected individuals, originating from Eastern Europe [8.9% (254/673) to 13.3% (60/195), p= 0.027], and the North Africa and Middle East region [1.34% (9/673) to 5.6% (11/195), p< 0.001] increased significantly after 2015. However, there were only three new non-B diagnoses after 2015 among individuals from the top 5 countries of origin of the 2015 immigrants (i.e. Syria, Kosovo, Afghanistan, Albania, Iraq). Of the 868 non-B HIV infected individuals, 119 (13.7%) were genetically linked, forming 42 transmission clusters (size 2-19 sequences) with heterosexual risk (36.1%; 43/119) and injection drug use (20.1%; 24/119) being predominant. There was an increase in genetically linked men who have sex with men (MSM) with two male only clusters before 2015 and the emergence of six more male only clusters (including 9/18 males, of whom 8/9 originating from Eastern Europe) after 2015 (Figure 1A&B).

Conclusion: The proportion of HIV-1 non-B diagnoses increased after 2015, particularly driven by individuals originating from Eastern Europe, North Africa, and Middle East. However, the number of new diagnoses among migrants originating from the top 5 countries of the European migrant crisis was minimal.

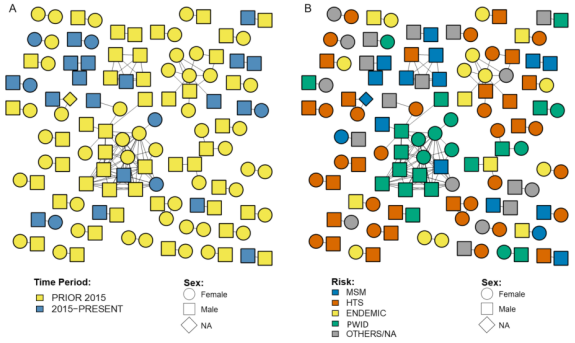


Figure 1. Transmission network of HIV-1 non-B subtypes in Germany (sequences are form individuals who received care at the University Hospitals Bonn, Cologne, Freiburg, Frankfurt, Hamburg, Hannover, and Munich, between 2001 and 2018). All edges represent a genetic distance of ≤1.5%. **A)** Color indicates the period prior 2015 (yellow) and after 2015 (blue). **B)** Color indicates the risk group: men having sex with men (MSM) in blue, heterosexuals (HTS) in red, people originating from an endemic country (Endemic) in yellow, people who inject drugs (PWID) in green, and others or unknown in grey.

920 EVALUATION OF HIV TRANSMISSION CLUSTERS AMONG NATIVES AND FOREIGNERS LIVING IN ITALY

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Background: Migrants account for nearly 30% of all new diagnoses of HIV infection in Italy in the last years. Aim of this study was to evaluate the characteristics of HIV-1 molecular transmission clusters (MTCs) among natives and foreign individuals diagnosed between 1998 and 2018 enrolled in the ICONA cohort.

Methods: Phylogenetic analyses were performed on HIV-1 pol sequences (seq) to characterise subtypes (Neighbor Joining method, 1000 replicates) and identify MTCs, divided into small (SMTCs, 2-3 seq), medium (MMTCs, 4–9 seq) and large (LMTCs, ≥10 seq). MTCs were first deduced by the HIV-TRACE tool (genetic distance ≤0.01). The robustness of MTCs was further tested using the Maximum Likelihood method, using MEGA6 software. Factors associated with MTCs were evaluated using logistic regression.

Results: Among 3,499 drug-naïve participants in the ICONA cohort (2,804 natives; 695 migrants), 726 (20.8%; 644 natives, 82 migrants) were involved in 228 MTC, including 6 LMTCs (N=140 subjects), 36 MMTCs (N=184) and 186 SMTCs (N=402), respectively. Subjects involved in MTCs were prevalently native (88.7% vs 77.8%, p<0.001), male (94.3% vs 78.9%, p<0.001) and MSM (74.7% vs 45.0%, p<0.001), younger (median [IQR] yrs: 32 [27–40] vs 38 [31–46], p<0.001), more recently diagnosed (median [IQR] yrs: 2012 [2009–2014] vs 2011 [2007–2014], p<0.001), and with higher CD4 count compared to subjects out of MTCs (median [IQR]: cells/mm$_3$: 459 [322–624] vs 353 [177–523], p<0.001) (Table). HIV-1 non-B subtype was found in 51 MTCs (22.4%); of note, non-B infections involved in MTCs were more commonly found in natives (N=47, 92.2%) than in foreigners (N=4, 7.8%). Logistic regression confirmed that factors such as Italian origin, being MSM, younger age, more recent diagnosis and higher CD4 count were significantly associated with MTCs (Table). The presence of both natives and foreigners was found in 66.7% of LMTCs, 33.3% of MMTCs and 23.1% of SMTCs. By focusing on migrants, they contributed for 14.4% to SMTCs, 7.6% to MMTCs and 7.1% to LMTCs, respectively. The 24 migrants involved in LMTCs and MMTCs were mainly from Central/South America or other European countries.

Conclusion: HIV-1 newly diagnosed subjects are involved in several MTCs in the last two decades in Italy. Clustering transmission, especially for large clusters, is prevalently driven by natives, mainly MSM and frequently infected with HIV-1 non-B subtype. Our findings can contribute to monitoring of the HIV epidemic and guiding the public health response.

Patient's characteristichs and factors associated with HIV-1 molecular transmission clusters

Variables	Overall	Out of cluster	In cluster	P-value[a]	Adjusted model[b]		
	N=3499	2773 (79.3%)	726 (20.7%)		OR	(95% CI)	P-value
Female gender, n (%)	627 (17.9%)	586 (21.1%)	41 (5.7%)	<0.001	-	-	-
Age, years, median (IQR)	37 (30-45)	38 (31-46)	32 (27-40)	<0.001	0.65	0.59-0.72	<0.001
Mode of HIV transmission							
F heterosexual	553 (15.8%)	513 (18.5%)	40 (5.5%)	<0.001	1.00	-	-
F IVDU	32 (0.9%)	31 (1.1%)	1 (0.1%)		0.49	0.06-3.81	0.499
M heterosexual	713 (20.4%)	628 (22.7%)	85 (11.7%)		1.77	1.16-2.72	0.009
M IVDU	161 (4.6%)	145 (5.2%)	16 (2.2%)		1.45	0.76-2.77	0.261
M MSM	1789 (51.1%)	1247 (45.0%)	542 (74.7%)		3.64	2.50-5.30	<0.001
Other/unknown	251 (7.2%)	209 (7.5%)	42 (5.8%)		2.59	1.57-4.26	<0.001
Nation of birth, n (%)							
Italy	2804 (80.1%)	2160 (77.8%)	644 (88.7%)	<0.001	1.00	-	-
Africa	219 (6.3%)	212 (7.7%)	7 (0.1%)		0.18	0.08-0.39	<0.001
Central and South America	241 (6.9%)	201 (7.3%)	40 (5.5%)		0.53	0.36-0.77	0.001
Europe	187 (5.3%)	159 (5.7%)	28 (3.9%)		0.33	0.10-1.11	0.074
Asia	38 (1.1%)	35 (1.3%)	3 (0.4%)		0.63	0.41-0.99	0.044
Other	10 (0.3%)	6 (0.2%)	4 (0.6%)		3.15	0.74-13.51	0.122
Education, n (%)							
Primary school	169 (4.8%)	158 (5.7%)	11 (1.5%)	<0.001	0.92	0.47-1.81	0.810
Secondary school	585 (16.7%)	505 (18.2%)	80 (11.0%)		0.90	0.68-1.21	0.492
College/University	1762 (50.4%)	1329 (47.9%)	433 (59.6%)		1.00	-	-
Missing	983 (28.1%)	781 (28.2%)	202 (27.8%)		1.04	0.84-1.30	0.707
Employment, n (%)							
Employed	1476 (42.2%)	1148 (41.4%)	328 (45.2%)	<0.001	1.00	-	-
Unemployed	461 (13.2%)	389 (14.0%)	72 (9.9%)		0.87	0.63-1.19	0.371
Self-employed	526 (15.0%)	413 (14.9%)	113 (15.6)		0.99	0.76-1.29	0.932
Student	146 (4.2%)	93 (3.4%)	53 (7.3%)		0.80	0.53-1.20	0.277
Housewife	94 (2.7%)	88 (3.5%)	6 (0.8%)		1.04	0.42-2.61	0.927
Other	278 (8.0%)	244 (8.8%)	34 (4.7%)		0.68	0.45-1.03	0.066
Missing	518 (14.8%)	398 (14.4%)	120 (16.5%)		0.93	0.70-1.23	0.609
HIV RNA, copies/mL							
<1000	122 (3.5%)	99 (3.6%)	23 (3.2%)	0.005	0.68	0.40-1.16	0.155
1.000/10.000	559 (16.0%)	445 (16.1%)	114 (15.7%)		0.84	0.63-1.13	0.249
10.000/100.000	1470 (42.0%)	1126 (40.6%)	344 (47.4%)		0.93	0.75-1.16	0.545
>100.000	1118 (32.0%)	905 (32.6%)	213 (29.3%)		1.00	-	-
Missing	230 (6.6%)	198 (7.1%)	32 (4.4%)		0.79	0.39-1.60	0.513
CD4, cells/mm^3, n (%)							
<=200	791 (22.6%)	721 (26.0%)	70 (9.6%)	<0.001	1.00	-	-
200-500	1485 (42.4%)	1165 (42.0%)	320 (44.1%)		2.26	1.67-3.06	<0.001
>500	1003 (28.7%)	703 (25.3%)	300 (41.3%)		3.10	2.25-4.25	<0.001
Missing	220 (6.3%)	184 (6.6%)	36 (5.0%)		1.90	0.93-3.90	0.079
Year of diagnosis, median (IQR)	2011 (2008-2014)	2011 (2007-2014)	2012 (2009-2014)	<0.001	1.08	1.06-1.10	<0.001
Subtype							
A1	104 (3.0%)	85 (3.1%)	19 (2.6%)	<0.001	-	-	-
B	2556 (73.1%)	2038 (73.5%)	518 (71.4%)		-	-	-
C	148 (4.2%)	119 (4.3%)	29 (4.0%)		-	-	-
CRF02_AG	187 (5.3%)	141 (5.1%)	46 (6.3%)		-	-	-
CRF60_BC	64 (1.8%)	12 (0.4%)	52 (7.2%)		-	-	-
F1	179 (5.1%)	157 (5.7%)	22 (3.0%)		-	-	-
Other	261 (7.5%)	221 (8.0%)	40(5.5%)		-	-	-

[a]By Mann-Whitney test (for quantitative variables) and χ2 test or Fisher's exact test (for categorical variables), as appropriate. P
[b]Adjusted for: Sex, age, mode of HIV transmission, nation of birth, education, employment, plasma HIV-RNA, CD4 cell count, year of
Acronyms: F, female; IVDU, intravenous drug user; M, male; MSM, men who have sex with men.

921 MOLECULAR ANALYSIS SUGGESTS POST-MIGRATION HIV-1 ACQUISITION AMONG MIGRANTS IN PARIS

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Background: Almost half of the new HIV diagnoses were among people originating from outside the reporting country (migrants) in Europe the last few years. We aimed to trace the geographic origin of HIV-1 CRF02_AG infections, the most prevalent non-B clade in France, for migrants in Paris, using molecular epidemiology methods.
Methods: We studied the first available pol gene sequence for all patients infected with HIV-1 CRF02_AG (N=2,146) diagnosed in two large Parisian University hospitals. HIV-1 subtyping was carried out using automated subtyping tools (COMET, REGA). We analyzed phylogenetically the CRF02_AG sequences from migrants (N=567) along with all the available CRF02_AG sequences from non-migrant patients (N=1,579). We also included all publicly available CRF02_AG sequences (N=3,476), and unpublished CRF02_AG sequences from Spain, Italy and Greece (N=1193), as references. Local transmission networks (LTNs) were phylogenetic clusters including sequences from France at proportions >70%, receiving bootstrap value >70% or SH-support >0.8. Phylogenetic trees were estimated by the maximum likelihood method (RAxML, FastTree). The origin of HIV-transmissions was traced by phylogeographic analysis using the criterion of parsimony (Mesquite).
Results: Phylogenetic analysis revealed that 198 (34.9%) sequences from migrants clustered within LTNs. The distribution of transmission risk group in migrants infected with CRF02_AG strains was: Heterosexuals (N=447; 78.8%), MSM (N=37; 6.5%), Others/Unknowns (N=83; 14.7%). The proportion of migrant MSM within CRF02_AG LTNs was significantly higher (83.8%) than the corresponding proportion of heterosexuals (31.5%) (p<0.001). Phylogeographic analysis showed that 29.3% of the CRF02_AG HIV-transmissions within migrants occurred in France. Multivariate analysis showed that parameters associated with clustering within the large LTNs (≥10 sequences) were MSM risk group (MSM vs heterosexuals OR: 10.3, 95% CI: 6.5-16.5) and French origin (non-migrants vs migrants OR: 2.4, 95% CI: 1.5-3.9).
Conclusion: We found that 29.3% of CRF02_AG HIV-transmissions within migrants originated in Paris. Transmissions among migrants within LTNs were associated with MSM risk group. Moreover, transmissions within large clusters are more frequent among MSM and non-migrants. This is one of the few molecular studies showing that even for CRF02_AG, which is prevalent in Sub-Saharan Africa, a large proportion of transmissions among migrants occur in Paris.

922 GEOGRAPHIC PATTERNS IN HIV TRANSMISSION CLUSTERS IN LOS ANGELES COUNTY

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Background: Clusters of HIV transmission can serve as alerts for public health action. These clusters can comprise (i) geographic clusters of diagnosis in time and space or (ii) clusters of genetically linked cases. We assessed the impact of geography across the Los Angeles County (LAC) HIV genetic transmission network and its relevance to directing HIV prevention and treatment.
Methods: Deidentified surveillance data reported for 8150 persons residing in LAC (2010 through 2016) were used to construct a transmission network using HIV-TRACE. Persons were linked if their pairwise genetic distance was ≤0.015 substitutions/site. Residential information at diagnosis was examined at ZIP code, health district (HD), and service planning area (SPA). We used 3 approaches to characterize this relationship: (i) geographic assortativity, the tendency for people to link to others within the same geography (ii) concordant time-space pairs, the proportion of genetically linked pairs from the same geography and diagnosis year, and (iii) Jaccard coefficient (JC), the intersection divided by the union of geography and cluster sets. Significance was determined using 1000 random network permutations. A generalized linear model was used to identify characteristics associated with the JC.
Results: The 4150 (50.6%) HIV cases that were clustered were assortative by ZIP, HD, and SPA (0.02, 0.09, 0.15; p<0.001). Geography was less assortative than race/ethnicity and transmission risk. 58% of genetically linked cases were diagnosed in the same year, and 44% were diagnosed in the same HD; however, only 19% were diagnosed in the same year and HD. This time-space concordance among genetically-linked pairs was also low across ZIP and SPA (p<0.001). In the JC analysis, cis-men (b=0.20; p<0.001) and those younger at diagnosis (b=0.189; p=0.01) had more overlap between clusters and geography; we observed an inverse association for trans-women (b=-0.51; p<0.001) and African-Americans (b=-0.18; p<0.001).
Conclusion: We found significant, but weak associations between the HIV transmission network and residence at diagnosis. Within an urban setting with endemic HIV, genetic clustering may serve as a better indicator than time-space clustering to understand transmission patterns and direct public health action.

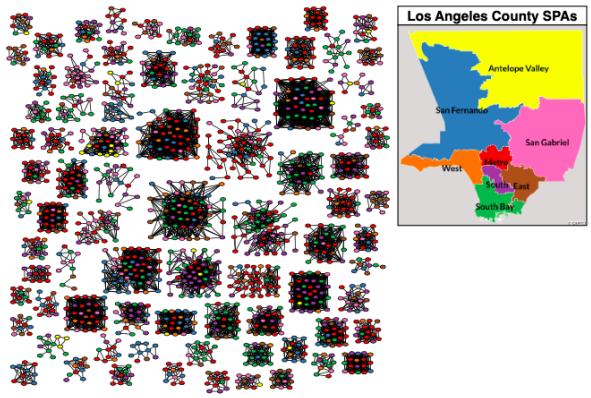


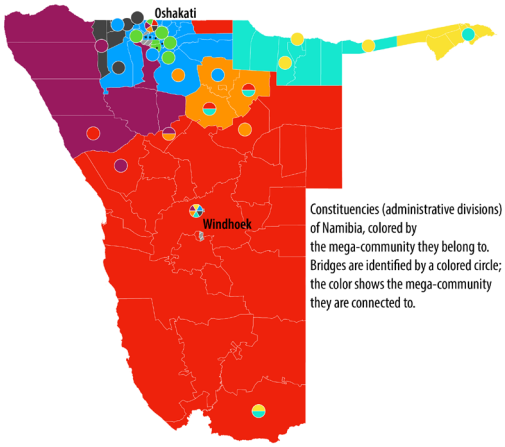
Figure. Geographic assortativity of the Los Angeles County HIV genetic transmission network by Service Planning Area (SPA) at diagnosis. For ease viewing, only clusters with ≥10 individuals are depicted.

923 HUMAN MOBILITY PATTERNS GENERATE GEOGRAPHICALLY STRUCTURED SUB-EPIDEMICS IN NAMIBIA

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Background: Populations in Sub-Saharan Africa are highly mobile. Therefore, an individuals' "social/sexual community" can consist of multiple communities: we define such a social/sexual community as a mega-community (MC). If MCs exist, they would geographically structure a generalized HIV epidemic into loosely connected sub-epidemics. This would have significant implications for designing effective epidemic control strategies. Here we use mobile phone data from Namibia, where HIV prevalence is ~14%, to search for MCs.
Methods: Call detail records (CDRs) were collected from 90% of subscribers in Namibia over a 12-month time period; they represent 9 billion communications from 1.19 million unique SIM cards. We analyzed these data at the constituency level, from all constituencies with cell towers: 96 out of 110. Our analyses enabled us to discover countrywide travel patterns, and determine how much time travelers from each constituency spent in other constituencies. We then used a technique from network science (a community-detection algorithm) to determine if MCs exist.
Results: Residents of Namibia spent ~22% (median, Interquartile range: 18-26%) of their time outside their home constituency, over a year. Population-level travel patterns divide Namibia's population of 2.5 million into eight MCs that vary in size (15,000 to 650,000 individuals) and compactness (figure). Namibia's generalized epidemic consists of eight connected sub-epidemics: each contained within a MC. We were also able to identify "bridges" that link sub-epidemics: a bridge is a constituency in one MC that is linked, by travel, to another MC. We identified two "types" of bridges (figure): short bridges (linked constituencies are spatially contiguous) and long bridges (linked constituencies are separated by at least one constituency). Notably, the capital of Namibia (Windhoek) is a long bridge and connects to six MCs and sub-epidemics. Oshakati, the capital of one of 14 regions in Namibia, is also a long bridge; it is connected to five MCs and sub-epidemics.
Conclusion: As a result of travel patterns, the population of Namibia is divided into MCs. These MCs are not visible, but they spatially structure Namibia's

generalized epidemic into eight loosely connected sub-epidemics. This suggests that interventions may be the most effective if they are implemented at the level of the MC. Furthermore, it may be very difficult to reduce incidence in Windhoek and Oshakati, as they are connected (by travel) to multiple other sub-epidemics.

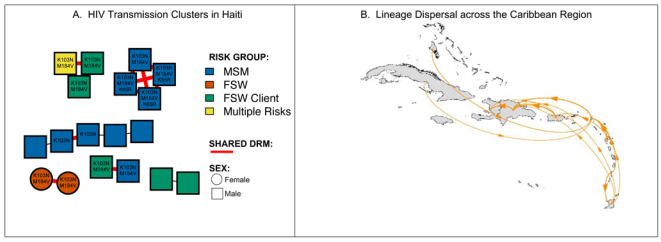


924 LOCAL AND REGIONAL DYNAMICS OF HIV EPIDEMICS AMONG HIGH-RISK POPULATIONS IN HAITI

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Background: Although the overall HIV prevalence in Haiti has been stable around 2% for the past 15 years, the prevalence in high risk groups, such as men having sex with men (MSM) and female sex workers (FSW), are much higher, 12.9% and 8.7% respectively. To characterize the HIV epidemics in the Caribbean, we explored: (1) the dynamics of HIV transmission among persons with HIV (PWH) from high risk groups in Haiti, and (2) viral dispersal across the Caribbean.
Methods: 78 HIV-1 pol sequences were newly sampled and analyzed from MSM, FSW and sexual partners of FSW from Haiti. We also analyzed 3,908 publicly available HIV-1 pol sequences from the Caribbean and 33,100 from the rest of the world. Phylogenetic and network analyses were performed to infer local HIV transmission in Haiti. Sequences were screened for drug resistant mutations (DRM). Next, we applied a multistep phylogenetic approach to evaluate dispersal across the Caribbean: (1) identify all well-supported monophyletic clades; (2) all clades of size ≥ 3 identified were used to perform a discrete phylogeographic inference to evaluate the dispersal history across Caribbean countries; (3) we applied a generalized linear model (GLM) to test the association of epidemiologic factors and connectivity (i.e. geographic distances and air traffic passenger flow) with lineage dispersal.
Results: We first evaluated HIV transmission dynamics within Haiti: Genetic network analyses found that 23% (18/78) had a putative linkage with ≥1 sequence forming 6 clusters (size: 2-5 PWH), Fig.A. Clustering Haitian PWH were mostly MSM (10/18) or FSW clients (5/18). Considering DRM, K103N or M184V were shared in 83.3% clusters. Next, we evaluated geospatial dynamics in the Caribbean's: Discrete phylogeographic analysis revealed viral trafficking from the Dominican Republic (DR) toward Haiti but also from Puerto Rico (PR) and Trinidad and Tobago toward DR and PR respectively (Fig.B). As might be expected, the GLM analysis showed that closer countries were the most likely to show viral exchange.
Conclusion: HIV transmissions occurs across risk groups in Haiti with high rates of shared DRMs. This study also found that local epidemics are likely sustained by regional human migration. Thus, prevention efforts to curb local epidemics will need to consider all risk groups and also epidemics from other countries.

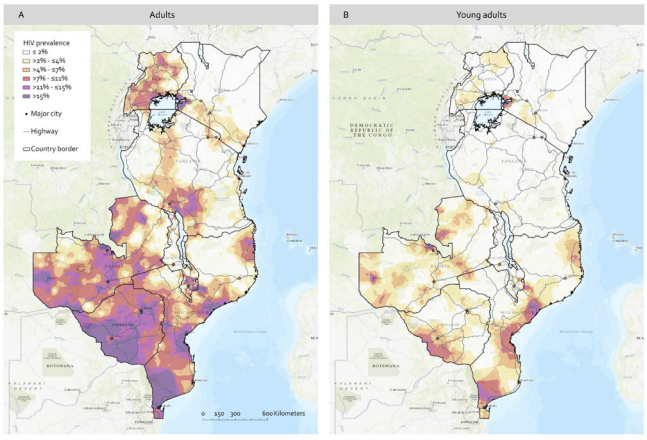
Figure. Local HIV Transmission Dynamics in Haiti and Geospatial Dispersal across the Caribbean's Region. A. HIV Transmission Network. The nodes are colored by risk group, squares and circles indicating male and female. All edges represent a genetic distance of ≤1.5%. Lines in bold red indicate individuals who shared DRMs. FSW: Female Sex Worker. MSM: Men who have sex with men **B. HIV Lineage Dispersal across the Caribbean Region inferred by discrete phylogeographic analysis.** Only transition curves that represent ≥2 transition events are shown. .



925 MAPPING AND CHARACTERISING HIV TRANSMISSION HOTSPOTS IN SUB-SAHARAN AFRICA

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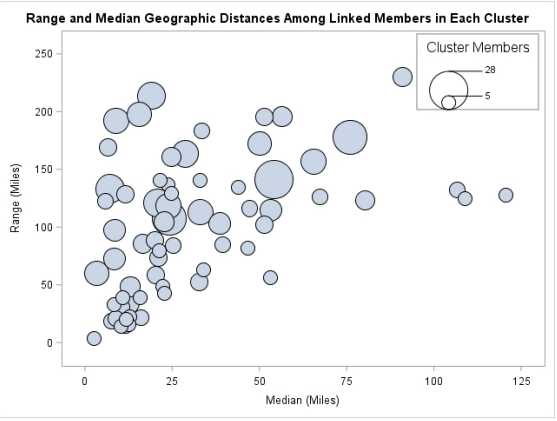
Background: In the generalised epidemics of sub-Saharan Africa (SSA), HIV prevalence shows patterns of clustered micro-epidemics. We mapped and characterised these so-called 'hotspots' for young adults (15-29 years of age), as a proxy for transmission hotspots, for seven countries in Eastern and Southern Africa: Kenya, Malawi, Mozambique, Tanzania, Uganda, Zambia, and Zimbabwe.
Methods: We used geolocated survey data from the most recent USAID Demographic and Health Surveys and AIDS Indicator Surveys, which included 53,234 young adults from 3,665 sample locations. Ordinary kriging was applied to predict HIV prevalence at unmeasured locations. We explored to what extent behavioural, socioeconomic and environmental factors explain HIV prevalence at the individual- and sample location-level, by developing a series of multilevel multivariable logistic regression models. We then compared and geospatially visualised how heterogeneity and hotspots can be explained by the models, using the sample location random effect estimates from each model.
Results: We found substantial HIV prevalence heterogeneity among both adults (Figure 1A) and young adults (Figure 1B) througout all countries, with clear geospatial hotspots among young adults characterised by areas with prevalences of over 11% or 15% alternating with areas of prevalences between 0% and 2%. The heterogeneity in young adults could be explained for 15.6% by an interplay of known behavioural, socioeconomic and environmental factors. Maps of the interpolated random effect estimates show that environmental variables, representing indicators of economic activity, were most powerful in explaining HIV hotspot locations.
Conclusion: In young adults, micro-epidemics of relatively high HIV prevalence alternate with areas of very low prevalence, clearly illustrating the existence of transmission hotspots. These hotspots are partially characterised by high economic activity, relatively high socioeconomic status, and risky sexual behaviour. Localised HIV prevention interventions specifically tailored to the populations at risk will be essential to curb transmission. More fine-scale geospatial mapping of key populations, such as sex workers, and migrant populations, could help to further understand the drivers of these transmission hotspots, and to determine to what extent they fuel the generalised epidemics in SSA.



926 GEOGRAPHIC CHARACTERISTICS OF HIV GENETIC CLUSTERS AMONG NEWLY DIAGNOSED CASES IN NC

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Background: Identifying both geographic clusters and genetic clusters are routine parts of HIV surveillance aiming to help focus prevention efforts. Integrating geographic and genetic analyses, especially beyond traditional surveillance borderlines, will inform the ability of geographic clustering to identify linked HIV transmission networks and help allocate prevention efforts.
Methods: We assessed genetic clusters among those >=13 years old newly diagnosed with HIV in North Carolina (NC) between 2016 and 2019. Data of those with complete residential address information at the time of HIV diagnosis and either a pol sequence reported to NC or from sequence analysis of the diagnostic specimen received from the NC State Lab of Public Health were assessed (n=2,679 persons, approximately 69% of new diagnoses reported in NC). Clusters were constructed with <1.5% pairwise genetic distance (TN-93) between two members and restricted to >=5 total members for this analysis. Addresses were geocoded, and planar distances between those with genetically linked infections were calculated using address coordinates.
Results: In total, we identified 67 genetic clusters involving 565 persons. Cluster members were mostly male (93%), African American (67%), and men who have sex with men (78%). The median cluster size was 7 members (range: 5-28), and most clusters were composed of a majority of members who lived in the same NC Field Services Unit Region (87%), of which there are seven, or county (58%), of which there are 100 with a median area of 436 square miles, at the time of diagnosis. The median geographic distance among linked members across all clusters was 25 miles (range: 0, 234), and 40 genetic clusters (60%) had a median geographic distance <25 miles among their linked members. Most clusters had maximum distances >100 miles (54%) and minimum distances <10 miles (97%) among linked members. Genetic clusters with median geographic distances >=25 miles among linked members were more likely to have members who were African American (71% vs. 63%), younger at HIV diagnosis (53% vs. 46% 18-24 years old), and in non-metropolitan (micropolitan, small town, or rural) areas (16% vs. 6%) compared to clusters with median geographic distances <25 miles among linked members.
Conclusion: While most genetic clusters had a majority of members located within traditional surveillance borderlines of regions and counties, most also included greater geographic distances between genetically-linked infections.



927 HIV TRACE VS PHYLOGENETIC ANALYSIS: UNRAVELING TRANSMISSION CLUSTERS IN SPAIN

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Background: The HIV-1 TRACE (TRAnsmission Cluster Engine) is a new computational tool to identify molecular transmission clusters in large databases. This approach is based on viral genetic relatedness to a reference sequence in order to construct and visualize the connections among clusters. Our objective was to identify transmission clusters in CoRIS cohort (2018 update) by using HIV-1 TRACE computational tool focusing on subtype B patients and to compare TRACE identified clusters with phylogenetic approaches.
Methods: We used the RT available regions from newly HIV diagnoses in 2018 in CoRIS. HIV-1 TRACE (http://hivtrace.datamonkey.org/hivtrace) was used to estimate transmission clusters in 484 subtype B antiretroviral-naïve patients enrolled in the CoRIS cohort. Phylogenetic analysis was conducted by maximum likelihood method (ML) with bootstrap using the GTR+G as nucleotide substitution model. Sequences were phylogenetically analysed along with all the most similar sequences as identified by a BLAST search. Local transmission networks (LTNs) were defined as phylogenetic clusters including sequences from Spain at proportions >70%, receiving bootstrap value >70%.
Results: HIV-1 TRACE results showed that 354 patients (73.1%, n=354/484) were not involved in any cluster and 130 patients (26.9%, n=130/484) were grouped in 54 clusters: 39 clusters with 2 nodes, 11 clusters with 3 nodes, 2 clusters with 4 nodes, 1 cluster with 5 nodes and 1 cluster with 6 nodes (range 2-6). Phylogenetic analysis revealed that 330 (68.2%, n=330/484) and 154 patients (31.8%, n=154/484) were involved in 63 clusters: 48 clusters with 2 nodes, 7 clusters with 3 nodes, 4 clusters with 4 nodes and 4 clusters with 5 nodes (range 2-5). Overall, the concordance between phylogenetic approaches and HIV-1 TRACE tool was 84.4%. The discrepancies were not observed only in the number of clusters, as previously described, but also in the distribution, since phylogenetic tools identified 8 clusters with more than 3 nodes and HIV-1 TRACE identified only 4 of these clusters.
Conclusion: The implementation of HIV-1 TRACE is an easy to use tool and it allows identification of transmission clusters. Our results revealed that HIV-1 TRACE identified fewer clusters among B-subtype patients than traditional phylogenetic approaches. Those discrepancies were due to the non-use of a threshold in the patristic distances in phylogenetic analysis.

928 RECONSTRUCTION AND ESTIMATION OF DIRECTED HIV-1 TRANSMISSION USING DEEP SEQUENCES

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Background: Key population in Uganda are disproportionately affected by HIV-1 relative to the general population (GP). Serial crossectional surveys were carried out in several HIV-1 high-risk and general population cohorts of the MRC/UVRI & LSHTM Uganda research unit to generate near full length (NFL) deep sequences. The aim of this study was to perform a source attribution analysis in the sampled populations to assess the extent to which high-risk groups contribute to the HIV epidemic in the general population and to further inform location focused interventions in key populations.
Methods: We used the phyloscanner program developed to phylogenetically infer transmission from with-in and between-host HIV genetic diversity to reconstruct directed HIV-1 transmission networks from NFL deep sequences (n=2,531) from communities of women at high risk to HIV (WHR), the fisherfolk (FF) and the general population (GP). We used the phyloflows package implemented in the R software to correct for sampling heterogeneity and estimate HIV-1 transmission flows between the three populations.
Results: Of the 2,531 HIV-1 NFL deep sequences analyzed in phyloscanner,105 highly supported HIV transmission pairs were identified with phylogenetic evidence for the direction of transmission (criteria for linkage: >60% and >60% for one direction). Our observed transmission counts showed majority of HIV-1 transmissions to be intra-population [GP-GP (34%)>FF-FF (31%)>WHR-WHR (10%)]. Between populations, transmission counts were more prevalent from the GP to FF (11%) followed by those from the FF to the GP (10%) (Figure 1). An estimation of HIV transmission flows showed results that were comparable

to the observed counts within and across populations with the exception of transmissions within the WHR that increased more than four-fold.
Conclusion: Majority of HIV-1 transmissions were largely localized within the three studied populations. An estimation of the viral transmission flows suggests that the high-risk FF population considered a hotspot for HIV infection could act as a sink of virus flowing from the GP. Although consistent with our earlier findings, interpretation of these results highlights the importance of correcting for sampling heterogeneity that could underestimate transmission flows. Results further imply that location focused interventions could be key for effective epidemic control in high-risk populations but should not negate the need for broader prevention.

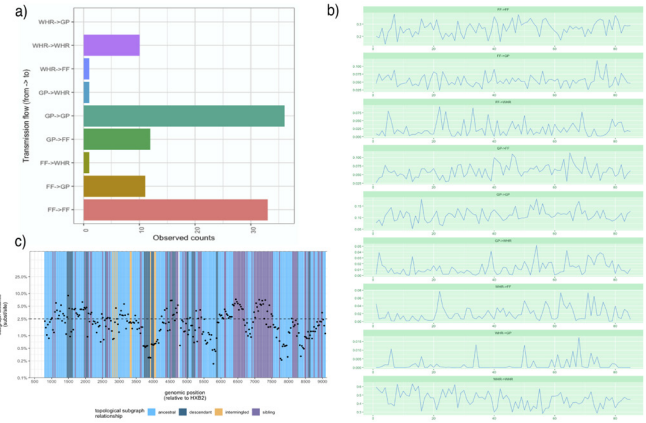


Figure 1. a) A bar graph showing the observed transmission counts from a transmitter to a recipient population. b) Markov Chain Monte Carlo (MCMC) simulation trajectories for estimated transmission flows within/between populations after adjusting for sampling heterogeneity c) a phyloscan plot showing deep-sequence phylogenies reconstructed at 250bp genomic window intervals across the genome. For a pair of individuals, the scan plots show the shortest patristic distance between subgraphs of both individuals (y-axis) and the topological relationship between subgraphs of both individuals (colours) across the genome [ancestral to one another (light blue), siblings (purple), intermingled (yellow) or descendant (dark blue)]

929 CONCORDANCE OF METHODS IN IDENTIFYING MOLECULAR HIV CLUSTERS

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Background: Molecular epidemiology is increasingly used to understand HIV transmission and monitor outbreaks and can be a critical tool in their prevention. Different methods are available to identify transmission networks, and their choice can be arbitrary. The impact of method choice on cluster identification has not been comprehensively assessed and may affect public health interventions that rely upon their results.
Methods: We studied 8 commonly used methods (7 model-based, and distance-based HIV-TRACE) and used them to identify clusters of HIV-1 subtype B pol sequences from 1,656 persons, ~80% of a densely-sampled Rhode Island epidemic during 2004-2018. For each method, we compared proportion of clustered sequences within and between methods using various distance and bootstrap thresholds; and clustering concordance between methods (including percentages of identical sequence pairs that cluster together; percentages of cluster similarity at 100% and at 80%; and percentages of identical non-clustered sequences). We conducted comparisons under (i) strict (bootstrap ≥0.95; TN93 distance 0.015 substitutions/site) and (ii) relaxed (bootstrap 0.8-0.9; distance 0.03-0.045 substitutions/site) thresholds, intended to address different public health objectives (e.g. strict for outbreak; relaxed for epidemic characterization).
Results: Of the 1,656 sequences, 18-53% formed 114-217 clusters, depending on thresholds used. Clustering proportion within methods depended on bootstrap and distance, with distance having stronger effects. Variation in clustering proportion across methods was more pronounced with stringent bootstraps and relaxed distances. For strict thresholds, HIV-TRACE identified 5-15% higher proportion of clustered individuals than model-based methods ($p<0.005$ for all pairwise comparisons). In contrast, for relaxed thresholds, HIV-TRACE identified 3-19% lower proportion of clustered individuals than model-based methods ($p<0.05$ for all pairwise comparisons). Distributions of percent concordance between methods, stratified by threshold type (strict, relaxed), are presented in the Table.
Conclusion: Clustering similarity between common molecular epidemiology methods varied, with some substantial discordance. In the context of integration of molecular epidemiology into public health, this implies that the choice of clustering method and threshold may impact precision of public health interventions.

Table. Distributions of Concordance Percentage between Analyzed Methods by Threshold Stringency

Concordance Criteria	Strict Thresholds n=56 pairwise method comparisons					Relaxed Thresholds n=56 pairwise method comparisons				
	Min	Q1	Median	Q3	Max	Min	Q1	Median	Q3	Max
Percentages of identical sequence pairs that cluster together	14%	79%	91%	97%	100%	45%	71%	82%	97%	100%
Percentages of clusters that are 100% similar	57%	76%	84%	92%	97%	39%	63%	75%	83%	94%
Percentages of clusters that are 80% similar	82%	95%	97%	99%	100%	77%	88%	93%	98%	100%
Percentages of identical non-clustered sequences	79%	92%	98%	99%	100%	70%	87%	96%	98%	100%

930 USE OF PHYLOGENETIC ANALYSIS TO INFER THE DIRECTION OF HIV TRANSMISSION

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Background: Phylogenetic analysis can provide important information about the spread of HIV in cohorts and populations. Methods are well established for identifying genetically-linked viral infections and clusters. Improved methods are needed to infer the direction of HIV transmission. We used next-generation sequencing (NGS) to generate whole-genome HIV sequences from couples with known linked HIV infection and known transmission direction. These data were used to evaluate methods for inferring the direction of HIV transmission.
Methods: NGS was performed using samples from 32 index-partner pairs (couples) enrolled in the HIV Prevention Trials Network (HPTN) 052 trial (up to two samples per person, collected on different dates). Index samples were obtained up to 5.5 years before partner infection; partner samples were obtained near the time of HIV seroconversion. The bioinformatics method, phyloscanner, was used to infer transmission direction. We evaluated inferred transmission direction using whole-genome NGS data for individual couples, for all couples as a group (one sample/person; group analysis) and for all couples using all available samples (multi-sample group analysis). We also evaluated inferred transmission direction using NGS data from individual HIV genes (gag, pol, env).
Results: Ultra-deep whole-genome NGS data was obtained for 116 samples from indexes and partners, including 105 unique index-partner sample pairs. Transmission direction was correctly inferred (index to partner) for 98/105 (93.3%) of the individual sample pairs, 99/105 (94.3%) of the sample pairs using group analysis, and 31 (96.9%) of the 32 couples using multi-sample group analysis. For the remaining cases, linkage was established but transmission direction could not be inferred. There were no cases where the incorrect transmission direction (partner to index) was inferred. The methods were more likely to infer transmission direction when there was a longer time between index and partner sample collection. Pol region sequences performed better than env or gag sequences for inferring transmission direction.
Conclusion: Accurate predictions of transmission direction were obtained using whole-genome and pol NGS data. Further research is needed to evaluate the performance of these methods in other settings and cohorts and in cases where both individuals (source and recipient) have long-term infection.

931 NEAR REAL-TIME IDENTIFICATION OF RECENT HIV INFECTION BY PID-NGS IN NORTH CAROLINA

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Background: The identification of recent (incident) HIV infections among people with newly diagnosed infections is critical to HIV prevention. We developed a Multiplexed Primer ID-Next Gen Sequencing (MPID-NGS) approach to identify recent infection by measuring the intra-host viral diversity over multiple regions of the HIV genome. Here we summarize the field implementations of this approach to identify recent infection, and include surveillance of drug resistance mutations (DRMs) in new diagnoses from the Public Health Laboratory in the state of North Carolina in 2018.
Methods: The MPID-NGS libraries were constructed covering the coding regions for protease (PR), a portion of reverse transcriptase (RT), integrase (IN), and the V1 to V3 region of the env gene from the HIV positive serums. The MiSeq platform was used for sequencing. The TCS-DR pipeline was used for bioinformatics analysis and to identify DRMs. Recent infection was defined as within 9-month of infection, and the RT and V1/V3 regions were used to define recency.
Results: A total of 547 HIV+ samples from diagnostic testing in 2018 were subjected to sequencing; of these 294 were considered new diagnosis and ART naïve as the sample used for testing was less than 30 days from diagnosis date reported by Health Dept. The sequencing success rate for the newly diagnoses was 91.2%. Overall recent infection was identified in 94 subjects (35%). Multivariate regression shows that people between 18 to 24 were more likely to be diagnosed at recent infection (OR=3.34, p=0.018) and those with unknown risk factors were less likely to be diagnosed at recent infection (OR=0.34, p=0.047). We observed that RT regions had more SDRMs than PR and IN, and RT K103N was the most common mutation overall. RT mutations M184V, R65R and major IN DRMs were rarely seen (Table 1). We used the RT sequence to explore close transmission clusters and we found a total of 28 clusters (size 2 to 4) using a similarity cut-off at 1%.
Conclusion: MPID-NGS combines recency identification and DRM screening for new HIV diagnosis in near real-time. Young individuals had highest recent infection rate while those with unknown risk factors had the lowest. The overall DRM rate was high but clinically important mutations were low. Rapid identification of transmission clusters containing recently infected individuals facilitates targeted prevention efforts.

Table 1. Surveillance drug resistance mutation (SDRM) summary for newly diagnosis (<30 days between diagnosis and sample collection) at different SDRM detection sensitivity levels.

SDRM sensitivity and minimal TCS # required	30%, TCS#≥10	10%, TCS#≥34	1%, TCS#≥350	0.3%, TCS#≥1208
PR region				
Specimens with minimal TCS # and above at PR region	254	218	86	38
Any PR SDRMs	6 (2.4%)	5 (2.3%)	19 (24.4%)	23 (60.5%)
M46I	1 (0.4%)	1 (0.5%)	14 (16.3%)	19 (50.0%)
M46L	4 (1.6%)	3 (1.4%)	3 (3.5%)	5 (13.2%)
RT region				
Specimens with minimal TCS # and above at RT region	260	226	83	33
Any RT SDRMs	49 (18.8%)	49 (21.7%)	23 (27.7%)	17 (51.5%)
Any NRTI SDRMs	9 (3.5%)	9 (4.0%)	6 (7.2%)	8 (24.2%)
K65R	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
M184V	1 (0.4%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Any NNRTI SDRMs	43 (16.5%)	43 (19.0%)	19 (22.9%)	13 (39.4%)
K103N	32 (12.3%)	29 (12.8%)	11 (13.3%)	5 (15.2%)
IN region				
Specimens with minimal TCS # and above at IN region	252	217	92	44
Any IN SDRMs	9 (3.6%)	10 (4.6%)	3 (3.3%)	1 (2.3%)
T97A	7 (2.8%)	6 (2.8%)	3 (3.3%)	1 (2.3%)

932 IMPLICATIONS OF NEXT-GENERATION SEQUENCING FOR DRUG RESISTANCE AND CLUSTER DETECTION

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Background: HIV-1 polymerase (pol) sequences from routine HIV drug resistance (DR) testing are used to monitor DR and identify molecular transmission clusters as part of public health (PH) surveillance. Proviral DNA DR testing using next-generation sequencing (DNA-NGS) has been used clinically since 2015 to provide DR information in the setting of viral suppression. Since DNA-NGS covers the same part of the HIV genome and DNA-NGS consensus sequences mimic traditional RNA-Sanger (RNA-S) sequences, they have likely been reported to PH as RNA-S sequences. Some clinical labs are also using (and others are considering) NGS for RNA-based DR testing (RNA-NGS). We evaluated whether shifts in testing methods and sequencing technology have implications for PH surveillance of DR and transmission clusters.
Methods: We identified ~115,000 RNA-S, ~11,000 DNA-NGS, and ~5,000 RNA-NGS sequences reported to New York during 2010-2019 from a single commercial lab. Inferred DR was compared for 1,350 persons with two or more sequence types. For cluster analyses, pairwise genetic distances were calculated between sequences for the same person with collection dates within 1 year (n=7,771 comparisons from 2,823 individuals) using Secure HIV-TRACE default settings and a 2% genetic distance threshold, stratified by sequence type.
Results: Overall, DR was 37% more likely to be inferred from DNA-NGS sequences than RNA-based sequences from the same individual. Time between tests was not a significant factor, and individual drug classes showed similar results. For clustering, over 25% of DNA-NGS were rejected by Secure HIV-TRACE due to high levels of ambiguities compared to RNA-NGS (11%) and RNA-S (8%). Based on pairwise distances for sequences from the same individual, RNA-NGS and especially DNA-NGS sequences, clustered less frequently than RNA-S sequences and at a higher distance threshold if they did cluster. Mean number of years since diagnosis was high and varied by sequence types but did not explain the results (Table 1).
Conclusion: We found significant differences between consensus DNA-NGS and RNA-NGS sequences compared to RNA-S sequences for cluster inference and between DNA-NGS and RNA-based sequences for DR. Hence, reporting of sequence type for PH surveillance is critical for ensuring appropriate inclusion of sequences for accurate HIV DR and transmission cluster analyses. Monitoring changes in sequencing technology is critical for assessing impact on PH and clinical decisions.

Table 1: Within-individual pairwise TN93 distances by sequence type[1]

Sequence Comparison	N	% clustering at <1.5% distance level[2]	% clustering at <0.5% distance level[3]	Mean Years since Dx
DNA-NGS to DNA-NGS	229	60.7	19.2	16.8
DNA-NGS to RNA-NGS	121	67.8	25.6	13.5
DNA-NGS to RNA-S	857	69.7	23.0	14.7
RNA-NGS to RNA-NGS	262	69.8	16.4	16.8
RNA-NGS to RNA-S	707	75.7	27.3	14.8
RNA-S to RNA-S	5,595	79.0	30.6	19.1

[1] Comparisons are within an individual from *pol* sequences collected < 1 year apart
[2] 1.5% distance threshold is the Secure HIV-TRACE default
[3] Clustering at the 0.5% distance threshold indicates recent and rapid transmission per CDC

933 PERVASIVE AND NONRANDOM RECOMBINATION IN NEAR FULL-LENGTH HIV GENOMES FROM UGANDA

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Background: Recombination is an important feature of HIV evolution, occurring both within and between the major branches of diversity (subtypes). The Ugandan epidemic is primarily composed of two subtypes, A1 and D, that have been co-circulating for 50 years, frequently recombining in dually infected patients. We have investigated the frequency of recombinants in this population (both inter- and intra-subtype), and the location of breakpoints along the genome.
Methods: As part of the PANGEA-HIV consortium project 1472 consensus genome sequences over 5kb were obtained from 1857 samples collected by the MRC/UVRI & LSHTM Research Unit in Uganda, 465 (31.6%) of which were near-full length (NFL) genomes (>8kb). The subtyping tool SCUEAL was used with a reference dataset of 218 full length subtype and circulating recombinant form genomes to identify recombination events both between and within subtypes. Genomic distribution of inter-subtype breakpoints was characterised using K-means clustering and generalized linear modeling.
Results: 233 of the 465 (50.1%) NFL genomes contained only one subtype; 143 A (30.8%), 82 D (17.6%) and 8 C (1.7%), while 232 (49.9%) contained more than one subtype (including A1/D (n=164), A1/C (n=13), C/D (n=9), A1/C/D

(n=13), and 33 complex types). No reported circulating recombinant forms were identified. Almost all of the NFL genomes (91.8%) contained at least one breakpoint, either intra- or inter-subtype.
The frequency of recombination breakpoints along the genome was similar in intra- and inter-subtype recombinants. K-means clustering of recombinant A1/D genomes revealed a particular genome region which was often inherited intact, extending from C2 in gp120 to TM in gp41. In addition, a generalized linear model showed significantly fewer breakpoints in the gag-pol and envelope C2-TM regions compared with accessory gene regions. There was little evidence of large-scale transmission of recombinants within this sample: almost all (153/164; 93%) of the A1/D recombinants are unique recombinant forms.
Conclusion: Recombination in HIV genomes is pervasive within and between subtypes in the populations studied and exhibits clear biases in breakpoint location. Its distorting effect on genealogical inference should therefore be acknowledged and taken into account more widely.

934 JACKHAMMER RT-PCR RECOVERS DIVERSE ARCHIVAL VIRAL GENOMES FROM KINSHASA, 1983

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Background: Viral genome data are a key means for characterizing current epidemics as well as reconstructing past epidemiological and evolutionary histories. To reliably infer the past, genome data stored in archival samples can provide essential calibration points for dated phylodynamic analyses. In the case of epidemics with a long pre-discovery history, such as the HIV/AIDS pandemic, specimens from early phases in the epidemic are very scarce, and the remaining viral genetic material are by now often degraded, thus warranting very sensitive sample-to-sequence procedures.
Methods: Here we expand our 'jackhammer' multiplex PCR approach to amplify and sequence HIV-1 RNA from 45 serum/plasma specimens from Democratic Republic of Congo (DRC) sampled in 1983 from the very first diagnosed AIDS patients of Africa. A sequential set of 63 primer pairs, compatible with most known subtypes, were designed that target 63 150-300 nucleotide overlapping regions across the coding HIV-1 genome. Primers with non-overlapping targets were combined into six pools, so that reverse transcription and a pre-amplification PCR could efficiently be performed in only six reactions per sample, before the final amplifications in 63 reactions.
Results: On average 80 % of PCRs produced reliable (Sanger) sequences after this <2 day general procedure, resulting in an average of +- 7000 nt of HIV-1 sequence data per sample. Performing additional PCRs with shuffled primers from an augmented primer set resulted in complete coding genomes for all samples. Twenty of the sequenced genomes were designated as a 'pure' subtype (A1, D, C, F1), two genomes were of an unknown subtype, six were known circulating recombinant forms (01_AE, 02_AG, 13_CPX, 25_cpx), and the remaining seventeen were each unique recombinants.
Conclusion: The recovered diversity spans essentially the entire global HIV-1 group M diversity, which (1) provides direct evidence that the breadth of HIV-1 group M diversity was already present when AIDS was first identified in Africa, and (2) indicates our method can efficiently recover virtually any (even degraded) HIV-1 group M genome. We analyze these genomes together with other time-stamped sequences from central Africa in a phylodynamic framework to refine the timings of the major early growth phases of the HIV-1 epidemic in this region.

935 A THIRD COMPLETE GENOME ESTABLISHES HIV-1 SUBTYPE L

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Background: As part of the region where HIV-1 initially expanded early in the global pandemic, the Democratic Republic of Congo (DRC) is where the most diverse HIV isolates have been found, including all recognized Group M subtypes and many unclassifiable sequences. Two divergent non-recombinant sequences, 83CD003 and 90CD121E12, collected in 1983 and 1990 in DRC were previously proposed as a new subtype, L. However, HIV nomenclature standards require three epidemiologically distinct genomes for a new classification.
Methods: Specimen CG-0018a-01 was collected in DRC in 2001 as part of an HIV prevention of mother to child transmission (PMTCT) study. Previous subgenomic HIV-1 sequences branched closely with the proposed subtype L references, but small sample volume and low viral load limited efforts to expand genome coverage. In the present study, the complete genome was assembled through application of metagenomic Next-Generation-Sequencing (mNGS) and target enrichment (HIV-xGen) methods. Neighbor-joining phylogenetic and recombinant analyses were completed to classify the genome using Phylip v3.5 and Simplot v3.5.1.
Results: The combined mNGS and HIV-xGen approach yielded 4,363,031 of 11,046,542 total reads (39.5%) that mapped to the final 9681 bp complete genome at an average coverage depth of 47,783x. The CG-0018a-01 genome branched with the putative subtype L references with a bootstrap value of 100 in a phylogenetic tree. Notably, the CG-0018a-01 branch was basal to the junction of 83CD003 and 90CD121E12, which suggests CG-0018a-01 may be more closely related to an ancestral strain. Recombinant analysis did not identify any breakpoints and indicated the putative subtype L references had the highest percent identity to CG-0018a-01 across the genome except in the well-conserved pol region. Subgenomic phylogenetic analysis of the pol region confirmed that CG-0018a-01 branched with L references with bootstrap support of 97.
Conclusion: The subtype L classification has now been established by the non-recombinant HIV-1 genome of CG-0018a-01 as the third isolate in this divergent Group M branch. The identification of CG-0018a-01 decades after the first two subtype L strains were collected suggests rare transmission of subtype L may be ongoing in DRC. Although it was collected most recently, CG-0018a-01 appears to be more closely related to the ancestral subtype L strain than the other two isolates and will be important for determining the origins of subtype L.

936 WHOLE-GENOME SEQUENCING SHOWS INCREASING HIV-1 SUBTYPE COMPLEXITY AMONG MSM IN THE UK

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Background: HIV recombination can occur following co-infection with two or more different strains. HIV whole genome sequencing (WGS) provides a better understanding of the recombination process and characterization of circulating strains. This helps to better define virus evolution and transmission dynamics.
Methods: HIV-1 WGS was undertaken on 382 samples from men-who-have-sex-with-men (MSM) collected between 2000-2006 (n=201) and 2015-2016 (n=181). The former consisted of chronic (n=157) and recent (n=44) infections whereas the latter of recent infections only. Recency of infection was defined by avidity assay. More than 110,000 partial pol gene sequences from routine HIV-1 genotyping in the UK were obtained from the UK HIV Drug Resistance Database (UKHDRD). Subtyping was performed using REGA HIV subtyping tool and Cluster Picker was used for transmission cluster analysis (1.5% genetic distance and 90% bootstrap support). Linked clinical and demographic data were extracted from the HIV and AIDS Reporting System at PHE.
Results: Partial pol gene sequence data shows a gradual increase in diagnosed infections involving complex recombinants among MSM in the UK from 0.8% (n=630) in 2000 to 9.3% (n=2655) in 2014 (p>0.001). Among recently infected MSM the proportion of complex recombinant infections was 11.0% (55/501) in 2014. WGS data shows even higher proportion of recent infections involving complex recombinants in 2015-2016 at 18.1% (33/181) compared to 2.3% (1/44) in 2000-2006. Furthermore, 32.4% (11/34) of WG sequences classified as complex recombinants were similarly classified using partial pol gene only. The most common subtypes involved in recombination were A and B (n=17 each; 50.0%). Most men infected with complex recombinants were born in the UK (63.6%; n=21) and probably acquired HIV in the UK (84.8%; n=28). Using WGS data only, 18.2% (n=6) of the complex recombinants formed 2 transmission clusters, containing 2 and 4 sequences. When analyses included partial pol sequences from the UKHDRD, 27.3% (n=9) of the complex recombinants were in 5 transmission clusters, each containing 2-9 sequences. Partial pol sequences were classified as pure subtypes or CRFs (B or CRF02_AG) in 3 clusters and complex recombinants in 2.
Conclusion: WGS shows that routine HIV-1 genotyping significantly underestimates the prevalence and complexity of circulating recombinant

strains among MSM in the UK. These data suggest an evolving MSM epidemic and transmission dynamics.

937 ASSISTED PARTNER NOTIFICATION SERVICES IN KAMPALA, UGANDA

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Background: Of the estimated 1.2 million people living with HIV (PLHIV) in Uganda, 77% knew their status as of 2017, falling short of the UNAIDS 95% target of PLHIV who know their status. To address this gap, we implemented World Health Organization-recommended assisted partner notification (APN) in routine clinical services.

Methods: Health workers were trained to implement APN at 69 health facilities in two urban Ugandan districts (October 2017–September 2018). Health workers identified eligible HIV-positive clients aged ≥15 years who had sexually transmitted infections, or a non-suppressed viral load and notifiable sexual partners with unknown HIV status. Eligible index clients provided written consent for an interview to elicit partner information and eventual notification. Health workers contacted partners through a phone call or home visit and notified them of their possible exposure and offered HIV testing. All those tested were linked to treatment and prevention services. We followed up with index clients to determine whether they experienced gender-based violence (GBV) after partner notification. We also determined APN acceptability and completion of the HIV cascade.

Results: Of 55,312 index clients eligible for APN, 37,289 (67.4%) participated. Of these, 20,732 (55.6%) were men aged ≥25 years. APN teams identified 49,314 sexual partners, and 40,177 (81.5%) were notified of their exposure. Of those notified, 6925 (17.2%) knew they were HIV positive and were on treatment. Of those with previously negative or unknown status, 20,284 (61.0%) were tested at the notifying facility, and 6028 (29.7%) were HIV positive. APN identified more HIV-positive women across all age groups than men. Following testing, 5803 (96.3%) of all newly identified HIV-positive partners initiated ART. 368 (0.9%) of index clients (women, 258 [70.1%]) reported experiencing post-notification GBV.

Conclusion: We found moderate APN acceptability and high linkage to care for HIV-positive partners. However, we need to understand why fewer partners were elicited than suggested in the literature and why 40% of notified partners declined testing at notifying facilities. A follow-up of those who declined facility testing is needed to ascertain if they tested elsewhere and were linked to care. Also, although <1% of index clients reported GBV, our findings suggest that monitoring and strengthening linkage to GBV services could help improve APN programs.

938 TARGETED PEER MOBILISATION AND ASSISTED PARTNER NOTIFICATION SERVICES IN KENYA

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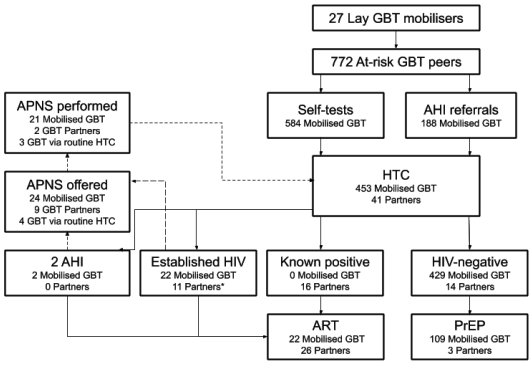
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Background: Peer mobilisation, HIV self-testing, acute HIV infection (AHI) screening, and assisted partner notification services (APNS) among gay, bisexual, other men who have sex with men and transgender women (GBT) may have great potential in penetrating hidden epidemics, and identifying GBT and their sexual partners with undiagnosed HIV. We operationalised these strategies in coastal Kenya and assessed safety, feasibility and linkage to antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) services after testing.

Methods: Twenty-seven lay GBT mobilisers offered OraQuick HIV self-tests to at-risk peers and immediate clinic referral for peers with AHI symptoms in April-August 2019. Regardless of the self-test result, mobilised GBT received HIV testing and counselling (HTC) with two HIV antibody rapid tests in series, according to Kenyan guidelines. GBT with negative or discordant rapid tests received GeneXpert point-of-care HIV-RNA testing. GBT newly diagnosed with HIV were offered immediate ART and APNS. HIV-negative GBT were offered PrEP. A subgroup of index participants returned to the study clinic one month after initiating APNS to assess potential social harms.

Results: Of 584 GBT mobilised for self-testing and 188 for AHI symptoms, 453 GBT (76.2%, 445/584 self-tests, and 4.3%, 8/188 AHI referrals) completed HTC (Figure 1). Median age was 26 (IQR: 22-30) years. Of these, 5.3% (24/453) were newly diagnosed with HIV, including 2 with positive HIV-RNA and negative (n=1) or discordant (n=1) rapid tests. 91.7% (22/24) initiated ART following a median of 2 (IQR: 1-7) days. In addition to the 24 newly diagnosed GBT, 9 partners and 4 GBT diagnosed through routine HTC were offered APNS and 70.3% (26/37) accepted. Of 41 enrolled partners, 26.8% (11/41) were newly diagnosed and 39.0% (16/41) were known positive. Of these, 90.9% (10/11) initiated ART, while all 16 known positive partners were on ART. Among 17 index participants, no social harm (100%, 17/17) was reported. PrEP initiation among HIV-negative participants was 25.4% (109/429) for mobilised GBT and 21.4% (3/14) for partners.

Conclusion: A targeted peer mobilisation approach offering self-tests, screening for AHI symptoms, and APNS for newly diagnosed GBT appears feasible and safe. These strategies can effectively penetrate hidden epidemics among GBT and link newly diagnosed GBT to care.



939 SCALE-UP OF ASSISTED PARTNER SERVICES (APS) IN BOTSWANA

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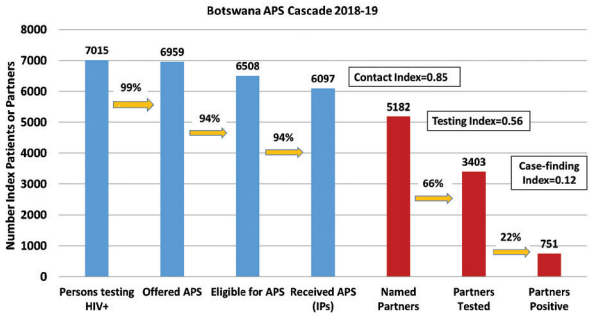
Background: Controlled studies have shown that APS is efficacious, and World Health Organization guidelines recommend that all persons diagnosed with HIV be offered APS. We evaluated APS implementation in the PEPFAR supported districts of Botswana to define program coverage and outcomes.

Methods: Starting in October 2018, the Government of Botswana Ministry of Health and Wellness and the International Training and Education Center for Health implemented a new APS program in 52 clinical sites. Guidelines during the evaluation period recommended that all persons with newly diagnosed HIV infection be offered APS; APS recipients (index cases [IPs]) chose to notify partners themselves or to notify partners in collaboration with counselors. Counselors used structured paper registers to record information about each named partner, including if the partner HIV tested and their test result. Aggregate outcomes from registers were entered into a database. We analyzed data collected between October 2018 and June 2019 to define conventional partner notification indices. These indices measure the number of partners named, tested and testing HIV positive per IP (i.e. contact index, testing index and case-finding index, respectively).

Results: Staff at 52 clinics performed 130,889 HIV tests during the evaluation period, of which 7015 (5.4%) were positive. A total of 6959 (99%) persons who tested HIV positive were offered APS, of whom 6508 (94%) were eligible for the intervention and 6097 (88% of HIV positive persons) received APS and were defined as IPs. IPs named 5182 sex partners (contact index=0.85, range across sites 0.68-0.93), electing to notify 3760 (73%) themselves and requesting counselor assistance to notify 1425 (27%). A total of 3403 (66%) partners tested for HIV (testing index=0.56, range 0.2-0.68) of whom 751 (22%) were HIV positive. The case-finding index was 0.12 (range 0-0.17).

Conclusion: Botswana clinics have successfully implemented APS, with high levels of program coverage and high HIV positivity among tested partners. However, fewer than one partner is named and tested per index case, suggesting areas for program improvement. The case-finding index

is substantially below that reported in most published evaluations, likely reflecting a combination suboptimal program implementation and the high proportion of HIV infected persons in Botswana who already know their HIV status.



940 OPTIMIZING TESTING INCREASES YIELD IN HIV CASE FINDING IN 24 COUNTRIES, 2018–2019

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Background: In 2019, the U.S. President's Emergency Plan for AIDS Relief prioritized the scale-up of testing contacts of HIV-positive index patients (contact testing) and optimizing provider-initiated testing and counseling services (PITC) to boost the first 90 goal (90% of people living with HIV know their HIV status) of the UNAIDS strategy. We assessed the impact of changes in HIV-testing modalities on the first 90 goal.
Methods: We used PEPFAR data from 24 countries that reported at least 2,000 HIV-positive test results per quarter. We compared second quarter (Q2) HIV testing data from 2018 and Q2 2019 and calculated the number of HIV tests and the yield (percentage of HIV-positive tests) by testing modality.
Results: Overall, HIV test volume decreased by 12%, and the number of HIV-positive results decreased by 4%, whereas overall yield increased by 9% (3.6% to 3.9%). In 2019, the 5 modalities that contributed to most (85%) of the HIV test volume were routine PITC in outpatient departments (OPDs; excluding emergency rooms, in-patient services, and tuberculosis and sexually transmitted infection clinics; 50%), voluntary counseling services (11%), mobile clinics (6%), contact testing (4%), and prenatal clinics (14%). Between 2018 and 2019, test volume increased in contact testing but decreased in others (Table). PITC in OPDs remained the leading contributor to the number of HIV-positive results, but the contribution of this modality to overall HIV-positive results decreased from 54% in 2018 to 45% in 2019. By modality, contact testing had the highest yield (8.9%, 2018; 14.3%, 2019) and was the second largest contributor to overall HIV-positive results (112,433/709,544 [15.8%]) in 2019. Increased test volume in other modalities (emergency wards, pediatrics, and TB and malnutrition clinics; 15% of all tests in 2019) did not increase yield (2018, 3.5%; 2019, 3.2%).
Conclusion: Overall, contact testing and optimization of other testing modalities increased HIV testing yield between 2018 and 2019. Increased yield and scale from contact testing was, however, insufficient to compensate for the decrease in HIV-positive results. Both yield and absolute number of cases should be considered in assessing the impact of scale-up of contact testing and optimization of case-finding approaches.

Table. HIV testing and yield[1] in 24 PEPFAR countries, 2018-2019

	2018 Q2 Number of tests	2019 Q2 Number of tests (% of total tests)	Change in number of tests	2018 Q2 Positive tests, N (yield)	2019 Q2 Positive tests, N (yield)	Change in yield
Overall	20,706,740	18,169,778	-12%	740,523 (3.6%)	709,544 (3.9%)	9%
Adults	19,348,914	16,074,097(89)	-17%	728,449(3.8%)	680,945 (4.2%)	13%
Men	7,009,076	5,465.842 (34)	-22%	267,581 (3.8%)	251,389(4.6%)	21%
Women	12,339,838	10,608,255(66)	-14%	460,868 (3.7%)	429,556(4.1%)	8%
Testing modalities						
PITC[2] in OPDs*	11,475,529	9,000,842 (50)	-22%	401,299 (3.5%)	317,555 (3.5%)	1%
Antenatal clinics	2,587,333	2,479,980 (14)	-4%	65,112 (2.5%)	63,779 (2.6%)	2%
Voluntary testing	2,857,293	1,954,145 (11)	-32%	112,486(3.9%)	78,893 (4.0%)	3%
Mobile clinics	1,487,264	1,041,431 (6)	-30%	48,338 (3.3%)	44,267 (4.3%)	31%
Contact testing	601,738	788,849 (4.3)	31%	53,616 (8.9%)	112,433 (14.3%)	60%
All other**	1,697,583	2,904,931(15)	71%	59,672(3.5%)	92, 613(3.2%)	-10%

[1]Percent positive HIV tests
[2]Provider-initiated testing and counseling services.
*Routine PITC in outpatient clinics excluding emergency rooms, in-patient services, and TB and STI clinics.
** Include tests conducted in emergency wards, and pediatrists, TB, STI, and malnutrition clinics.

941 PARTNER TESTING SERVICES TO ACHIEVE HIV EPIDEMIC CONTROL IN 9 PEPFAR COUNTRIES, 2019

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Background: The US President's Emergency Plan for AIDS Relief (PEPFAR) supports HIV prevention in most HIV endemic countries. Programs provide partner notification services (PNS) or index testing as an HIV case finding strategy.Data is collected on PNS, contacts of index cases and HIV indicators as Monitoring, Evaluation and Reporting (MER) data.These data measures progress towards HIV epidemic control by reaching the first UNAIDS 90.
Methods: To evaluate progress towards reaching the 1st 90, we performed a descriptive analysis of MER data reported by 9 countries during October 2018-March 2019 through a Data for Accountability, Transparency and Impact Monitoring database. The 9 countries were prioritized based on HIV prevalence and the need to scale up HIV prevention activities. The five variables selected represent key elements of the HIV testing cascade indicators.
Results: Three countries that were within 6% of achieving the 1St 90 (Namibia 4%, South Africa 5%, Rwanda 6%) had the lowest proportion of HIV-positive cases who accepted partner notification services (Namibia 66%, South Africa 52%, Rwanda 28%). In contrast, countries that had a larger gap to the 1st 90 target (Mozambique 18%, Nigeria 23%, Cote d'Ivoire 40%) showed a higher index case acceptance (Mozambique 87%, Nigeria 74%, Cote d'Ivoire 94%). Three countries met the PEPFAR benchmark of 1.5 contacts per index (Namibia 1.6, Uganda 1.7, Mozambique 1.5) but only two countries showed a high percentage of HIV positives as a result of the index exposure to contacts (Namibia 98%, Mozambique 94%). Despite being high HIV prevalence countries (Eswatini 27.4%), (Namibia 12.1%), (South Africa 18.8%) and closest to the 1st 90, these countries reported low HIV pos per 100 index (Eswatini 14, Namibia 19, South Africa 3).
Conclusion: These findings suggest that select countries closer to achieving the 1st 90 target with high HIV burden (Namibia, Southern Africa and Rwanda) tend to have a lower rate of index case acceptance. However, index testing is an important modality for countries that have a large gap to achieving the 1st 90s. Non-aggregated data within these countries should be evaluated to fully understand the most effective modality in each country.

Table 1. Select HIV testing cascade indicators from PEPFAR Monitoring Evaluation and Reporting Data and percent gap to the first 90, (15+ years) US PEPFAR Data for Accountability, Transparency and Impact Monitoring database, October 2018-March, 2019

COUNTRY	% GAP TO 1ST 90*	PEOPLE LIVING WITH HIV WHO KNOW THEIR STATUS % (95% CI)‡	INDEX CASES ACCEPTANCE OF PNS** (N) %	CONTACTS ELICITED PER INDEX CASE 15+ YEARS (N), RATIO	NEWLY IDENTIFIED HIV POS (N) %++	#OF NEW HIV POSITIVES PER 100 INDEX CASES	HIV PREVALENCE (%)
ESWATINI	3	92 (86 - >95)	(17, 239) 95	(17,858) 1.0	(1317) 30	14	27.4*
NAMIBIA	4	91 (84 - >95)	(843) 66	(1331) 1.6	(1193) 98	19	12.1*
SOUTH AFRICA	5ǂ	90 (83 - >95)	(59,495) 52	(50,163) 0.8	(10013) 57	3	18.8ǂ
RWANDA	6	94 (83 - >95)	(12, 359) 28	(15,420) 1.3	(577) 31	16	2.7ǂ
ETHIOPIA	17	79 (60 - >95)	(18,791) 80	(14,785) 0.8	(1216) 52	39	3.0*ǂ
UGANDA	17	84 (78 – 90)	(98,949) 85	(141, 388) 1.7	(16837) 64	17	5.9*
MOZAMBIQUE	18ǂ	72 (58 – 89)	(46,208) 87	(67,473) 1.5	(17793) 94	14	12.5*
NIGERIA	23ǂ	67 (49 – 89)	(53,888) 74	(55,270) 1.0	(6390) 48	11	1.4ǂ
COTE D'IVOIRE	40	63 (50 - 80	(78,579) 94	(64,718) 0.8	(10,227) 71	36	2.9*

Abbreviations: CI = confidence interval; PNS = partner notification services; N = number

* Source: Population-based HIV impact assessment (PHIA) survey. This is the most recent country data
ǂ The Fifth South African National HIV Prevalence, Incidence, Behavior and Communication Survey, 2017 (SABBSM V
‡ Source: UNAIDS, UNAIDS https://www.unaids.org/en/regionscountries/countries, 2018, The confidence interval is as reported by UNAIDS
**Partner notification services
++The percent represent newly identified positives/all positives contacts identified
* EPHIA results is the HIV prevalence among adults 15-64 years in urban areas

942 COMPARISON OF INDEX TESTING APPROACHES TO IMPROVE HIV-TESTING EFFICIENCY IN RWANDA

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Background: In 2016, WHO released guidelines on partner notification services / index testing. In these guidelines several approaches were recommended. In order to gain experience and understand the relative contribution of each approach towards epidemic control, Rwanda implemented client referral, provider testing, and contract referral. We report our findings here of their relative performance in reach, testing uptake, yield, and linkage to care.
Methods: Index testing is implemented in all 23 health facilities in Kigali city. Three index testing strategies are used to actively find new cases of PLHIV: client referral, provider testing, and contract referral. The cases identified are linked

to care and followed up longitudinally. The case surveillance system captures core demographic, epidemiological and service delivery variables. Paper forms and electronic Case Report Forms (eCRF) hosted within the District Health Information System 2 are used to collect these data variables and for storage. The data were exported to Microsoft Excel and STATA statistical package for analysis.
Results: Between October and June 2019, 2598 index cases were registered. Of them, 1792, 624, 156 and 26 Index cases were registered from voluntary counseling and testing, provider initiated testing, antenatal clinic and maternity respectively. From the total index cases, 2316 (89.1%) provided partner's information for the last 12 months with an index case to partner ratio of 1.5 (3844 elicited partners, mean=1.5). Of those, 3344 (86.9%) partners were successfully contacted; 37% were reached through client referral, 32% by provider and 31% by contract referral. Of all partners contacted, 2833 (84.7%) came to the health facility for HIV testing and 118 (4.2%) were already aware of their HIV+ status. Of 2715 who previously self-reported testing negative or never tested, 2442(89.9%) were tested for HIV. Of those 2442, 218 (8.9%) tested HIV+ and 203 (93.1%) of those were linked to treatment. Compared to client referral, provider testing was more effective in identifying people with HIV, odds ratio 1.86 (95% confidence interval, CI, 1.02-3.38).
Conclusion: The High level of partner testing through Active case finding highlight the substantial impact that active case finding can have on Rwanda's pathway towards HIV epidemic control.

943 EXPANDING HIV IDENTIFICATION BY TESTING CONTACTS OF DECEASED HIV INDEX CLIENTS

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Background: Tanzania is at 61% and among countries that lag behind on UNAIDS first 95 target, which requires 90% of all people living with HIV (PLHIV) to know their status. Index HIV testing is an optimized HIV testing modality, aimed at accelerating progress towards UNAIDS first 90, which targets identification of undiagnosed HIV infected individuals through testing of sexual contacts, and biological children of index PLHIV. There is, however, a missed opportunity in reaching contacts of deceased HIV clients. In October 2018, THPS extended Index Testing Initiative (TEI) was designed, an innovation where sexual contacts and biological children of deceased PLHIV were reached and given opportunity to test for HIV infection.
Methods: The study aimed to to expand HIV positive clients' identification, through testing index contacts of deceased HIV positive clientsDetails of deceased HIV clients, at 24 supported health facilities in Kigoma (15) and Pwani (9) regions were accessed through CTC2 cards and HIV status of sexual partners, treatment supporter's mobile number and home address documented. Peer educators contacted sexual partners through mobile phone and arranged home visits for HIV testing sensitization and education. HIV testing was performed by healthcare providers.
Results: A total of 906 archived files of deceased HIV clients were reviewed and a list of 530 sexual partners extracted, among whom 168 (32%) had known HIV status. The remaining 362 sexual partners had unknown HIV status, 233 (64%) were reached for HIV testing whereby 45 (19%) were newly identified HIV positive. All 45 positives were linked to HIV care and treatment.
Conclusion: There is an opportunity to expand HIV identification from deceased HIV clients. Correct contact information documentation improves tracing of index contacts. We recommend scale up of this initiative to reach potential groups of HIV infected individuals such as contacts of deceased clients.

944 NONENROLLMENT AMONG HIV-POSITIVE KENYAN FEMALE INDEX CLIENTS IN PARTNER NOTIFICATION

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Background: Assisted partner services (aPS) involves notification and HIV testing for sexual partners of persons diagnosed HIV-positive (index cases). Since the impact of aPS is contingent on high acceptance rates, we sought to assess the characteristics and reasons for non-enrollment of female index cases in an ongoing implementation science study of aPS scale-up in western Kenya.
Methods: We analyzed data from HIV-positive females (age ≥15 years) who were offered aPS in 31 health facilities in western Kenya from May 2018 to August 2019. Socio-demographics of females were compared by aPS enrollment status (accepted, refused, ineligible) and reasons for refusal and ineligibility were tabulated. We used multivariate binomial regression to assess the association between demographics and aPS refusal.
Results: Across facilities, 28,031 females received HIV testing and 1,050 tested HIV-positive (yield: 3.8%). Overall, 839 females accepted aPS (80%), 59 refused (6%) and 152 were ineligible (14%). APS acceptance did not differ by age, testing history or testing type (provider vs. client initiated). Females who refused aPS were more likely to have completed secondary school (adjusted relative risk (aRR) 2.03, 95% CI: 1.13 - 2.82) and be divorced/separated (aRR: 3.09, 95% CI 1.39 - 6.86) or single (2.66 95% CI:1.31 - 5.42) compared to married/cohabitating. The most common reason for refusing aPS was not feeling emotionally ready (31%) and claiming not to have any sexual partners (15%). Common reasons for aPS ineligibility included fear or risk of intimate partner violence (9%), previous HIV diagnosis (9%) or not enough time for aPS provision (3%).
Conclusion: APS has high acceptability among HIV-positive females regardless of age or testing history. More counseling may be needed to increase uptake among females with higher education and those who are separated or single. Follow-up for females who are not emotionally ready for aPS or had insufficient time for aPS in their clinic visit can improve program coverage.

945 SCALING UP ASSISTED PARTNER NOTIFICATION SERVICES IN WESTERN KENYA

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Background: Despite high HIV prevalence in Kenya, a substantial proportion of persons living with HIV are not aware of their status. Assisted partner services (aPS), or notification for sexual partners of persons diagnosed HIV-positive, has been shown to increase HIV testing and linkage to care. The World Health Organization (WHO) guidelines recommend scale-up of partner notification services in Africa yet optimal strategies for implementation and aPS performance in a real-world setting are not well-defined.
Methods: We report findings from an ongoing implementation science study of aPS in western Kenya. Starting in May 2018, aPS was scaled up by the Ministry of Health in 31 health facilities in Kisumu and Homa Bay counties. Newly diagnosed HIV-positive females ≥15 age years were offered aPS. Those who accepted provided contact information for all male sexual partners in the past 3 years. Healthcare providers notified partners of their potential HIV exposure and provided HIV testing and referral services.
Results: From May 2018 to mid-September 2019, 29,249 females tested for HIV across facilities and 1,120 were diagnosed HIV-positive (yield: 3.8%). Overall, 899 HIV-positive females were enrolled into aPS (acceptance rate: 80%) and reported an average of 1.7 male partners each (1,497 male partners total). Healthcare workers located and tested 68% of reported male partners, of whom 19% were newly diagnosed HIV-positive. At 6 weeks follow-up, 90% of female index cases and 87% of male partners reported to be on antiretroviral therapy (ART) with few adverse events (2% of female indexes reported relationship dissolution and 0.7% reported intimate partner violence).
Conclusion: APS has been safely incorporated into healthcare facilities in western Kenya, with high coverage among female index cases and their male partners and high linkage to ART. APS is a promising strategy to increase HIV testing and linkage and achieve the 95-95-95 targets in Kenya.

946 HIV TESTING AND INTEGRATED HIV/STI/HEPATITIS TESTING, OREGON, 2016

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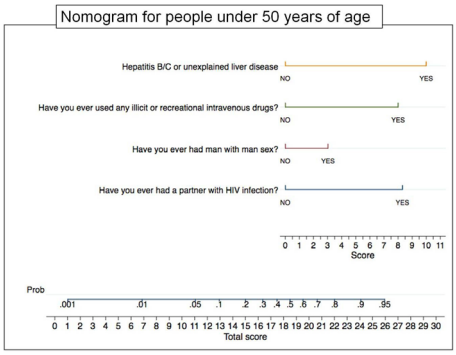
Background: Both the US Preventive Services Task Force and the Centers for Disease Control and Prevention recommend routine, voluntary, "opt-out" HIV testing for all adolescents and adults. Despite these recommendations, HIV testing is not routine practice. Furthermore, integrated HIV, STI, and hepatitis testing is even less common.
Methods: We analyzed outpatient HIV, STI, and viral hepatitis-related insurance claims from the Oregon All Payers All Claims Database (APAC) for 2016. Using ICD-10 and CPT codes, we identified the number of patients that had an HIV test, an STI test, and a hepatitis B or hepatits C test. We excluded those aged <13 years and >64 years, pregnant women, and those previously diagnosed with HIV. We examined demographic, healthcare, and geographic predictors of HIV testing and integrated HIV, STI and hepatitis testing.
Results: In 2016, 4.8% of the sample (n=1,780,612) had an HIV test, 13.0% had a test for an STI or hepatitis B or C,and 4.2% had integrated HIV and STI or hepatitis testing. At visits that included an HIV test, 88.3% were tested for an STI or hepatitis. Conversely, at visits that included an STI or hepatitis test, 31.5% were tested for HIV. HIV tests were most commonly accompanied by gonorrhea/chlamydia (62.4%), syphilis (53.0%), and hepatitis B (47.2%) testing. Women were more likely to be tested for HIV and experience integrated testing than men. Those aged 18-29 were most likely to have an HIV test and HIV/STI/hepatitis co-testing, while those aged 50-64 were least likely to be tested. Black/African Americans were most likely to be tested for HIV and to have integrated testing while Native American/Alaska Natives were least likely to experience these testing services. Compared to those with other insurance coverage, those with Medicaid were more than two times more likely to be tested for HIV and to have integrated testing. Those in rural and frontier regions were less likely to be tested for HIV and STI/hepatitis than those in urban areas.
Conclusion: Routine HIV testing and integrated HIV/STI/hepatitis testing are not widespread practice. Routine, rather than risk-based, testing, is critical to the timely diagnosis and treatment and, thus, prevention of onward HIV, STI, and hepatitis transmission.

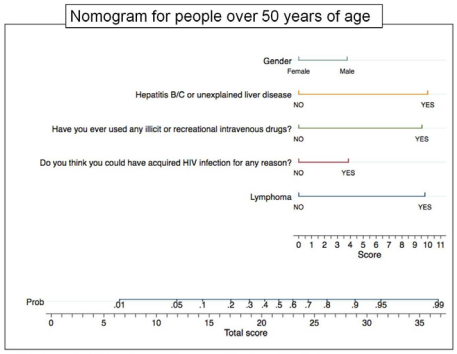
		Any HIV test		Any STI/HCV/HBV test		Any STI/HCV/HBV test among those receiving HIV test at same visit		Any HIV test among those receiving STI/HCV/HBV test at same visit
	Total	N	% of group	N	% of group	N	% of any HIV test	% of any STI/hepatitis test
Age								
13-17	184,610	3,226	1.7	14,190	7.7	2,892	89.6	20.4
18-29	381,032	35,703	9.4	92,585	24.3	32,303	90.5	34.9
30-39	339,986	24,578	7.2	57,335	16.9	22,181	90.2	38.7
40-49	318,334	10,602	3.3	31,363	9.9	8,866	83.6	28.3
50-64	556,650	11,084	2.0	43,803	7.9	9,017	81.4	20.6
Gender								
Female	995,017	58,673	5.9	177,475	17.8	53,239	90.7	30.0
Male	785,595	26,520	3.4	61,801	7.9	22,020	83.0	35.6
Race/ethnicity								
White, NH	388,287	22,879	5.9	57,779	14.9	20,203	88.3	35.0
Hispanic or Latino/a, any race	48,908	3,337	6.8	8,157	16.7	2,944	88.2	36.1
Black or African American, NH	20,853	2,006	9.6	4,101	19.7	1,757	87.6	42.8
American Indian or Alaska Native, NH	12,731	699	5.5	1,927	15.1	620	88.7	32.2
Asian, NH	12,027	960	8.0	2,023	16.8	775	80.7	38.3
Native Hawaiian or Pacific Islander, NH	2,064	132	6.4	376	18.2	123	93.2	32.7
Multiracial or other	3,985	211	5.3	534	13.4	176	83.4	33.0
Missing race and ethnicity	1,291,757	54,969	4.3	164,379	12.7	48,661	88.5	29.6
Insurance Type								
Other insurer	1,108,137	33,337	3.0	117,623	10.6	29,106	87.3	24.7
Medicaid	672,475	51,856	7.7	121,653	18.1	46,153	89.0	37.9
Region								
Urban	1,181,213	60,854	5.2	169,401	14.3	53,535	88.0	31.6
Rural	563,644	23,000	4.1	66,233	11.8	20,498	89.1	30.9
Frontier	35,755	1,339	3.7	3,642	10.2	1,226	91.6	33.7
All	1,780,612	85,193	4.8	239,276	13.4	75,259	88.3	31.5

947 AN AGE-ADAPTED, EASY-TO-IMPLEMENT SCORE FOR INTEGRATED BUNDLED, RAPID HIV/HCV TESTING

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Background: Undiagnosed or unlinked HIV-and/or HCV-infected populations still remain an issue worldwide. Integrated, bundled, rapid HCV/HIV testing has been proposed, but testing recommendations slightly differ between the two diseases: HCV testing is recommended for high-risk groups and all persons born between 1945 and 1965; HIV testing is recommended for everyone between the ages of 13 and 64. Our objective is to evaluate which HCV self-reported risk factors are associated with higher rates of infection, considering age as differences may exist. We also focus on creating an easy-to-implement score.
Methods: We conducted a sub-analysis of the DRIVE03 study (NCT03145753), which was carried out at four primary care centers, including non HIV-infected people aged, 18 and 70 years. After participants completed an HIV/HCV risk questionnaire, HCV screening was performed using rapid tests for these with any positive response and all participants between 50 and 70 years. Two multivariable models were created, one for participants younger than 50 and other for these older than 50. These models included the questions that exhibited the strongest association with a positive HCV result in the univariate analysis
Results: A total of 7,936 questionnaires were completed and 4,705 HCV tests were performed, 46 of these (0.98%) were positive. Model identified, four out of the 22 questions, that predicted 90% of HCV status for participants younger than 50: HIV- or HCV-infected partner OR 26.6 95% CI (7.6–92.9), Male Sex Male 3.3 (0.8–13.5), illicit or recreational drug use 23.6 (4.2–131.8), and hepatitis or unexplained liver disease 51.0 (17.4–154.9). For patients over 50, five questions predicted 89% of HCV status: male gender 3.1 (1.4–7.2), illicit or recreational drug use 18.1 (4.2–77.8), the belief that there is any possibility of being HIV/HCV infeted 3.2 (1.4–7.5), a previous lymphoma 19.4 (2.1–183.3), and hepatitis or unexplained liver disease 20.8 (8.6 - 50.3). Nomograms appear in Figure
Conclusion: Two easy-to-implement models that are age adapted can predict the majority of HCV status, in general population. This work contributes to the implementation of integrated, bundled, rapid HCV/HIV testing programs.





**Prob: probability of presenting a positive hepatitis C virus test*

948 HIV TESTING CRITERIA TO REDUCE TESTING VOLUME AND INCREASE POSITIVITY IN BOTSWANA

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Background: Recent PEPFAR guidance seeks to diminish HIV testing volume and focus testing on higher positivity populations. We sought to define testing criteria to reduce total tests performed and increase positivity in Botswana.
Methods: We analyzed data collected October 2018-August 2019 as part of routine HIV testing provided in 134 Botswana Ministry of Health facilities supported by the International Training and Education Center for Health (I-TECH). We randomly split the data into prediction and validation datasets of equal size and used multivariate logistic regression to identify demographic characteristics, testing strategies, and testing sectors (e.g., antenatal) associated with HIV positivity; factors with significant adjusted odds ratios (aOR) ≥1.5 were included in the testing criteria. Testing strategies and sectors where cessation of testing was deemed unacceptable a priori (TB, STD, VCT, partner services, antenatal, labor & delivery, pediatrics and gynecology) were excluded from model development and included in the testing criteria. We

applied the new testing criteria to the validation dataset to determine the number of tests performed, test positivity, proportion of positives missed, and costs averted. Costs were derived based on total budgets allocated to I-TECH to support HIV testing and estimated costs of test procurement.

Results: The analysis included 262,230 tests of which 4.3% were HIV positive. Model derivation analysis identified ages 23-29, 30-39, and 40+, non-citizenship, and emergency department testing as significantly associated with positivity. Among 131,115 tests in the validation analysis, 5,580 (4.3%) were HIV positive. Restricting testing to persons age >30 years and other defined criteria would reduce testing volume by 23% and increase positivity to 4.9%; 649 (2.1%) of the 30,178 persons who would not be tested were HIV positive representing 11.6% of all positive tests in the validation dataset. Positives missed by the criteria had a median age of 25 years and were mostly female (67%) and tested in the general outpatient department (86%). Assuming no changes in staffing, implementing the new testing criteria would decrease total HIV testing costs by 13%, a savings of $18 per positive test missed.

Conclusion: In Botswana, a targeted approach to HIV testing could reduce testing volumes by 23% and modestly increase HIV test positivity while missing 11.6% of positive tests. Cost saving would be modest unless implementation was accompanied by changes in staff costs.

Table – Predictors of HIV Test Positivity, Botswana testing data

	Adjusted Odds Ratio	95% Confidence Interval	*p*-value
Female	1.27	(1.17-1.37)	<0.001
Non-citizen	2.38	(2.07 - 2.74)	<0.001
Age (ref=0-22)			
23-29	1.59	(1.37 - 1.86)	<0.001
30-39	2.81	(2.43 - 3.24)	<0.001
40+	3.1	(2.68 - 3.58)	<0.001
Testing Strategy*			
Emergency	1.56	(1.30 - 1.87)	<0.001
Inpatient	1.06	(0.76 - 1.49)	0.73
Testing Point**			
Accidents/Emergency	0.8	(0.67 - 0.94)	0.009
Outpatient - Departments	0.61	(0.52 - 0.72)	<0.001
Outpatient - Specialty Clinics	0.43	(0.28 - 0.65)	0.001
Inpatient - General	0.45	(0.14 - 1.47)	0.19
ICU	4.35	(0.50 - 38.18)	0.18
Inpatient - Medical	0.76	(0.50 - 1.31)	0.32
Inpatient - Orthopedics	1.25	(0.69 - 2.26)	0.47
Inpatient - Surgical	1.07	(0.64 - 1.79)	0.8

*reference = Other provider-initiated testing and counseling
**reference = OPD - General

949 FREQUENT HIV TESTING OF MSM AND TGW OF COLOR RESULTS IN EARLIER DIAGNOSIS

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[1]CDC, Atlanta, GA, USA

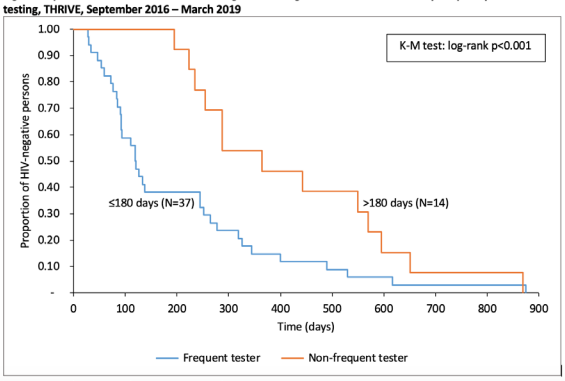
Background: Few clinical studies exist to support recommendations for more frequent than annual HIV testing of persons at increased risk for HIV. Frequent testing provides more opportunities for PrEP counseling and initiation, and earlier diagnosis of HIV and initiation of ARV medications to preserve immune function and prevent HIV transmission. We studied the effect of HIV testing frequency on time to diagnosis and yield of testing among MSM and TGW of color in the THRIVE demonstration project.

Methods: We analyzed a longitudinal database that included HIV tests and results for a cohort of persons enrolled in THRIVE from September 2016 to March 2019. All MSM and TGW of color in THRIVE were at increased risk for HIV. We excluded those who were PrEP users. Among persons who had an initial negative HIV test and at least one additional test, we estimated the median number of HIV tests and conducted Kaplan-Meier analyses to determine the time to diagnosis since an initial negative HIV test. We defined frequent testing as a mean interval between tests of ≤180 days and non-frequent testing as >180 days. We estimated the yield of HIV testing as the number of new diagnoses per tests performed. All results were stratified by testing frequency.

Results: In THRIVE, 20,956 clients received an HIV test. Of these, 26% (5408) had an initial negative test and at least one additional test. Among these 5408 persons, 1338 were MSM or TGW of color who did not use PrEP and 47 (4%) had a subsequent positive test. Overall, the median time to diagnosis was 235 days (IQR 92–364). Frequent testers were diagnosed earlier than non-frequent testers (p<0.001) (Figure). Among 34 frequent testers, the median time to diagnosis was 120 days (IQR 83–278), the median number of tests was 3 (IQR 2–4), and the median interval between tests was 84 days (IQR 53–119). Among 13 non-frequent testers, the median time to diagnosis was 364 days (IQR 255–569), the median number of tests was 2 (IQR 2–3), and the median interval between tests was 255 days (IQR 198–325). The diagnostic yield among MSM or TGW of color who were frequent testers was 1.2% (34/2846) and among non-frequent testers 1.0% (13/1281). Among all other THRIVE clients, the yield was 0.2% (12/6056).

Conclusion: The diagnostic yield was similar for MSM and TGW of color who were tested frequently or non-frequently, but frequent testing was associated with a shorter time to diagnosis. These data support the CDC recommendation to test persons at risk of HIV more often than annually.

Figure. Kaplan-Meier curve of time to HIV diagnosis among MSM and TGW of color by frequency of HIV testing, THRIVE, September 2016 – March 2019



950 INDETERMINATE HIV RAPID-TEST RESULTS: OUTCOMES AND RISK FACTORS

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Background: Little is known about the frequency, subsequent outcomes and factors associated with indeterminate HIV rapid results. We assessed final HIV serological outcomes for individuals with rapid indeterminate test results and associated risk factors in Rakai, Uganda.

Methods: 54,469 HIV rapid test results, defined by two parallel rapid tests, among 31,413 participants aged 15-49 years in the Rakai Community Cohort Study were assessed. 8361 participants were tested on two separate visits and 7354 had three time points tested. Each visit was approximately 18 months apart. Indeterminate results were defined as contradictory rapid test results or inconclusive concordant rapid test results. The final HIV status for each indeterminate observation was determined using previous HIV status information and additional testing, including PCR, ELISA and Western blot when necessary. Generalized estimating equations together with modified Poisson regression models with robust variance were used to assess prevalence ratios (PRs) of subsequent HIV serological outcomes and factors associated with indeterminate rapid test results.

Results: The prevalence of HIV rapid test indeterminate results was 2.7% (1490/54,469). Of the 1,490 rapid indeterminate observations, 26% were eventually classified as HIV positive. The proportions of persons with rapid indeterminate results progressing to HIV rapid positive, negative, or still indeterminate at the subsequent visit were 19%, 40% and 41%, respectively. For individuals with two consecutive indeterminate results who had a third follow-up visit (67 individuals), 21% (14/67) tested negative, 9% (6/67) were positive and 70% (47/67) were still indeterminate.

Factors associated with higher risk of an indeterminate result were: women vs. men (adjPR 2.07, 95% CI 1.77,2.41); >44 vs. <20 years of age (adjPR 1.69, 95% CI 1.26,2.26); student vs. farmer (adjPR 0.62, 95%CI 0.46, 0.83); shopkeeper vs. farmer (adjPR 0.81, 95%CI 0.68, 0.96); ART vs. not (adjPR 1.29, 95% CI 1.10,1.51). In total, 4.4% of individuals on ART had indeterminate test results.

Conclusion: The frequency of indeterminate rapid results was low (<3%), and a quarter ultimately tested HIV positive. 41% of individuals with an indeterminate result had an indeterminate result on a follow-up visit and 0.64% of the population had continuous indeterminate results over a 3 year period.

951 SIGNIFICANT UNDERQUANTIFICATION OF HIV RNA WITHIN ROUTINE SETTINGS IN SOUTH AFRICA

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Background: The extent to which pre-analytical variables impact HIV viral load (VL) accuracy is unknown. We describe VL log difference between paired point of care (POC) and centralized laboratory (lab) results within routine clinical settings, and determine whether result variability was associated with time to result, facility or season.

Methods: Secondary analysis of data from a POC implementation study at four tertiary facilities in South Africa between March 2018 - August 2019. Two 4ml EDTA tubes were collected from HIV-positive women at time of delivery. One sample was centrifuged and plasma tested within 24 hours on an HIV VL assay at POC (Cepheid Xpert) and the other sent for routine lab testing (Cobas 8800 or Abbott RealTime) but only centrifuged at the testing lab. Results were transformed into log scale with those below limit of detection assigned a log value of 0.001 and results below limit of quantitation assigned value of lower limit of quantitation. Median log differences were calculated as POC - lab result. Ranksum and K-tests for equality of medians were used to determine if log differences varied significantly by time to lab result, facility, and season. Proportion of paired results with >0.5log difference and discrepancy at 1000 RNA cps/ml threshold were compared using X2 tests. Multivariable binomial regression was performed to identify variables associated with discrepant VL results at 1000 cps/ml threshold.

Results: Among 1600 paired results, median POC VL was 2.1 (1.6–3.9) and lab VL was 2.0 (1.3–3.6) log (p<0.001), with median time to result of 1.6 (1.5–4.8) and 67.5 (45.5–99.1) hours, respectively. 475 (29.7%) specimen pairs had a VL difference >0.5log. Longer duration to lab result (p<0.001) and facility (p<0.001) were associated with >0.5log difference (Table 1). 59 (3.7%) paired samples had discrepant results at 1000 cps/ml threshold, of which 53 (3.3%) had a POC VL ≥1000 cps/ml but lab VL <1000 cps/ml. There was significant misclassification of lab VLs resulted ≥5 days compared to <5 days (aRR 1.82: 1.01–3.30).

Conclusion: Longer time to lab result and facility, but not season, increased likelihood of underquantifying HIV VL by >0.5log and misclassifying results as <1000 cps/ml. Timely centrifugation and testing should be prioritized.

Table 1. Distribution of HIV viral load differences between point of care and centralized laboratory results

	Numbers (%, column)	VL log10 difference*, Median (IQR)	p-value	VL log10 difference >0.5, Number (%, row)	p-value	Misclassification at ≥1000 cps/ml threshold, Numbers (%, row)	p-value
Overall	1600	0.2 (0 - 0.6)		475 (29.7)		59 (3.7)†	
Facility							
1Cobas	85 (5.3)	0.2 (0 – 0.4)		17 (20.0)		2 (2.4)	
2Cobas	283 (17.7)	0.1 (-0.1 – 0.3)	<0.001	62 (21.9)	<0.001	14 (5.0)	0.005
3Abbott	239 (14.9)	1.0 (0.4 – 1.6)		166 (69.5)		17 (7.1)	
4Cobas	993 (62.1)	0.2 (0 – 0.4)		232 (23.3)		26 (2.6)	
Lab VL result turn-around time (days)							
<1 day	43 (2.7)	0.1 (-0.1 – 0.3)		4 (11.6)		1 (2.3)	
1 - <3 days	833 (51.1)	0.2 (0 – 0.5)		217 (26.1)	<0.001	26 (3.1)	0.171
3 - <5 days	507 (31.7)	0.3 (0 – 0.8)	<0.001	163 (32.2)		18 (3.6)	
5 - <7 days	171 (10.7)	0.3 (0 – 1.0)		72 (42.1)		12 (7.0)	
≥7 days	46 (2.9)	0.3 (0 – 1.6)		18 (39.1)		2 (4.4)	
Seasons							
Colder	961 (60.1)	0.1 (0 – 0.6)		285 (29.7)		33 (3.4)	
Warmer	639 (39.9)	0.2 (0 – 0.6)	0.166	190 (29.7)	0.974	26 (4.1)	0.509

Cobas = tested on Cobas 8800 HIV-1 test (Roche Molecular Systems, inc., Branchburg, NJ); Abbott = tested on Abbott RealTime HIV-1 test (Abbott Molecular, Inc., Des Plaines, IL); IQR = interquartile range; VL = viral load; POC, point of care; log10 = logarithm base 10; Seasons defined as 6 calender months with warmest mean high temperatures compared to 6 colder months; *VL log10 difference calculation = point of care HIV VL – centralized laboratory HIV VL; †Misclassification at 1000 cps/ml: 53 POC VL ≥1000 cps/ml, 6 lab VL ≥1000 cps/ml

952 EVALUATION OF A TRUE POC VIRAL LOAD TEST: SAMBA LEUCO-DEPLETED WHOLE BLOOD HIV ASSAY

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Background: To meet the UNAIDS 90:90:90 targets, patients in developing countries require better access to HIV viral load (VL) testing to confirm anti-retroviral (ART) treatment success. Current laboratory-based assays are confined to cities with high infrastructure, limiting access to patients in remote settings. The SAMBA II HIV-1 Semi-Q Whole Blood (WB) Test is a portable, robust, heat-stable, point-of-care (POC) VL assay that automatically leuco-depletes 3 logs of cellular RNA and DNA, thus providing clinically meaningful results (VL <or> 1000 cp/ml) using a finger-prick blood sample.

Methods: Analytical sensitivity was determined by probit analysis on dilution series of HIV-1 standard and 11 seroconversion panels. Specificity was determined by testing 500 HIV-1 negative WB samples and those containing hepatitis B, C and HTLV-I or II as well as potentially interfering substances such as bilirubin and ART drugs. Clinical sensitivity and specificity was determined using venous and finger-prick capillary blood collected from consecutive HIV-positive patients attending clinics for routine testing in four countries (Cameroon, UK, Ukraine, Zimbabwe). 1,490 venous and 816 finger-prick samples were tested. SAMBA HIV VL results using WB were compared with to Abbott Real-time PCR assay using plasma and analysed as a binary results (<1000 cp/ml or >1000 cp/ml ±0.3 Log_{10}). Samples with discrepant results were tested with a second gold standard HIV VL assay (Roche, Hologic or BioMerieux).

Results: Limit of detection of the SAMBA II HIV-1 Semi-Q WB Test using Probit analysis is 1,037cp/ml (95% CI: 868-1,362cp/ml) with a 95% probability of detection at 1,000 cp/ml. Specificity was 100% in 500 HIV-1 negative samples (95% CI 99.4-100%). No cross-reaction or interference was observed with common ART drugs or samples containing other infections and potentially interfering substances. Concordance between SAMBA II WB POC assay and centralised gold standard assays in clinical samples at VL > or < 1,000 cp/ml ±0.3 Log_{10} is given in the Table.

Conclusion: The SAMBA II WB VL test is highly accurate using the WHO recommended > or < 1,000 cps/ml. Results can be obtained on site as soon as 95 minutes. Phlebotomy and centrifugation are not required, making SAMBA a simple 'sample-in/results-out' true POC assay for remote settings

Performance of the SAMBA-II Whole Blood Viral Load Assay (+95% Confidence Intervals)		
	Venous Samples	Capillary Samples
Total Samples tested	1490	816
True negative (<1000 cp/ml)	1257	624
True positive (>1000 cp/ml)	196	157
False negative (<1000 cp/ml)	13	24
False positive (>1000 cp/ml)	24	11
Concordance with gold standard	1453/1490 97.5% (96.7 - 98.3%)	781/816 95.7% (94.3 - 97.1%)
Sensitivity @ cut-off ≥1000 cp/ml	196/209 93.8% (90.5 - 97.0%)	157/181 86.7% (81.8 – 91.7%)
Specificity @ cut-off <1000 cp/ml	1257/1281 98.1% (97.4 to 98.9%)	624/635 98.3% (97.3 - 99.3%)
Positive Predictive Value (≥1000 cp/ml)	196/220 93.3% (90.0 - 96.6%)	157/168 93.5% (89.3 - 97.2%)
Negative Predictive Value (<1000 cp/ml)	1257/1270 99.0% (98.5 - 99.6%)	624/648 96.3% (94.9 - 97.8%)

953 MODELING POINT-OF-CARE NUCLEIC ACID TESTS (POC NAT) TO MINIMIZE HIV MISDIAGNOSES

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Background: The World Health Organization (WHO) adult HIV diagnostic testing strategy requires up to 4-7 rapid diagnostic tests (RDTs) prior to ART initiation. Although more expensive than RDTs, adding POC NAT to current testing strategies may minimize misdiagnoses and attrition, permitting ART initiation with fewer tests.

Methods: Using the Cost-Effectiveness of Preventing AIDS Complications model, we simulated a one-time HIV test in addition to status quo (SQ) testing practices in a low HIV-undiagnosed prevalence setting (1.3%): Côte d'Ivoire (CI). Model inputs included mean age (37y), SQ HIV testing (74 tests/1,000PY), and costs of ART ($6-22/m), HIV care ($27-38/m), and assays (RDT $1.50; POC NAT $27.92). We assessed 3 testing strategies: RDT-based strategies recommended by the WHO (RDT-WHO) and CI (RDT-CI), and a novel strategy: POC NAT to resolve RDT discordancy (NAT-Resolve). We calculated the number of true/false negative/positive (TN, TP, FN, FP) results for each strategy. We modeled 3 scenarios: A) sensitivity/specificity from WHO prequalification reports and no attrition between tests, B) sensitivity/specificity from WHO prequalification reports and reported attrition and result-delay rates, and C) field-based RDT sensitivity/specificity and reported attrition and result-delay rates. We reported life expectancy (LE) and costs per misdiagnosis and per person in the tested population, as well as incremental cost-effectiveness ratios (ICERs, in $/year-of-life saved [YLS]; threshold ≤$1,720 [CI per-capita GDP]).

Results: Relative to the tested population, there were few misdiagnoses in Scenarios A and B (Table 1). A FN diagnosis led to a LE loss of 5y (vs. a TP); this LE loss was most sensitive to HIV detection rates after developing an opportunistic infection. A FP diagnosis increased costs by $6,500 (vs. a TN); this cost increase

was most sensitive to costs of HIV care and ART, and time spent misdiagnosed. In Scenarios A and B, for the entire tested population, LE and costs were very similar between all 3 strategies. In Scenario C, with field-based RDT characteristics and attrition, NAT-Resolve averted more misdiagnoses and was cost-saving compared to RDT-WHO and RDT-CI.

Conclusion: With HIV Rapid Diagnostic Testing-based strategies, the impacts of misdiagnoses may be substantial. In combination with RDTs, in practice in a low HIV prevalence setting, POC NAT-based testing strategies will minimize misdiagnoses, improve attrition, and be cost-saving.

Table 1: Projected number of misdiagnoses, life expectancy, and lifetime costs resulting from RDT-WHO, RDT-CI, and NAT-Resolve testing strategies in Côte d'Ivoire (tested population = 10,000,000 adults).

Strategy [§]	FN diagnoses	FP diagnoses	Life expectancy (months, discounted)	Lifetime costs/person ($, discounted)	ICER ($/YLS)
Scenario A [a]					
RDT-WHO	364	1	264.84	144.89	Comparator
RDT-CI	348	3	264.84	144.90	100
NAT-Resolve	341	1	264.84	145.00	2,500
Scenario B [a + b]					
NAT-Resolve	422	1	264.84	144.76	Cost-saving
RDT-WHO	521	1	264.84	144.78	More costly, less effective
RDT-CI	506	2	264.84	144.79	More costly, less effective
Scenario C [b + c]					
NAT-Resolve	19,697	49,705	264.37	191.09	Cost-saving
RDT-WHO	25,075	54,717	264.26	194.68	More costly, less effective
RDT-CI	23,941	103,177	264.34	227.06	More costly, less effective

[§] Modeled strategies (scan QR code at bottom right for detailed graphic):

RDT-WHO: A reactive RDT1 is followed by RDT2. Concordant results are followed by RDT3; discordant results are followed by *repeat RDT1/RDT2* which, if are reactive/concordant, are followed by RDT3. A reactive RDT3 is diagnosed HIV+; a non-reactive RDT3 is sent to a *state reference laboratory* for a final RDT. Positive results are followed by pre-ART retesting.

RDT-CI: A reactive RDT1 is followed by RDT2. Concordant results are followed by RDT3; discordant results are followed by *repeat RDT1/RDT2*, which are sent to a *state reference laboratory* for a final RDT if discordant *or* reactive/concordant. A reactive RDT3 is diagnosed HIV+; a non-reactive RDT3 is sent to a *state reference laboratory* for a final RDT. Positive results are followed by pre-ART retesting.

NAT-Resolve: A reactive RDT1 is followed by RDT2. Concordant results are followed by RDT3. A reactive RDT3 is diagnosed HIV+; a non-reactive RDT3 is sent to a *state reference laboratory* for a final RDT. Discordant results are followed by POC NAT, which is the final arbiter. Positive results diagnosed by RDT-only receive pre-ART retesting.

[a] Base case sensitivity/specificity: 99%/99% [RDT] and 95%/100% [POC NAT]

[b] Attrition: 29% [*before repeat RDT1/RDT2*] and 32% + 3-month delay [*before state reference laboratory testing*]

[c] Field sensitivity/specificity: 89%/83% [RDT] and 95%/100% [POC NAT]

Abbreviations: RDT, rapid diagnostic test; POC NAT, point-of-care nucleic acid test; FN, false negative; FP, false positive; ICER, incremental cost-effectiveness ratio; YLS, year of life saved. Results are rounded. Discount rate: 3%/year.

954 EVALUATION OF QUALITATIVE AND SEMIQUANTITATIVE HIV POINT-OF-CARE NUCLEIC ACID TESTS

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Background: Point-of-care (POC) nucleic acid tests (NAT) could detect acute HIV infection, resolve discordant screening results, monitor patients taking pre-exposure prophylaxis (PrEP), and identify virologic failure among persons with HIV infection (PWH) on antiretroviral treatment (ART). Real-time communication of POC NAT results can improve HIV prevention and care. While the SAMBA II POC NAT is used in Europe and Africa, it has not been evaluated in the US.

Methods: From June 2018 to August 2019, PWH and persons testing for HIV participated in Project DETECT, a study evaluating POC HIV tests in real-time. From June 2018 to March 2019, the SAMBA II Whole Blood Qual test [limit of detection (LOD) 400 copies/mL] was used for all participants. From April to August 2019, the Qual test was used on participants who had never been on ART and the SAMBA II Leukodepleted Whole Blood Semi-Q (LOD 1000 [range 500-2000] copies/mL) test was used for PWH who had started ART. Both whole blood (WB) tests were performed on unprocessed venipuncture (VP) and finger-stick (FS) WB. Results from WB tests and the SAMBA II Plasma Semi-Q test performed on frozen plasma from PWH were compared to Abbott RealTime HIV-1 PCR results (PCR) on plasma. Sensitivity, specificity, and concordance between tests were calculated.

Results: SAMBA was used in 292 visits among 249 participants; 180 (62%) visits were from PWH, and 112 (38%) from persons testing HIV-negative. 58 PWH had undetectable RNA levels by PCR, 27 had detectable but unquantifiable levels, and 95 had quantifiable RNA levels with a median 7487 (IQR 576-89630) copies/mL. The Qual test was used at 224 visits. Sensitivity of the Qual test among PWH with plasma RNA >400 copies/mL was 92% in VP and 97% in FS WB [Table]. Sensitivity of the Semi-Q test among ART-treated participants with RNA >1000 copies/mL was 100% in VP and FS WB. Specificity of the Qual test in ART-naive participants with RNA <400 copies/mL and persons testing HIV-negative was 100% in VP (n=111) and FS (n=9) WB. Four (8%) of 52 persons on ART with plasma RNA <1000 copies/mL (<20, 469, 608, and 949 copies/mL) had VP WB Semi-Q test results reported as >1000 copies/mL. Among PWH, the plasma Semi-Q had 96% and 95% concordance to WB and PCR results, respectively.

Conclusion: SAMBA's high concordance in this population suggests a role for POC NATs when starting and monitoring PrEP, detecting acute infection, and for monitoring potential virologic failure among PWH on ART.

Table 1. Cumulative sensitivity of SAMBA POC NAT HIV-1 results at increasing plasma HIV-1 RNA thresholds by Abbott RealT*ime* HIV-1 PCR [a] in Project DETECT participants, Seattle, WA, US, June 2018-August 2019

Plasma HIV-1 viral load threshold [a]	SAMBA II Qual Whole Blood Test [b, c]		SAMBA II Semi-Q Whole Blood Test [d, e]		SAMBA II Semi-Q Plasma Test [f, g, h]
	Venipuncture whole blood	Finger stick whole blood [i]	Venipuncture whole blood	Finger stick whole blood [i]	
All samples	96/111 = 86%	38/46 = 83%	20/68 = 29%	3/21 = 14%	20/48 = 42%
Detectable HIV-1 RNA	67/75 = 89%	37/39 = 95%	19/46 = 41%	3/19 = 16%	20/32 = 63%
≥200 copies/mL	49/53 = 92%	32/33 = 97%	19/22 = 86%	3/5 = 60%	20/21 = 95%
≥400 copies/mL [j]	49/53 = 92%	32/33 = 97%	19/21 = 90%	3/4 = 75%	20/21 = 95%
≥1000 copies/mL [k]	43/46 = 93%	30/30 = 100%	16/16 = 100%	3/3 = 100%	19/19 = 100%
≥2000 copies/mL	39/42 = 93%	27/27 = 100%	16/16 = 100%	3/3 = 100%	18/18 = 100%
≥3000 copies/mL	38/41 = 93%	26/26 = 100%	15/15 = 100%	3/3 = 100%	17/17 = 100%

Abbreviations: POC=Point-of-care, NAT=nucleic acid test, PCR=polymerase chain reaction, ART=antiretroviral therapy, PWH=persons with HIV infection

a. Abbott RealT*ime* HIV-1 RNA quantitative viral load assay, Abbott Molecular Diagnostics, Des Plaines, IA, USA.
b. SAMBA II HIV-1 Qual whole blood test, Diagnostics for the Real World (DRW), San Jose, CA, USA: A qualitative assay for detection of HIV-1 RNA and DNA in whole blood specimens.
c. Test used on all participants between June 2018 and March 2019 and on any participant who was ART-naïve at their study visit between April and August 2019.
d. SAMBA II HIV-1 Semi-Q whole blood test, Diagnostics for the Real World (DRW), San Jose, CA, USA: A semi-quantitative test with an analytical sensitivity adjusted to 1000 copies/ml with 95% probability of detection.
e. Test used on PWH between April and August 2019 who had started ART prior to their study visit.
f. SAMBA II HIV-1 Semi-Q plasma test, Diagnostics for the Real World (DRW), San Jose, CA, USA: A semi-quantitative test with an analytical sensitivity adjusted to 1000 copies/ml with 95% probability of detection.
g. Venipuncture whole blood is collected in EDTA tubes, centrifuged within 24 hours of blood draw, and plasma is stored as 1 mL aliquots at -70°C in the Public Health – Seattle King County laboratory.
h. Test used on PWH between April and August 2019.
i. Unprocessed finger-stick whole blood only obtained from participants with acute HIV infection or those enrolled in Project DETECT extended follow-up. Acute HIV infection is defined as having a first positive HIV test within 90 days of the Project DETECT study visit.
j. SAMBA II Qual Whole Blood Test limit of detection.
k. SAMBA II Semi-Q Whole Blood Test and SAMBA II Semi-Q Plasma Test limit of detection.

955 COMMUNITY-LED HIV SELF-TESTING INCREASES TESTING AND LINKAGE TO CARE OF MEN IN UGANDA

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Background: Targeted strategies are needed to increase knowledge of HIV sero-status and improve the HIV care cascade among men. We implemented a community-led oral HIV self-testing (HIVST) intervention among men in a peri-urban district in Uganda and assessed uptake of HIV testing, identification of HIV+ persons and linkage to care.

Methods: We conducted an implementation study from October 2018 to June 2019 among 1628 men in 30 villages of Mpigi district in Uganda. Community health workers distributed one HIVST-kit and a tailored linkage-to-care insert to each consenting male aged 15+years and living in a sampled household. We allowed up-to 10 days to use the kit, 30 days to seek confirmatory testing at a health facility (HF) and up to 60 days to start care if confirmed HIV+. We collected baseline data including demographics, testing history and HIV risk behavior. At follow up, we measured HIVST-uptake (by proof of used kit) and linkage-to-care as HF-confirmation of HIV sero-positive status (by proof of HIV test result slip) and ART initiation. We summarized categorical data as proportions and used Poisson regression to determine predictors of HF-confirmation of HIV sero-status among men using HIVST.

Results: At baseline, 19.8% (322/1628) of participants had never tested for HIV and only 37.2% (606/1628) had tested in the last 12 months.

HIVST-uptake was 95.3% (1551/1628) with 3.9% (63/1628) testing HIV+. Of those who used HIVST, 81.0% (1257/1551) sought HF-confirmation of HIV sero-status, 76.2% (48/63) of positives by HIVST were confirmed HIV+ at a HF. 79.2% (38/48) of confirmed HIV+ were newly diagnosed and 20.8% were previously diagnosed but untreated with ART or had fallen out of care, and 96% (46/48) of the confirmed HIV+ initiated ART.

Participants seeking HF confirmation of HIV sero-status were more likely to be older aged 25+ years (9.52, 95%CI: 3.22-28.18), unaware of their partner's status (2.73, 95%CI: 1.46-5.11) and not to have used the HIVST-kits (14.94, 95%CI: 5.47-40.77).

Conclusion: Community-led HIVST may be an efficient way to increase male HIV testing and linkage to care of newly diagnosed HIV+ and known HIV+ who had fallen out of care. Further research is needed to assess cost-effectiveness and scalability of this intervention in resource-limited settings.

956 UPTAKE OF HIV SELF-TESTING AMONGST YOUTH IN TERTIARY EDUCATION COLLEGES IN ZIMBABWE

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Background: HIV testing may serve as an entry point for youth to engage with the HIV prevention and care cascade. Several barriers have been identified for youth attending for facility based HIV testing, thereby delaying knowledge of their HIV diagnosis and subsequent linkage to care. Here, we assess the uptake of a HIV oral mucosal transudate (OMT) self-testing amongst youth attending tertiary level colleges in Zimbabwe.
Methods: Youth aged 16-24 years of age, of unknown HIV status and not having had a HIV test in the past 3 months were offered an OMT HIV self-test. Distribution points were chosen through social mapping involving students and staff at tertiary level campuses in Harare and Masvingo, Zimbabwe. Youth had the option to perform the self-test onsite, unassisted, in a private booth or offsite in a location of their choice. From 16th July 2019, blood based confirmatory testing was offered on site using SD Standard Q HIV ½ Ab 4-Line® and Chembio HIV ½ Stat-Pak® in parallel. Linkage to care (either confirmation of reactive test or attendance for ART initiation) was determined through phone call follow up.
Results: Distribution took place over 57 days in a three-month period, 2,760 youth received a self-test kit, 1,310 (63%) female, median age 21 years (IQR 20-23). In total, 1792 (65%) said they previously had sex, median number of partners in past one year, 1 (IQR 1-2), 1140 (65%) reported condom use at last sex. Close to one third (30%) of males had been circumcised. In total, 917 (33%) were first-time testers. Of those who had previously tested, 422 (23%) had used a HIV self-test kit. Overall, 1206 (44%) of youth said they had heard of a HIV self-testing before. In total, 1592 (58%) opted to test themselves offsite. Of those who received a test kit, 1637 (59%) reported their results, 29 (1.8%) were reactive. Of these, 6 reported confirmatory testing off site, 5 had confirmatory testing on site (n=4 of positive, n=1 negative), 2 refused confirmatory testing on site, the remainder were unreachable through phone contact.
Conclusion: Community based HIV self-test distribution in tertiary colleges is an opportunity to reach youth who may be at risk of HIV acquisition. Given the low HIV prevalence, linkage to prevention services is key for those testing negative. Further research needs to invest in ensuring seamless linkage to care for those testing reactive.

957 IS AN UNASSISTED PHARMACY-BASED HIV SELF-TESTING STRATEGY IN MOZAMBIQUE SUFFICIENT?

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Background: HIV self-testing (HIVST) is a strategy recommended by WHO to increase testing, especially among key populations, men and young people. In May 2019, an HIVST pilot began in Zambézia province involving 14 public/ private pharmacies (4 urban, 10 rural), allowing clients to purchase up to two oral HIV self-tests at a subsidized price of 50Mzn (~$US 0.80). The study assessed the acceptability and use of this strategy.
Methods: Exit-surveys were conducted in a random sample of 20 clients per pharmacy, independently from test purchase. A survey was also done for a random sample of up to 10 clients per pharmacy who bought a test and accepted being contacted later. Structured questionnaires were used assessing perceptions on HIVST; clients contacted after test purchase were additionally asked about its use. Analysis (X2-test) was done for each variable comparing clients who purchased versus not. Sales were monitored using pharmacy-based registers.
Results: During the first 3 months, 517 adults purchased 603 tests (70% male, 41% <30 years).
A total of 351 pharmacy clients participated in the surveys: 259 who did not buy a test and 92 who bought one. Median age was 29 years [IQR 23-37], 65% male, 60% married and 63% with a ≥12th grade education level. The most frequently reported advantage of HIVST was confidentiality, while primary disadvantages were lack of counseling and fear of test result (Table 1). Eighty-five (24%) clients found the test expensive.
From the 92 who bought a test, 73 participated in the additional survey, of whom 67 (93%) performed the test. Self-reported easiness of test instructions and test performance was 34% and 45%, respectively. Almost all (97%) were confident in the result, but 27 (40%) felt they needed additional information or counseling. Before doing the test, 49% felt very anxious, and 37% felt very anxious after the test awaiting results. Self-test result was revealed by 40 (60%) (one HIV-positive), with 15% reporting linking to a health facility to confirm their result.
Conclusion: HIVST at public/ private pharmacies was successfully employed, reaching male and young people. The cost, although small, might be a barrier. The perceived lack of counseling is concerning, suggesting a need for specific tools at pharmacies and/or offering assisted testing. Moreover, to attain the first 95 of the UNAIDS 95-95-95 goals, other strategies (e.g. index-case HIVST) should also be considered.

Table 1. Perceptions on HIVST among pharmacy clients, among clients who bought and who did not buy a self-test

	Pharmacy clients who did not buy a HIVST (n=259) N (%)	*Pharmacy clients who bought a HIVST (n=92)* N (%)	p-value
Ever heard about HIV self-testing			***<0.001***
No	210 (81%)	44 (48%)	
Yes	49 (19%)	48 (52%)	
*Advantages of HIVST**			
Simple/ no need of health provider	118 (46%)	57 (62%)	***0.01***
Keeps confidentiality	204 (79%)	77 (84%)	0.31
Result is fast	89 (34%)	40 (44%)	0.12
To be able to test with my partner	35 (14%)	7 (8%)	0.13
Other	16 (6%)	8 (9%)	0.41
*Disadvantages of HIVST**			
Fear of test result	65 (25%)	22 (24%)	0.82
Fear of somebody discovering	28 (11%)	3 (3%)	***0.03***
Don't know how to use it	16 (6%)	4 (4%)	0.52
No counseling nearby	74 (29%)	35 (38%)	0.09
Don't feel at risk for HIV	3 (1%)	0 (0%)	0.30
Don't know where to buy	2 (1%)	0 (0%)	0.40
Too expensive	18 (7%)	2 (2%)	0.09
Not able to read the instructions	4 (2%)	2 (2%)	0.69
Doubts on the quality of the test	28 (11%)	9 (10%)	0.78
Other	9 (3%)	7 (8%)	0.10
Is the pharmacy a good place to get a HIVST?			***0.02***
Yes	222 (86%)	88 (96%)	
No	35 (14%)	4 (4%)	
Opinion on price of the test			***0.02***
Very cheap	22 (8%)	6 (7%)	
Cheap	22 (8%)	9 (10%)	
Acceptable price	142 (55%)	65 (71%)	
Expensive	73 (28%)	12 (13%)	
Preferred setting to get an HIVST			0.12
Public health facility	85 (33%)	21 (23%)	
Private health facility	9 (3%)	5 (5%)	
Private pharmacy	125 (48%)	48 (52%)	
Public pharmacy	20 (8%)	14 (15%)	
Pharmacy at health facility	12 (5%)	1 (1%)	
Market/shop	1 (0%)	1 (1%)	
Other	7 (3%)	2 (2%)	
Preferred test (oral versus finger-prick self-test)			0.08
Oral	141 (54%)	61 (67%)	
Finger-prick	103 (40%)	28 (31%)	
Either	15 (6%)	2 (2%)	
Willingness to buy self-test for somebody else			***<0.001***
Yes	72 (28%)	12 (13%)	
No	166 (64%)	78 (85%)	
Maybe	21 (8%)	2 (2%)	

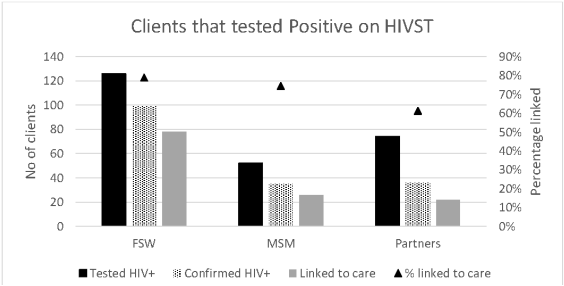
* Participants were instructed to mark all that apply for these survey questions

958 HIV SELF-TESTING AMONG KEY POPULATIONS AND SEXUAL PARTNERS OF NEW MOTHERS IN UGANDA

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Background: HIV self-testing (HIVST) was adopted for hard to reach populations (key populations and partners of pregnant and lactating women) in Uganda in September 2018. We report the preliminary findings from this program in Kampala, Uganda.
Methods: HIVST was rolled out to 38 facilities in Kampala in September 2018 using two distribution approaches. The facility-based approach targeted sexual partners of pregnant and lactating mothers with unknown HIV status. Before giving HIVST kits to female participants, we provided information about performing an HIV self-test through demonstration and videos in the local language. Women distributed the kits to their partners. The community-based approach targeted key populations (KPs), including female sex workers (FSWs) and men who have sex with men (MSMs) with unknown HIV status. Trained peers were given test kits at the facility to distribute to clients at KP hotspots. Clients who accepted were recorded in access-restricted distribution logs. Self-testers were asked to report results within 2 days; clients from the facility and the community who didnot report results received a follow-up phone call from a trained health worker. Those who reported HIV-positive results were offered confirmatory testing using the standard HIV testing algorithm. Data on kits distributed from October 2018 to June 2019, target population, testing yield, and linkage to care were summarized and analyzed in Excel.
Results: We distributed 9378 HIVST kits. In the facility, mothers received 5212 (56%) kits for their sexual partners. In the community, KPs received 4166 (44%) kits (MSMs, 2192 [53%]; FSWs, 1974 [47%]). Of the 9378 kits distributed, 9126 (97%) were HIV negative and 252 (3%) clients reported HIV-positive results: 74 (29%) were partners of mothers, 126 (50%) were FSW, and 52 (21%) were MSM. There were 17 (7%) known positives among those who reported. Of the 170 (67%) clients that returned for confirmatory HIV testing: 36 (49%) partners of mothers, 99 (79%) FSW, and 35 (67%) MSM. Linkage to treatment (126 [74%]) was <95% of the program target: 22 (61%) partners of mothers, 78 (79%) FSW, and 26 (74%) MSM. Fig 1
Conclusion: HIVST can identify patients with HIV among hard-to-reach populations. However, confirmatory testing and linkage to care are challenging.

Further research is needed to determine barriers to confirmatory testing and linkage to care for HIV-positive self-testers.

Figure 1 clients that tested HIV positive on self-test



959 ACCEPTABILITY OF HIVST DISTRIBUTION BY PREGNANT WOMEN TO MALE PARTNERS: A CLOSER LOOK

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Background: Provision of HIV self-test kits (HIVST) to HIV-positive pregnant women attending antenatal care for secondary distribution to partners of unknown HIV status may increase knowledge and linkage to HIV care and prevention among African men. Research to date indicates secondary distribution of HIVST by pregnant women greatly increases partner testing, but studies have not focused on experiences of women living with HIV who distribute HIVST to their partners.

Methods: The Obumu study is a randomized trial of secondary distribution of HIVST and linkage of male partners to HIV care or pre-exposure prophylaxis, compared to invitation letters as standard of care, among 500 pregnant women living with HIV in Kampala, Uganda. Women randomized to deliver HIVST to their partners are trained and given two kits to take home. Obumu includes qualitative interviews with a subset of 45 women. Interviews explore: 1) the partnered relationship; 2) HIV testing experiences; 3) discovery of HIV status; 4) experiences taking antiretroviral therapy; 5) pregnancy; 6) disclosure; 7) HIVST delivery; and 8) partner responses to HIVST. In this content analysis, qualitative data were examined inductively to characterize themes in the distribution process.

Results: Women in the qualitative sample were eager to have their partners test and receptive to HIVST. However, they were apprehensive about disclosing their own HIV status to their partners, believing disclosure would result in abandonment during pregnancy, when they felt vulnerable and dependent on their partner's support. Women were anxious to avoid the questions about HIV they feared delivering the kit would raise, and coped by: 1) delivering HIVST but misrepresenting its purpose; 2) avoiding explanations by leaving the kit –without comment -- where it would be seen; or 3) not delivering HIVST at all. When women delivered kits that were used by male partners, they often avoided discussing test results, and chose not disclose their own status when their partners asked. Women whose partners knew their HIV status delivered HIVST more easily.

Conclusion: Disclosure emerges as a major barrier to HIVST distribution to male partners by Ugandan pregnant women living with HIV. Counseling and support for disclosure as part of the distribution process may help to alleviate this barrier. HIVST distribution may be different, and more challenging, for HIV positive pregnant women than for women not living with HIV.

960 "FIRST TO KNOW MY STATUS": ACCEPTABILITY OF HIV SELF-TESTING AMONG SOUTH AFRICAN MEN

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Background: HIV self-testing (HIVST) is increasingly being used as a strategy to improve HIV testing coverage in sub-Saharan Africa, particularly in men, who are less likely to test for HIV in traditional health care settings. Understanding acceptability of HIVST is necessary to achieve optimal uptake of these new testing modalities.

Methods: HIVST kits were distributed to 4495 men in community-based venues in two regions in KwaZulu Natal, South Africa as part of a large implementation study. Individuals were offered self-administered oral fluid or blood-based tests and chose to use the tests on-site or at home. A subsample of 30 men who received and used HIVST kits took part in a single in-depth qualitative interview. Interviews covered: distribution of the test, experiences of HIVST, previous testing experiences, and preferences for HIV testing. Qualitative data were coded and inductively analyzed to identify themes representing men's perspectives on and experiences using HIVST.

Results: Men who participated in qualitative interviews responded positively to both types of HIVST and overwhelmingly preferred self-testing over testing at a health facility. Despite initial concerns about being able to administer the test correctly on their own, they found the HIVST kits easy and simple to use. Lack of familiarity with HIVST and the newness of the technology fueled some doubts about test efficacy, particularly oral tests. However, men gained confidence in the accuracy of HIVST when their results confirmed prior clinic-based tests. The fear of newly discovering an HIV-positive status through HIVST was an important concern for men, but this was far outweighed by the appeal of testing alone, in private. Being able to know their results "first," without having to trust a health care worker to protect the confidentiality of their results, was unexpectedly empowering for men. They reported that HIVST gave them a sense of independence and control over decisions about testing circumstances and disclosure. This, in turn, led them to talk about the experience of HIVST to others, generating additional interest in self-testing among their peers.

Conclusion: Our findings suggest that HIVST is an acceptable testing strategy among men. Men's perceptions of self-testing appear to evolve from an initial reluctance to an overall endorsement of HIVST through the experience of using the tests. Peer distribution of HIVST may be an effective method for scaling up HIV testing in communities where men do not test for HIV.

961 THE IMPACT AND COST OF HIV SELF-TEST DISTRIBUTION IN WORKPLACES IN SOUTH AFRICA

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Background: South Africa started distributing HIV self-test (HIVST) kits in 2017 in order to close remaining gaps in achieving the first 95 of the United Nations' 95-95-95 targets across all population groups. We analysed the ability of HIVST to reach rarely or never tested employees and the cost of distributing HIVST kits to rural workplaces compared to urban industries.

Methods: Distribution was targeted to small- and medium-sized workplaces with a predominantly male workforce and low baseline HIV testing in the mining, construction, manufacturing, security, petroleum and agriculture sectors in two predominantly rural and one urban province in South Africa and included both primary distribution (to employees) and secondary distribution (for their sexual partners). We used multivariate regression of the frequency of past testing to compare the probabilities of reaching never or infrequently tested populations with primary distribution in rural vs. urban workplaces. The cost of both primary and secondary distribution was analysed from the provider perspective and included the economic cost of the kit ($2, the current ex-works cost under an agreement with the manufacturer), freight, company sensitisation and HIVST demonstration, distribution and follow-up by peer educators.

Results: Between Nov. 2017 and Aug. 2018, the programme distributed 123,727 self-test kits in 2,313 companies (69% and 31% through primary and secondary distribution, resp.). The industries with the highest number of primary kits distributed were agriculture, construction, mining and petroleum in the rural provinces, and mining and construction in the urban province. Uptake was 85% across industries, and in men was twice that of women. 13% of test kits were distributed to employees who had never tested, and 38% to those who had last tested more than 12 months ago. The probability of self-test

uptake in infrequently and never tested populations was three times higher in rural workplaces (Table 1) and especially high in never tested employees aged <25 and in infrequently tested employees aged 25-34. The average cost of distributing HIVST in rural agricultural workplaces and urban industries was 4.30 USD vs. 4.35 USD, with 56% due to the cost of the kits (incl. freight), followed by distribution staff (32%), sensitisation (5%) and travel (3%).
Conclusion: HIVST distribution at the workplace leads to improved HIV testing coverage especially in underserved rural populations, at a similar cost to urban populations.

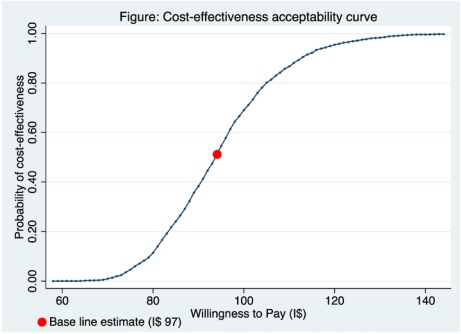
Table 1. Multivariate logistic regression model of the probability of reaching never and infrequently tested employees in urban and rural provinces
Note: ***, **, * denote p values of <0.001, 0.05 and 0.1, respectively

	Industries									
	Agriculture	Construction	Food	Manufacturing	Mining	Motor	Oil & Gas	Retail	Security	Service
Never tested (Urban)	2.214***	1.458**	1.612*	0.754	1.075***	0.967	0.907	1.022**	1.542***	1.883***
Std error	(0.384)	(0.254)	(1.263)	(0.145)	(0.137)	(0.123)	(0.038)	(0.194)	(0.281)	(0.162)
95% CI	[1.57;3.1]	[1.03;2.1]	[0.48;2.0]	[0.51;1.1]	[0.57;6.0]	[0.46;1.1]	[0.14;1.5]	[0.74;1.5]	[1.07;2.2]	[0.99;3.3]
Never tested (Rural)	4.118***	4.550***	2.945**	3.000**	2.106***	1.876**	2.311**	3.374**	2.741**	5.462***
Std error	(1.959)	(2.070)	(1.348)	(1.391)	(0.040)	(0.689)	(1.065)	(1.567)	(1.276)	(2.482)
95% CI	[1.62;9.2]	[1.86;11.3]	[1.21;7.2]	[1.21;7.4]	[1.68;10.0]	[0.94;5.8]	[1.20;5.7]	[1.11;8.3]	[1.35;6.8]	[2.23;13.2]
Infrequent testers (Urban)	2.670***	1.888***	0.848	0.905	1.082**	0.947	0.924	1.706***	1.067***	1.722***
Std error	(0.257)	(0.114)	(0.110)	(0.123)	(0.126)	(1.715)	(0.122)	(0.099)	(0.146)	(0.222)
95% CI	[1.19;2.2]	[0.69;1.14]	[0.65;1.0]	[0.69;1.2]	[0.76;1.3]	[1.18;9.1]	[0.71;1.2]	[1.37;10.7]	[0.85;1.4]	[1.30;2.2]
Infrequent testers (Rural)	3.941***	1.919***	1.234**	1.202**	1.832**	1.839*	1.094*	2.558***	1.150***	1.858***
Std error	(0.473)	(0.190)	(0.165)	(0.159)	(0.040)	(0.157)	(1.048)	(0.211)	(0.151)	(0.134)
95% CI	[3.34;4.9]	[1.25;2.0]	[0.94;1.6]	[0.92;1.5]	[1.12;1.8]	[0.96;1.6]	[0.31;0.5]	[1.20;2.0]	[0.88;1.5]	[0.82;1.4]

962 COST-EFFECTIVENESS OF HIV SELF-TESTING AMONG LONG-DISTANCE TRUCK DRIVERS IN KENYA

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Background: Awareness of HIV status is critical for achieving UNAIDS targets, particularly for sub-populations at high risk of acquiring and transmitting HIV. These sub-populations require targeted, resource-intensive strategies for HIV test uptake, a challenge when resources are limited. We conducted a trial-based cost-effectiveness analysis on offering the choice of HIV self-testing (CHIVST) in a high-risk population—long distance truck drivers—in Kenya.
Methods: We leveraged data from a randomized controlled trial of CHIVST (intervention, n=150) vs provider-administered testing—standard of care [SOC] (control, n=155). CHIVST included choice of SOC or clinic- or home-based self-test. Economic cost data (HIV test kits, medical supplies, labor, capital and overhead costs, patient time), including upper and lower bounds, came from the literature and reflected a societal perspective. Generalized Poisson and linear gamma regression models estimated the effectiveness (relative risk) and incremental costs (2017 I$), respectively, with incremental effectiveness calculated as the reciprocal of the absolute risk difference and reported as the number needed to receive CHIVST for an additional HIV test uptake. We reported incremental cost-effectiveness ratios, with 95% confidence intervals (CIs) calculated using Fieller's theorem. Deterministic sensitivity analysis identified key cost drivers; non-parametric bootstrapping generated cost-effectiveness acceptability curves to assess uncertainty in the ratio. We determined cost-effectiveness according to a willingness-to-pay threshold of 3x GDP per capita for Kenya (I$9774).
Results: HIV test uptake was 23% more likely for CHIVST vs SOC, with six individuals needed to receive CHIVST for an additional HIV test uptake (6.25, 95% CI 5.00-8.33). The mean cost per patient was more than double for CHIVST (I$26.56) compared to the SOC (I$10.47). The incremental cost-effectiveness of CHIVST was I$97.21 [95% CI 65.74-120.98] per additional HIV test uptake compared to SOC. Self-test kits and patient time were the main cost drivers, with findings robust even in a worst-case scenario of all upper bound economic costs. The probability of CHIVST being cost-effective at a given willingness-to-pay threshold approached one at a threshold of I$140 (Figure).
Conclusion: CHIVST is a highly efficient use of resources for improving HIV test uptake among high-risk populations. Policies supporting CHIVST in these populations may expedite achievement of country-specific UNAIDS targets.



963 CHARACTERISTICS OF MSM WHO REGISTER FOR HIV SELF-TESTING IN SAO PAULO, BRAZIL

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Background: HIV testing is a critical step of both HIV care and prevention. Since 2015 WHO recommends HIV self-testing (HIVST) as an additional screening strategy to improve testing coverage among key populations. Prior to implementation of HIVST in the public health system in Brazil, the demonstrative study "A Hora é Agora" evaluated the acceptance, interest in use and logistics of distribution of free HIVST kits among men who have sex with men (MSM) in Curitiba and Sao Paulo, two state capitals in Brazil. We here analyze the characteristics and prevention attitudes of participants registered to undertake HIVST in Sao Paulo
Methods: Between April-December/2018 potential participants were invited through social media and gay venues to complete a web-based anonymous survey on prevention attitudes, HIV infection risk and risk perception. We explored demographic and vulnerability characteristics associated with reported lifetime HIV testing using univariate analyses. We also compared participants with and without prior testing for their preferred testing strategy
Results: 6,477 respondents who provided valid answers were included. All were MSM, with median age of 28 years (IQR 23-34); 54% self-declared as white and 68% had at least 12 years of schooling. Sexual orientation was homosexual for 81%. Fifty percent of the participants reported at least 1 episode of unprotected anal intercourse in the past 6 months; 25% reported illicit drug use in the same period. Despite a high-risk profile, the perception of risk for HIV infection in the next year was high for only 4%. 78% reported being previously tested for HIV, with factors such as facility working hours (53%), exposure of personal issues to a provider (34%) and gender identity/sexual orientation-related stigma (21%) cited as barriers for testing. Older age, higher education, illicit drug use and gay orientation were associated with higher percentage of lifetime HIV testing (p<0.001). Most participants (67%) reported not knowing of the availability of HIVST before enrolling in the study. The preference for HIVST was higher among participants who had never been tested (71%) compared to those with previous HIV testing (61%; p<0.001)
Conclusion: In this study including high risk MSM, HIVST was the preferred testing strategy among participants who had never been tested. This shows HIVST may be an important tool to improve HIV testing, particularly among hard-to-reach key populations

Table 1: Characteristics of study participants, overall and according to prior HIV testing

	All respondents N=6477	Respondents with prior HIV testing N=5074	Respondents without prior HIV testing N=1403	p-value
Age	28 (23-34)	28 (24-34)	25 (21-30)	<0.001
Race*[1]				
White/caucasian	3452 (54)	2737 (55)	715 (52)	0.081
Other	2922 (46)	2264 (45)	658 (48)	
Education*[2]				
≤High school	2056 (32)	1441 (29)	615 (44)	<0.001
>High school	4377 (68)	3609 (71)	768 (56)	
Sexual orientation				
Gay	5249 (81)	4261 (84)	988 (70)	<0.001
Bisexual	678 (10)	494 (10)	184 (13)	
Heterosexual	550 (8)	319 (6)	231 (16)	
Steady partner*[3]	2328 (37)	1821 (37)	507 (38)	0.478
Illicit drug use*[4]	1549 (25)	1294 (26)	254 (19)	<0.001
Unprotected receptive anal intercourse in the past 6 months*[5]	3260 (54)	2579 (54)	681 (54)	0.924
Anticipated risk of HIV infection in the next year*[6]				
No risk	1314 (22)	1020 (21)	294 (23)	
Moderate risk	4506 (74)	3596 (75)	910 (72)	0.078
High risk	235 (4)	177 (4)	58 (5)	
Preferred HIV test*[7]				
Self-test	3816 (63)	2903 (61)	913 (71)	
Facility-based test	807 (13)	692 (14)	115 (9)	<0.001
Either	1451 (24)	1184 (25)	267 (21)	

Numeric variables are presented as medians and interquartile ranges
*[1]Missing/not declared for 103 participants; *[2]Missing/not declared for 44 participants; *[3]Missing/not declared for 186 participants; *[4]Missing/not declared for 226 participants; *[5]Missing/not declared for 449 participants; *[6]Missing/not declared for 422 participants; *[7]Missing/not declared for 403 participants

964 DOES PROVISION OF FREE HIV SELF-TESTING KITS INCREASE HIV DIAGNOSIS IN MSM?

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Background: High levels of HIV testing in men who have sex with men (MSM) remain key to reducing incidence, particularly in men who have condomless anal intercourse (CAI) with multiple partners. There is little evidence about the effectiveness of free HIV self-testing (HIVST) to increase HIV diagnosis rates in MSM. We aimed to assess if the offer of a single free HIVST kit led to increased diagnosis of HIV infections that linked to care.
Methods: SELPHI is an internet based, open-label, randomized controlled that used online advertising to recruit men potentially interested in HIVST. Enrolment criteria were male (including trans), aged ≥16 years, ever had anal intercourse (AI) with a man, not known to be HIV positive and consent to link to national HIV surveillance databases (to ascertain new HIV diagnoses and linkage to care). Participants were randomly allocated 3:2 at enrolment to a free HIVST (Baseline Test [BT]) versus no free HIVST (no Baseline Test [nBT]). Online surveys collected data at baseline, 2 weeks (2w) (BT only) and 3 months (3m) post-enrolment. Men in BT were asked about HIVST use and linkage to care if reactive. Primary outcome was a confirmed new HIV diagnosis within 3m of enrolment.
Results: 10,111 men were randomized (6049 BT; 4062 nBT); median age 33 years (IQR 26-44); 89% white; 20% born outside UK; 0.8% trans men; 47% degree educated; 15% never HIV tested; 8% ever and 4% currently on PrEP. At enrolment 89% reported AI and 72% CAI with ≥1 male partner in previous 3m. 4194/4695 (89%) in BT reported using the HIVST kit. No significant difference at 3m in confirmed new HIV diagnoses (primary outcome)(p=0.64, 19 [0.3%] in BT vs 15 [0.4%] in nBT). Men randomized to BT were more likely to HIV test in 3m after enrolment (96% vs 42%; risk ratio 2.27 95%CI 2.13, 2.40), but a higher proportion in nBT tested for HIV in the 3m after enrolment (42%) compared to 3m before (21%). STI testing rates between arms were similar (22% BT vs 25% nBT).
Conclusion: Reflecting national declines in MSM, new HIV diagnoses were low in both arms by 3 months after enrolment, with no significant difference between men randomized to receive an HIVST kit (BT) and those who were not (nBT). Men randomized to nBT may have been motivated to HIV test through other routes in the 3 months after enrolment. However, HIV testing rates were overall higher in the 3 months after enrolment in those offered HIVST, with similar rates of STI screening.

Table 1: HIV diagnoses, HIV testing, risk behaviours (CAI) and STI testing in the first 3 months after enrolment to SELPHI

	Offered HIVST kit (N=6049)	Not offered HIVST kit (N=4062)
Confirmed HIV diagnosis within 3 months	19 (0.3%)	15 (0.4%)
Diagnosed using a HIVST kit	10	0
Last HIV test prior to enrolment		
<3 months	3	2
3 months-2 years	6	6
>2 years	6	5
Never previously tested	4	2
Responded to 3-month survey	4036 (67%)	1565 (39%)
Tested for HIV in 3m after enrolment	3856 (96%)	661 (42%)
Tested for HIV using HIVST after enrolment	4194/4695 (89%)	89 (6%)

965 THE RATIONALE FOR A 3-TEST HIV DIAGNOSTIC ALGORITHM: BALANCING ACCURACY AND COST

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Background: To ensure >99% positive predictive value (PPV) for HIV testing strategies (HTS) in all settings, WHO 2015 Guidelines recommended two consecutive reactive HIV tests to diagnose HIV infection in high-prevalence (>5%) and three consecutive reactive tests in low-prevalence (≤5%) settings. As awareness of HIV status and treatment coverage reaches high levels, positivity among HTS clients is now below 5% even in high HIV prevalence settings. Consequently, countries employing the 'high-prevalence' strategy should consider if, when, and how to transition to a strategy with three-assays for HIV diagnosis. We estimated the HIV testing outcomes, commodities required, and incremental cost for the 3-test versus 2-test strategy.
Methods: We created a probability model to simulate HIV testing outcomes of the high- and low-prevalence strategies recommended in WHO 2015 HTS Guidelines, including recommended repetition of discrepant assays. We assumed each assay in the algorithm had 99% sensitivity and 98% specificity, minimum thresholds required to obtain WHO prequalification. Fully loaded costs indicative of a low/middle-income setting were US$2 per client plus commodity costs of $1.30, $2.30, and $2.50 per A1, A2, and A3 assay used, respectively. We calculated expected HIV testing outcomes per 100,000 persons tested with positivity ranging from 0.1% to 20%: expected number of false-positive and false-negative misclassifications, positive and negative predictive value, number of each assay used, and total cost.
Results: The expected number of false-positive misclassifications reduced from around 45 to fewer than 1 per 100,000 tested for the 3-test strategy at all positivity levels (Table 1). The PPV of the testing strategy was well above the 99% target at all positivity levels for the 3-test strategy. The number of A1 and A2 assays utilized did not change; the number of A3 assays required was expectedly greater with the 3-test strategy but still much lower than the number of A2 required. The total cost of the 3-test strategy was only 2.5% greater than the 2-test strategy at 5% positivity, reflecting that HTS cost programme cost is primarily determined by the number of A1 conducted.
Conclusion: The 3-test strategy ensured high PPV at all HIV positivity levels for a modest incremental cost relative to the 2-test strategy. In light of low positivity, we suggest all countries transition to a unified strategy with three reactive tests for HIV diagnosis in accordance with latest WHO guidance released in 2019.

Table 1. HIV testing strategy outcomes per 100,000 persons tested for 10%, 5%, 1%, and 0.5% true positivity amongst persons presenting for HIV testing.

	10% positivity		5% positivity		1% positivity		0.5% positivity	
	2-test	*3-test*	*2-test*	*3-test*	*2-test*	*3-test*	*2-test*	*3-test*
HIV-negative classifications	90,022	90,049	94,968	94,985	98,924	98,934	99,419	99,427
HIV-positive classifications	9922	9781	4985	4891	1035	979	542	490
HIV-inconclusive	55.3	170.0	47.2	124.1	40.7	87.4	39.9	82.8
Observed positivity	9.93%	9.80%	4.99%	4.90%	1.04%	0.98%	0.54%	0.49%
False HIV-positive	43.1	0.86	45.4	0.91	47.4	0.95	47.60	0.95
False HIV-negative	100	120	50.2	59.9	10.0	12.0	5.0	6.0
PPV of entire testing strategy	99.6%	>99.9%	99.1%	>99.9%	95.4%	99.9%	91.2%	99.8%
NPV of entire testing strategy	99.9%	99.9%	99.9%	99.9%	>99.9%	>99.9%	>99.9%	>99.9%
Assay 1 used	101,863	101,863	101,912	101,912	101,950	101,950	101,955	101,955
Assay 2 used	13,563	13,563	8762	8762	4920	4920	4,440	4,440
Assay 3 used	365	9922	375	4985	382	1035	383	542
Cost (US$)	$384,903	$408,796	$373,956	$385,482	$365,198	$366,830	$364,103	$364,499

*2-test and 3-test denotes the number of consecutive tests needed to provide an HIV-positive diagnosis, not number of tests used or in a given strategy or algorithm. Note that specimens with repeated discrepant test results under the 2-test strategy proceed to a third test (Figure 1). Under a 3-test strategy specimens with repeat discrepant test results on the first two tests are ruled negative.

966 FALSE-POSITIVE 4TH GENERATION HIV TEST RESULTS IN THE EMERGENCY DEPARTMENT

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Background: Universal opt-out HIV screening in low prevalence settings such as emergency departments (EDs) has increased identification of persons with HIV infection. However, false positive (FP) 4th generation HIV test results may impact the positive predictive value (PPV) and lead to a delay of disclosure of HIV diagnosis. The objective of this analysis was to assess factors associated with false-positive test results.

Methods: Opt-out HIV screening was conducted among adults at four California locations (two EDs at UC San Diego from July 2017 - March 2019 and two EDs at Alta Bates Summit Medical Center in Oakland from May 2017 - March 2019) using a 4th generation HIV Ag/Ab combination assay. We identified all individuals with FP HIV Ag/Ab results. Demographics, clinical data (ED chief complaints, discharge diagnoses, and medical conditions), and HIV risk factors were extracted from electronic medical records and compared with data from individuals with true positive (TP) HIV test results using non-parametric statistical tests.

Results: A total of 32,450 HIV tests were performed across four EDs using a 4th generation Ag/Ab assay (Architect® and Roche Elecsys®) resulting in 104 TP cases and 34 FP cases (PPV: 75.4%; FP rate: 0.1%). Among FP cases, the median age was 42 (IQR: 32-55), more than half (64.7%) were female, and more than half (58.8%) were White (Table). In univariate analyses, FP cases were significantly more likely than TP cases to be female (64.7% vs 28.9%, $p < 0.05$), White (63.6% vs 35.6%, $p < 0.05$), and pregnant (9.7% vs 0%, $p < 0.05$). None of the false-positive cases were in men who have sex with men and none were persons who inject drugs. Several factors were common (>20%) but not statistically significant: history of flu vaccination (lifetime) (65.5%), history of multiparity (30.0%), and obesity (24.2%). Additionally, 3 cases had a history of FP HIV tests and 1 case had autoimmune hepatitis.

Conclusion: The PPV of 4th generation HIV tests was suboptimal during universal opt-out HIV screening in EDs at two medical centers in California. Individuals who were female, White, and pregnant were more likely to have FP tests. Understanding these factors associated with FP test results in a population with low pretest probability may be important for early HIV disclosure as universal HIV testing in low-prevalence settings becomes more commonplace.

Table. Demographic and clinical factors among individuals with false-positive HIV test results.

Factor		Groups: False-positive cases	Groups: True-positive cases	*p* value
Age *Median (IQR)*		42 (32 – 55)	36 (28 – 46)	0.151
Gender *N* (%)	Female	22 (64.7%)	13 (28.9%)	**0.002**
Race *N* (%)	White	21 (63.6%)	16 (35.6%)	**0.014**
	Black	2 (5.9%)	12 (26.7%)	**0.017**
	Other/Mixed	5 (14.7%)	15 (33.3%)	0.059
	Asian	5 (14.7%)	2 (4.4%)	0.112
	Unknown/Refused	1 (2.9%)	0 (0%)	-
Ethnicity *N* (%)	Hispanic/Latino	6 (17.6%)	16 (35.6%)	0.129
	Not Hispanic/Latino	28 (82.4%)	28 (62.2%)	-
	Unknown	1 (2.2%)	0 (0%)	-
MSM *N* (%)		0 (0%)	15 (41.7%)	**0.000**
IDU *N* (%)		0 (0%)	8 (21.6%)	**0.005**
Current pregnancy *N* (%)		3 (9.7%)	0 (0%)	**0.040**
History of multiparity *N* (%)		6 (30%)	5 (11.4%)	0.067
Obesity *N* (%)		8 (24.2%)	7 (15.6%)	0.336
Flu vaccination (lifetime) *N* (%)		19 (65.5)	18 (56.3%)	0.459
Flu vaccination (recent) *N* (%)		12 (41.4%)	16 (50.0%)	0.500

MSM: men who have sex with men; IDU: injection drug use.

967 EVALUATION OF VIRAL SUPPRESSION ON RAPID HIV TEST REACTIVITY AMONG MSM, NHBS, 2017

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Background: Antiretroviral therapy (ART) leads to viral suppression (VS) and potentially seroreversion. However, the impact of sustained VS on the ability of rapid tests (RTs) to identify HIV infection has not been extensively reported. To assess RT performance in populations with likely exposure to antiretrovirals, we evaluated RT results among self-reported HIV-positive (SRP) men who have sex with men (MSM) in 23 U.S. cities participating in 2017 National HIV Behavioral Surveillance (NHBS).

Methods: Sites performed at least one point-of-care RT on all consenting SRP MSM. Participants with RT-nonreactive (RT-NR) results were considered discrepant and resolved with further laboratory testing using plasma or dried blood spots (DBS) at the CDC or locally. At CDC, those consenting to storage of DBS were confirmed using Abbott RealTime HIV-1 assay (VL), Bio-Rad GS HIV Combo Ag/Ab EIA and Geenius HIV-1/2 assays. Self-reported data and valid test results were analyzed using SAS.

Results: The false-negative rate was 2.3% (45/1936). Of 1936 participants, 42.4% were tested with INSTI (21/820, 2.6% RT-NR), 31.1% with Determine (10/603, 1.7% RT-NR), 12.3% with Sure Check (5/239, 2.1% RT-NR), 11.6% with OraQuick (5/224, 2.2% RT-NR) and 2.6% with Uni-Gold (4/50, 8.0% RT-NR). The table shows reactivity of RTs from participants by VL results and self-reported ART use. Of 1655 RT-R participants, 1311 (79.2%) had undetectable VL or detected <2.92 $\log_{10}$ (cop/mL) of whom 1263 (96.3%) reported being on ART. Of 18 RT-NR participants, 17 (94.4%) had undetectable VL of whom 16 (94.1%) reported being on ART. The laboratory-based serology testing algorithm did not confirm HIV-positive status in 5 of 18 RT-NR persons self-reported to be living with HIV and on ART (2 Determine, 1 OraQuick, 1 Uni-Gold, 1 Sure Check).

Conclusion: False non-reactivity of rapid HIV tests occurred but was low and consistent across most RTs. In a small number of samples, VS was associated with non-reactivity possibly due to seroreversion; however, the percent of participants virally suppressed on ART was similar among those who were RT-R and RT-NR. Given the sensitivity limitation of RTs, our results highlight challenges with relying on rapid HIV testing alone, particularly in circumstances of VS in which non-reactivity could lead to misinterpretation of HIV status. This could have implications for monitoring for virologic breakthroughs with PrEP and surveillance systems that use RTs to gauge HIV prevalence.

Reactivity of FDA-approved rapid HIV tests using whole blood among men who have sex with men by viral load results and self-reported ART use—National HIV Behavioral Surveillance, 23 U.S. cities, 2017

		INSTI (N=820)		Determine (N=603)		SureCheck (N=239)		OraQuick (N=224)		Uni-Gold (N=50)		Total (N=1936)	
	N	R	NR	R	NR	R	NR	R	NR	R	NR	R	NR
Overall	1936	799	21	593	10	234	5	219	5	46	4	1891	45
By VL and ART use[1]	1673											1655	18
VL undetectable[1]	1172	497	7	351	2	153	3	121	4	33	1	1155	17
Currently on ART	1128	479	7	340	2	147	2	117	4	29	1	1112	16
VL detectable <2.92$\log_{10}$(cop/mL)[1]	156	79	0	40	0	10	0	26	0	1	0	156	0
Currently on ART	151	77	0	38	0	10	0	25	0	1	0	151	0
VL detectable ≥2.92$\log_{10}$(cop/mL)[1]	345	129	1	115	0	62	0	32	0	6	0	344	1
Currently on ART	284	104	0	98	0	50	0	27	0	5	0	284	0

Abbreviations: INSTI: BioLytical INSTI HIV -1/ HIV-2 Antibody Test, Determine: Alere Determine HIV-1/2 Ag/Ab Combo Rapid Test, SureCheck: Chembio SureCheck HIV-1/2 Assay, OQ: OraQuick ADVANCE Rapid HIV-1/2 Antibody Test, Unigold: Trinity Biotech Uni-gold Recombigen HIV-1/2, R: Rapid Test Reactive, NR: Rapid Test Nonreactive, VL: viral load, ART: antiretroviral therapy

[1] Of 1,936 eligible participants with rapid test results, 255 were missing viral load results either because they did not consent to storage of specimens or consented to storage but did not send specimens, did not have enough specimens for laboratory testing, or had errors when specimens were tested. An additional 8 were missing data on current ART use.

968 PERFORMANCE OF ORAQUICK RAPID TEST ON HIV DIAGNOSIS AMONG CADAVERS IN KISUMU, KENYA

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Background: Ascertaining HIV status at time of death can be useful for identifying missed opportunities to diagnose and treat HIV infection. Routinely testing HIV status among deaths, though not commonly practiced, may complement vital statistics in Kenya, where cause-specific attribution to death is often not documented. Currently available and validated rapid test kits (RTKs) in Kenya require a blood sample, which is hard to draw from cadavers. To avoid logistical difficulties of blood-based HIV testing, a minimally invasive assay using oral fluid such as OraQuick®, may be an alternative. OraQuick® has previously been used in Kenya for HIV self-testing, showing a higher specificity than sensitivity. We verified the feasibility and diagnostic accuracy of OraQuick® for HIV screening among cadavers.

Methods: Trained morticians collected pre- and post-embalming oral fluids from 132 cadavers >18 months old at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) mortuary in Kisumu, Kenya. These were tested for HIV using OraQuick®. Test results from OraQuick® were compared with those obtained using national RTK algorithm on matched pre-embalming whole blood specimens as a gold standard (Determine® HIV and First Response® HIV 1-2-0). We calculated positive predictive value (PPV), negative predictive value (NPV), false detection rate (FDR), false omission rate (FOR), sensitivity and specificity of OraQuick® compared to the gold standard.

Results: OraQuick had a sensitivity of 92.6%, (95% CI: 75.7 - 99.1) on pre and post-embalmed samples when compared to the gold standard. The specificity was 97.1% (95% CI: 91.9 - 99.4) and 95.2%, (95% CI: 89.2 - 98.4) pre and post-embalming respectively (Table1). The pre-embalming PPV of OraQuick® was 89.3% (95% CI: 71.8 - 97.7) and 83.3%, 95% (95% CI: 65.3 - 94.4) post-embalming. FDR was lower on pre-embalming compared to post embalming at 10.7% (95% CI 2.3 – 28.2) and 16.7%, (95% CI: 5.6 - 34.7) respectively. Only 2/27 (7%) were false negative. FOR pre-embalming (1.92%) and post-embalming (1.96%) were similar.

Conclusion: OraQuick® was found to more specific than sensitive on oral specimens from cadavers. Similar performance has been reported among living subjects. It is a convenient less invasive screening test for surveillance of HIV among cadavers within a mortuary setting.

Table 1: Performance of OraQuick® on HIV diagnosis among cadavers admitted to JOOTRH mortuary in Kisumu: a high HIV-burden region in Kenya

a) Pre-embalming

		Gold standard (national HIV diagnostic algorithm)		
		NO. Positive (%)	No. Negative (%)	Total (%)
OraQuick® results	Positive	25 (89.3)	3 (10.7)‡	28(21.2)
	Negative	2 (1.9)§	102 (98.1)	104(78.8)
	Total	27 (20.5)	105 (79.5)	132

b) Post-embalming

		Gold standard (national HIV diagnostic algorithm)		
		No. Positive (%)	No. Negative (%)	Total (%)
OraQuick® results	Positive	25 (83.3)	5 (16.7)‡	30(22.7)
	Negative	2 (2.0)§	100 (98.0)	102(77.3)
	Total	27 (20.5)	105 (79.5)	132

Gold standard results were based on final HIV result on pre-embalming whole blood. If Determine® was reactive, a First Response® confirmatory test was performed. The final HIV status was positive if the First Response was reactive, otherwise if First Response was negative it was based on a positive DNA PCR test as tiebreaker.
‡False positives/false detection rate
§False negatives/false omission rate

969 DRIED BLOOD SPOTS PROVIDE SIMPLIFIED ACCURATE MEASUREMENT OF HIV VIRAL LOAD

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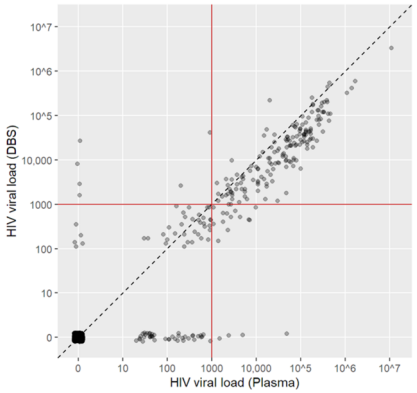
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Background: HIV viral load (VL) is a robust measure of adherence and treatment efficacy when monitoring antiretroviral therapy (ART), facilitating timely switching to second line regimens. However, collection of plasma for VL requires phlebotomy, controlled transport conditions, and is costly, thereby limiting its use in community-based settings. The use of dried blood spot (DBS) cards of finger-prick blood transported at ambient temperature to a central laboratory for VL testing would simplify monitoring, but requires validation against the gold standard method of plasma VL.

Methods: In a randomized study of community-based delivery of ART in KwaZulu-Natal, South Africa (the DO ART Study) persons living with HIV provided concurrent EDTA plasma and DBS specimens. Specimens were transported 100 - 250 km to Global Labs (Durban), which used the bioMérieux NucliSENS EasyQ HIV-1 assay to measure plasma VL (limit of quantification [LOQ]: 20 copies/mL) and a modified version of the same assay for DBS whole blood specimens (LOQ: 100 copies/mL). Values below the LOQ are represented as 1 (0 when log transformed). We compared 856 pairs of results from 678 DO ART participants using intra-class correlation, two by two tables, scatterplots, and mean-difference plots in R.

Results: There was high correlation between log-transformed DBS and plasma VL results, with an intra-class correlation coefficient of 0.93 (95% CI: 0.93 - 0.94). DBS viral loads tended to be lower overall with a mean difference between DBS and plasma results of -0.17 $\log_{10}$ copies/mL (95% of the differences were from -1.42 to 1.09 $\log_{10}$ copies/mL). Using the WHO threshold for viral suppression of 1000 copies/mL, in a population with 13% virological failure, the sensitivity and specificity of DBS were 91% and 99%, respectively, with positive and negative predictive values of 93% and 99% for detecting treatment failures. In this population, for every 100 persons undergoing viral load monitoring via DBS, an estimated one treatment failure would be miscategorized. There were no clinically meaningful differences by sex or CD4 count.

Conclusion: DBS provides a highly accurate result compared to plasma VL and could be used in a simplified approach to population-based ART monitoring in resource-limited settings. Self-collection of DBS cards should be evaluated as a means of further simplifying specimen collection and ART monitoring.



* The red lines indicate the WHO viral suppression threshold of 1000 copies/mL. Jitter was applied to values of 0 to better visualize over-lapping points. The cluster of results at (0, 0) contains 589 points.

970 AUTOMATED HIGH-THROUGHPUT QUANTIFICATION OF LOW-LEVEL HIV-1 PLASMA VIREMIA

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Background: Low-level plasma HIV-1 viremia persists in the majority of HIV-1 positive individuals despite long-term clinically-effective ART. Clearance of HIV-1 viremia remains a critical goal towards an HIV cure, but complex and low-throughput single copy assays (SCA) limit the capacity to monitor the effects of interventions on persistent viremia. Here we report the evaluation of two high-throughput methods on the Hologic Panther platform to automate quantitation of low-level viremia in comparison with a SCA targeting integrase (iSCA2.0; Tosiano, et al. J Clin Micro 2019).

Methods: The assay methods performed on the Hologic Panther platform were: 1) testing of nine 0.5mL replicates (Panther 9x) with estimation of HIV-1 RNA concentration using statistical inference based on binary outcome; and 2) concentration of 5mL plasma to one 0.7 mL replicate by centrifugation (Panther spun). Plasma HIV-1 RNA standards (20, 5, 2.5, 1.25, 0.625, and 0 copies/ml) from the Quality Assurance (VQA) at Rush University were tested in 5 independent runs of 5 replicates. Both Panther methods were compared to the manual iSCA 2.0. Mean, standard deviation and percent positive assays were calculated for each run and the 95% LOD was assessed using maximum likelihood estimation.

Results: Assay results are summarized in the Table. The 95% LODs (95% CI) were 2.3 (1.6, 3), 3.0 (2.1, 3.8), 3.9 (2.8, 5) for iSCA2.0, Panther 9x and Panther spun, respectively, indicating that iSCA2.0 was most sensitive but that Panther 9x was only marginally less sensitive. Panther spun had reduced sensitivity compared to the other methods. Each assay had 100% specificity across 25 replicates of 0 copies/ml. The weekly estimated throughput for the Panther 9x method is 5-10 times that of iSCA 2.0.

Conclusion: Although the manual single copy assay targeting HIV-1 integrase (iSCA 2.0) has the lowest 95% limit of detection for plasma HIV-1 RNA, multiple replicate testing (9x) on the Hologic Panther platform has similar sensitivity and could be used as a screening tool for higher throughput monitoring in clinical trials of interventions aimed at clearing persistent viremia towards a functional cure of HIV-1 infection.

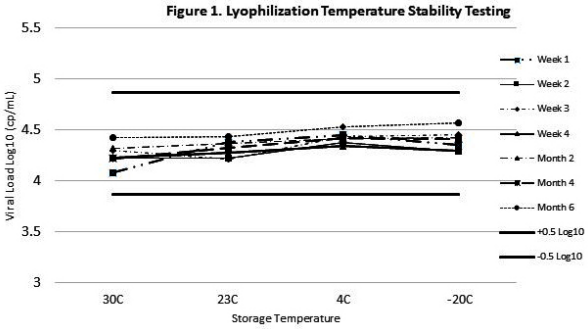
Method	Expected Concentration (cps/mL)	Mean Observed Concentration (cps/mL ± SD)	No. Detected	Total Tests	Percent Detection
iSCA 2.0	20.0	17.12 ± 16.40	25	25	100
	5.0	3.52 ± 1.92	25	25	100
	2.5	1.30 ± 0.90	25	25	100
	1.2	0.90 ± 1.0	17	25	68.0
	0.6	0.80 ± 0.80	16	25	64.0
Panther 9x	20.0	6.08 ± 1.93	25	25	100
	5.0	1.27 ± 0.63	25	25	100
	2.5	0.85 ± 0.33	22	25	88.0
	1.2	0.50 ± 0.20	18	25	72.0
	0.6	0.27 ± 0.09	13	25	52.0
Panther Spun	20.0	11.70 ± 2.56	25	25	100.0
	5.0	1.70 ± 0.58	24	25	96.0
	2.5	1.03 ± 0.59	21	25	84.0
	1.2	0.28 ± 0.15	16	25	64.0
	0.6	0.09 ± 0.04	11	25	44.0

971 HEAT-INACTIVATED/LYOPHILIZED HIV VIRUS FOR USE IN PROFICIENCY TESTING PROGRAMS

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Background: Proficiency testing (PT) for labs performing HIV viral load (VL) is critical to determining that acceptable patient monitoring standards are being established. Current PT programs utilize infectious material which requires a cold chain for shipping and local laboratory storage. We set out to develop QCMs to reduce the infectious risk of the QCM and overall cold chain requirements.
Methods: A Clade C virus from the NIAID EQAPOL program was heat inactivated and shown inability to replicate, as determined by VL and p24 Ag testing; then lyophilized at 50,000 copies/ml. Testing was performed at four storage temperatures (-20°C, 4°C, 23°C, 30°C) at seven time points. Linear modeling was performed to make descriptive statistics (e.g., estimation of means) and a descriptive evaluation of the means for storage temperatures and time points at the alpha 0.05 level.
Results: The heat-inactivated non-lyophilized viral material showed a VL of 4.698 (-05.=4.198 and +0.5=5.198) Log_{10} (copies/ml) during 12 months of repeat testing under -800C conditions. Shown below are VL results for the lyophilized material held at different storage conditions over time and then tested. We found statistical evidence of a 0.007 Log_{10} increase per week of storage and that month 6 VL was higher than the average time point VL (see Figure 1). There was no statistical evidence of storage temperature differences. The model based means for storage temperatures range from 4.26 – 4.42 Log_{10} copies/ml and the model based means for the time points range from 4.28 – 4. 49 Log_{10} copies/ml. Displayed in Figure 1 below are the VL results for the lyophilized material held at different storage conditions over the various time points. The average VL is 4.38 with the standard acceptance criteria of +/- 0.5 Log_{10} copies/ml at 3.88 and 4.88.
Conclusion: These data we collected provides a proof of concept that the heat inactivated and lyophilized material remains stable and well within a the 0.5 Log_{10} acceptance criterai at all temperature storage conditions for up to six months. Studies are underway to determine suitably of this material for use in quality assessment of drug mutation sequencing assays. Reducing cold chain requirements, shipping costs and infectious status of QCMs offers significant improvements to current PT approaches. Work supported by NIAID EQAPOL HHSN27220170061C.

Figure 1. Lyophilization Temperature Stability Testing

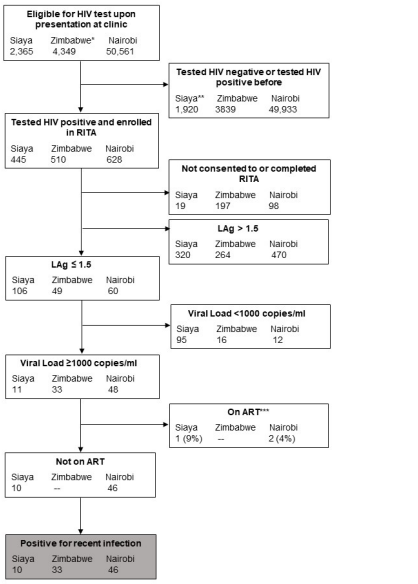


972 IDENTIFYING RECENT HIV INFECTIONS IN REAL-WORLD SETTINGS IN KENYA AND ZIMBABWE

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Background: Distinguishing recently acquired infection from "long-standing" infection among persons newly diagnosed with HIV can help guide prevention programming. Focusing on the procedures required to accurately determine recent infection, we present the results of three pilots of HIV recency testing in Kenya and Zimbabwe.
Methods: Using Maxim HIV-1 LAg-Avidity EIA dried blood spot and plasma kits, we conducted HIV recency testing in a variety of routine service-provision contexts, namely: antenatal clinics providing PMTCT services in Siaya County, Kenya, routine HIV testing clinics in Nairobi, Kenya, and a national programme for female sex workers (FSW) in Zimbabwe. Our recency test results were interpreted as part of a Recent Infection Testing Algorithm (RITA), to which we included prior testing history, viral load and ART exposure. LAg results with a normalized optical density (ODn) of <1.5 and a viral load > 1000 copies/mL were classified as testing positive for recent infection.
Results: Having tested participants for HIV, investigated HIV status and sought consent, in total 1,272 HIV positive women and men were tested for recent infection across the three pilots (see figure 1). Based on LAg test result alone, our crude recency percentages were 24.9% (106/426) in Siaya County, 11.3% (60/530) in Nairobi, and 15.6% (49/313) in Zimbabwe. Figure 1 highlights how combining our recency assay results with viral load greatly reduced the number of people classified as recent positive in all three settings. In Nairobi (ART metabolite testing) and Siaya County (linked clinic records) the number classified as recent positive was further reduced due to evidence of ART use (in Zimbabwe women with a history of a previous positive test or ART use were excluded). The final percentages of participants classified with a recent infection were 2.3% (10/426) among women in Siaya County, 8.7% (46/530) among men and women in Nairobi, and 10.5% (33/314) among FSW in Zimbabwe.
Conclusion: We successfully identified recently acquired infections among persons diagnosed with HIV in real-world settings. Our recency percentages would have been substantially inflated without the inclusion of clinical information. In using recency assays to accurately distinguish recent from long-standing infection in routine settings, we highlight the importance of considering a person's previous HIV test history, ART use, and viral load.

Figure 1: HIV recent infection recruitment and testing



* People were eligible for HIV testing if they had not been tested in previous 3 months or were not on ART
** 1,914 tested HIV negative, 6 had unknown HIV status (based on routine practice, prior HIV positive test was not an exclusion criteria)
*** In Siaya County, ART status was determined using clinic records; in Nairobi, ART status was determined using ARV metabolite testing; in Zimbabwe, reporting of ART use was an exclusion criteria

973 STAGING OF HIV-1C INFECTION AMONG PATIENTS ON ART IN BOTSWANA USING PROVIRAL DNA

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Background: HIV genetic diversity increases during infection and can be used to infer time since infection; however published analyses have included only antiretroviral treatment (ART) naïve individuals.
Methods: Demographic and clinical information from HIV-1C-infected patients were collected within the Botswana Combination Prevention Project from 2013 to 2018. HIV genetic sequencing efforts have been intensified under

the PANGEA-HIV initiative. The vast majority of participants were on ART. Amplification and near full-length HIV genome sequencing were performed from proviral DNA. Duration of HIV infection was dichotomized, as < or > 1 year for 1153 participants based on longitudinal follow-up before and after diagnosis. We calculated viral diversity at each nucleotide site and for gag, pol and env based on nucleotide frequency files. We optimized a logistic regression model to predict recency <1 year and assessed model performance by cross-validation.

Results: In our dataset, 140 individuals had been infected for less than a year at diagnosis. Most patients (954/1143, 83.5%) were on ART at the time of sampling. We split our data randomly into training (70%) and testing (30%) subsets. Our best predictive model included genetic diversity for pol, gag and env, viral load, age, gender and ART-status. Prediction accuracy in the test dataset was 94.4% (91.3%-96.6%) compared to a null model accuracy of 87.8% (p<0.0001). Model sensitivity was 74.4%, specificity 97.2% and positive predictive value was 78.4%. Accuracy was consistent across 1000 cross-validation tests. The model including only genetic diversity measures, without any demographic or clinical variables, was not significantly better than the null model (p>0.05) because of the confounding effect of ART-status.

Conclusion: In contrast to previous analyses, most of our sequences came from proviral DNA from individuals on suppressive ART. Among treated patients, genetic diversity measures (e.g. entropy) displayed overlap between recent and chronic infections (Figure 1) but including clinical and demographic data improved prediction of recency. We are currently evaluating whether machine learning can incorporate additional information (e.g. sites under selection) to further distinguish between recent and chronic infections in treated individuals.

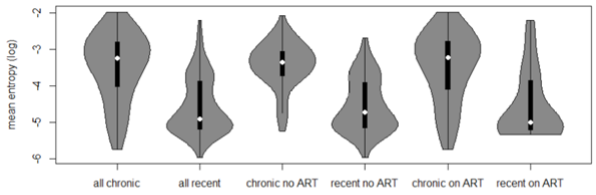


Figure 1: Vioplot displaying entropy (a measure of viral diversity) for patients based on time since infection (recent, i.e. <1 year, or chronic) and antiretroviral treatment (ART) status. Entropy was averaged across all informative sites in the genome.

974 NOVEL CRITERIA FOR DIAGNOSING ACUTE HIV IN A MULTINATIONAL ART-INITIATION STUDY

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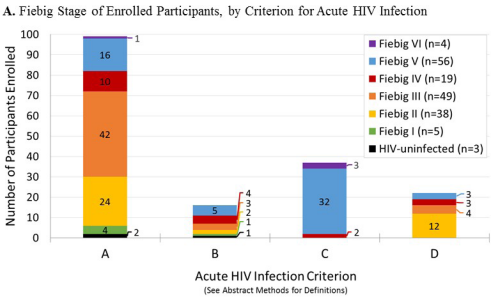
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Background: Antiretroviral therapy (ART) initiation during acute HIV infection (AHI) limits HIV reservoirs, enhances reservoir decay, restricts viral genetic diversification and may facilitate post-ART control. Identifying and treating persons with AHI is highly desirable but logistically challenging. We describe the performance of new AHI diagnostic criteria for an ongoing multi-national study of ART initiation during AHI.

Methods: ACTG 5354 enrolls adults during AHI at 29 sites in the Americas, Africa, and Southeast Asia. Participants must meet one of the following criteria: (A) detectable HIV RNA and non-reactive HIV antibody; (B) detectable HIV RNA or reactive antibody and negative/indeterminate Western blot (WB) or Geenius; (C) negative HIV RNA or antibody within 90 days and reactive antibody, WB (p31-), or Geenius (p31-) within 7 days; (D) ARCHITECT or GSCOMBO antigen/antibody (Ag/Ab) combo signal-to-cutoff ratio (S/CO) ≥10 and non-reactive HIV antibody. Participants start ART at enrollment. HIV infection and Fiebig stage at ART initiation are subsequently confirmed by centralized testing that includes HIV RNA, ARCHITECT Ag/Ab, Bio-Rad HIV-1/2 Ab (IgM sensitive), and Geenius HIV-1/2 lateral flow antibody assay.

Results: From January 2017 through August 2019, 174 were enrolled and completed centralized confirmatory testing. Their median age was 27 (interquartile range 23-38) years and 29 (17%) were female. ART was started by 154 (89%) on the day of enrollment and 20 (11%) the next day, mostly with study-provided elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (n=136, 78%). AHI was confirmed in 167 (96%) participants after centralized testing and varied in Fiebig stage according to the AHI criteria used (Figure Panel A). Three participants with locally detectable HIV RNA had no evidence of infection on centralized testing, discontinued ART and were withdrawn. Four others were in Fiebig VI, not AHI, at enrollment. Centralized ARCHITECT S/CO ≥10 combined with nonreactive or indeterminate HIV antibody on the Geenius assay correctly identified 87 of 106 (82%) Fiebig II-IV AHI cases (Figure Panel B).

Conclusion: Novel efficient AHI criteria incorporating ARCHITECT S/CO into diagnostic algorithms facilitated rapid ART initiation pending confirmation. False-positive diagnoses of AHI were rare. These new criteria may facilitate AHI diagnosis, staging, and immediate ART initiation in research studies and clinical practice.



The bottom and top edges of the box indicate the intra-quartile range (IQR). The line inside the box indicates the median. Filled circles represent actual data points.

975 IMPROVING CLASSIFICATION FOR RECENT HIV INFECTION USING TOP SCORING PAIRS

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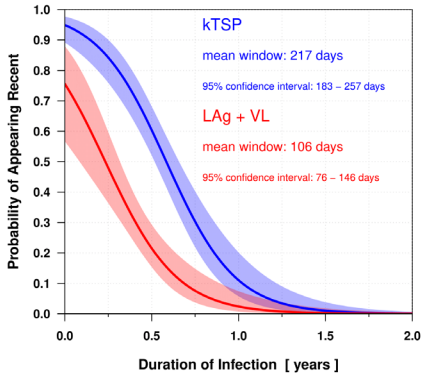
Background: HIV cross-sectional incidence assays often measure characteristics of the antibody (Ab) response, such as titer, class, and avidity. These responses are affected by various factors including viral suppression. Since older guidelines recommended ART initiation later in infection, incidence algorithms often use viral suppression as a surrogate for non-recent infection. As new guidelines recommend ART initiation early in infection, viral suppression no longer indicates non-recent infection, and new approaches are needed to identify recent infections.

Methods: We analyzed Ab profiles for 258 samples from 57 individuals with HIV subtype C infection and known duration of infection (2 mo. - 8.7 yrs.) using phage immunoprecipitation sequencing (PhIP-Seq). PhIP-Seq quantifies Ab binding to 3384 peptides spanning the HIV genome. Our novel classifier for recent (2-6 mo.) and non-recent (18+ mo.) infection is based on the k-top scoring pairs (TSP) classifier. For each peptide pair, relative Ab abundances

classify each sample as recent or non-recent. Overall sample classification is determined by a majority voting system. Optimal classification cutoffs and the number of voting pairs were identified using a training set of 176 samples from 38 individuals and subsequently tested on the remaining 82 samples from 19 individuals. We compared these results to results from a standard Limiting Antigen Avidity (LAg-Avidity) protocol.

Results: In the final model with 4 voting pairs, 79% (71/90) recent samples and all 168 of non-recent samples were correctly classified. In contrast, the LAg-Avidity protocol classified 43% (35/81) recent samples and all 165 non-recent samples correctly. Comparison of TSP vs. LAg-Avidity showed that the TSP approach captured a greater proportion of recent infections with a mean window period of 217 days (95% CI: 183-257 days; see figure). In contrast, the mean window period of the LAg-Avidity protocol is 106 days (95% CI: 76-146 days).

Conclusion: We identified four 4 peptide pairs that outperformed the standard LAg-Avidity protocol for identifying samples from individuals with recent HIV infection. These peptides can be incorporated into a simple assay for field use. With a larger mean window period, the TSP classifier yields more precise incidence estimates without relying on viral load to identify non-recent samples. The TSP approach can also easily be applied to other populations and virus subtypes to identify novel peptide signatures for recent infection.



976 EVALUATION OF CROSS-SECTIONAL HIV INCIDENCE TESTING IN THE HPTN 071 (POPART) TRIAL

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Background: The Limiting Antigen Avidity (LAg) assay is used to estimate HIV incidence in cross-sectional surveys. Testing algorithms often include low HIV viral load (VL) as a marker of non-recent infection. We compared the accuracy of cross-sectional incidence (CSI) estimates to observed incidence in the community-randomized HPTN 071 (PopART) trial, where a substantial proportion of HIV+ participants were virally suppressed.

Methods: HIV incidence was assessed in a Population Cohort (PC) 1-2 years after study initiation (between the PC12 and PC24 surveys). Observed incidence was based on confirmed seroconversion events between PC12 and PC24. The CSI analysis of the PC24 survey included 15,845 who remained HIV negative, 221 persons who seroconverted between PC12 and PC24 (SC12-24), 217 who seroconverted between PC0 and PC12 (SC0-12), 4,022 who were HIV+ at PC0; and 689 who enrolled HIV+ during the PC12 survey. The VL at PC24 was <1,000 copies/mL for 72.7% of HIV+ persons, including 31% (70/221) of the SC12-24 group. All HIV+ PC24 samples were tested using the Sedia LAg-Avidity assay. Recent infections were defined as having a LAg result <1.5 normalized optical density units (ODn) and HIV VL >1,000 copies/mL. The CSI estimate was determined using a mean duration of recent infection of 130 days (95% confidence interval [CI]: 117-143) and a false recent ratio (FRR) of 0%.

Results: The LAg result was <1.5 ODn in 11.3% (582/5149) of all HIV+ persons; 74/582 had a VL >1,000 copies/mL and were classified as recently infected. These included 27% (60/221) of the SC12-24 group, 2.7% (6/217) of the SC0-12 group, 0.15% (1/689) of those who enrolled HIV+ at PC12, and 0.17% (7/4022) of those who enrolled HIV+ at PC0 (most infected for >2 years). Use of a higher cutoff for the LAg assay (2.0 or 2.5 ODn) increased the proportion of the SC12-24 group classified as recently infected from 27% to 32% or 41%, respectively, but increased the FRR among those infected >2 years from 0.17% to 0.42% or 0.72%, respectively. In each study country and overall, the CSI estimates were nearly identical to observed incidence (Table).

Conclusion: In this large community-randomized study, a widely-used CSI algorithm that included the LAg assay and HIV VL yielded accurate point estimates of incidence, despite high rates of viral suppression among those with both prevalent and incident infection. However, the CSI estimates were considerably less precise than observed incidence measured from cohort follow-up.

Table. Comparison of CSI and observed incidence between the PC12 and PC24 surveys*.

	# participants			PY F/U	Annual incidence per 100 PY (95% CI)	
	POS	NEG	SC		Observed incidence*	Cross-sectional incidence estimate
Zambia	3,157	9,000	132	9,409	1.40 (1.17-1.66)	1.37 (0.95-1.80)
South Africa	1,992	6,845	89	7,045	1.26 (1.01-1.55)	1.23 (0.77-1.69)
Overall	5,149	15,845	221	16,454	1.34 (1.17-1.53)	1.31 (0.99-1.64)

Abbreviations: POS: HIV-positive; NEG: HIV-negative; SC: seroconverter; PY: person-years; F/U: follow-up. *Based on PC participants with known HIV status at PC12 and PC24.

977 URINE TENOFOVIR LEVELS BY IMMUNOASSAY PREDICT HIV PROTECTION IN A LARGE PrEP TRIAL

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Background: New tools are needed to support PrEP use for individuals at high risk for HIV in sub-Saharan Africa, including objective adherence metrics that allow for provision of real-time feedback. Urine tenofovir (TFV) levels have been proposed as a marker of PrEP use that could be measured with low-cost, point-of-care (POC) antibody-based tests. We hypothesized that TFV levels in urine, measured via a recently-developed immunoassay, would be comparable to those in plasma, the gold standard for short-term PrEP adherence in clinical trials, and associated with protection from HIV.

Methods: We measured TFV levels in stored urine samples collected from a randomly sampled cohort of HIV-negative men and women from the active PrEP arms in the Partners PrEP Study using enzyme-linked immunosorbent assay (ELISA) (lower limit of quantification [LLOQ] 1000 ng/mL). Date-matched plasma TFV concentrations were measured via liquid chromatography-tandem mass spectrometry (LC-MS/MS) with an LLOQ of 0.31 ng/mL. Using the same cohort and all HIV seroconverters on PrEP, we conducted a case-cohort analysis to assess association between recent urine TFV level >1500 ng/mL, a threshold which accurately classifies recent PrEP dosing, and protection from HIV. The 1500 ng/mL cut-off will be used for the first iteration of the POC assay. Estimates of the hazard ratio for the Cox model are adjusted for age, sex, and sexual behavior.

Results: We included 292 participants in the cohort and 45 cases who contributed 722 and 91 urine samples, respectively; 39% of the cohort and 51% of cases were female. Detectable urine TFV levels showed 87% sensitivity (95% CI: 84-90%) and 73% (65-79%) specificity for detectable plasma TFV concentration, which is predictive of HIV protection. Using the urine level at first detection of seroconversion in the adjusted model, a urine TFV level >1500 ng/mL was associated with a 71% (95% CI: 24-89%; p=0.01) adjusted reduction in HIV risk.

Conclusion: In a large completed PrEP trial, urine TFV levels measured via a novel immunoassay were predictive of protection from HIV. Detection of TFV in urine showed good sensitivity and specificity for detection of TFV in plasma measured via LC-MS/MS, an established metric of short-term PrEP adherence. The urine immunoassay has now been developed into a lateral flow assay which can provide results at the POC. Our findings suggest that a real-time assay to assess TFV levels in urine could be a valuable addition to existing objective metrics for PrEP adherence.

978 PUBLICLY FUNDED HIV PrEP IN BRITISH COLUMBIA: PROGRAM RETENTION AND NEW HIV DIAGNOSES

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Background: In January 2018, a province-wide HIV pre-exposure prophylaxis (PrEP) program was launched in British Columbia (BC), Canada, to complement the existing publicly-funded HIV treatment as prevention strategy. BC residents were eligible to receive publicly-funded emtricitabine-tenofovir DF through the centralized BC Centre for Excellence in HIV/AIDS program if they were at risk of HIV acquisition according to BC PrEP Guidelines. We sought to evaluate program retention and the rate of new HIV diagnoses.
Methods: Individuals enrolled in the BC PrEP program between 1-Jan-2018 and 30-Jun-2019 were characterized by clinical, demographic, and prescriber characteristics. For those who initiated PrEP, we determined program status at end of follow-up (31-Aug-2019). Multivariate logistic regression was used to evaluate factors associated with program non-retention (defined as >6 month lapse beyond expected PrEP refill date). Rate of new HIV diagnoses in the cohort was calculated.
Results: In the first 18 months, 4648 individuals applied for PrEP and 4570 enrolled in the program [98% male, median age 33 years (Q1-Q3, 27-44)]. Most participants (90%) qualified based on an HIV Incidence Risk Index (HIRI) for MSM Score of ≥10 [median 19 (Q1-Q3, 15-25)]. The majority of participants (83%) resided in Greater Vancouver and received care at sexual health clinics (47%), HIV-focused clinics (23%) or general practice/other settings (30%). Of the 4451 participants who initiated PrEP, 84% were retained in the program as of 31-Aug-2019 (See Figure 1). Factors associated with program non-retention were higher HIRI-MSM score [adjusted OR 1.29 (95% CI, 1.12-1.48) per 10 score increment] and prescriber-reported on-demand PrEP use [adjusted OR 4.09 (95% CI, 3.01-5.55)] but not age, urban vs. rural location, or provider antiretroviral treatment or PrEP prescribing experience. Among participants who initiated PrEP, there were 8 HIV seroconversions in 4141 person years of follow-up, including 6 persons with >30 day lapse in PrEP medication prior to HIV diagnosis. Overall, new HIV diagnosis rate was 0.19 per 100 person years (95% CI, 0.08-0.38).
Conclusion: In the context of a publicly funded, centrally distributed PrEP program, retention was high at 18 months, and the rate of new HIV diagnoses low relative to the expected rate for individuals reporting these risk behaviours. Persons with higher HIRI-MSM score were at increased risk of program non-retention, and thus may benefit from enhanced support.

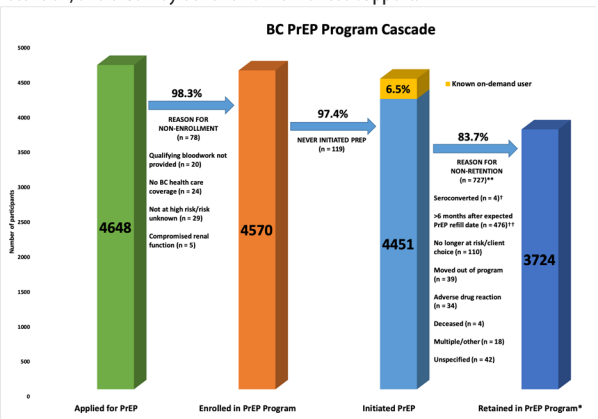


Figure 1: Proportion of participants in the BC-CfE PrEP program engaged at each stage of the PrEP cascade.
Includes applicants between 1-Jan-2018 and 30-Jun-2019, with follow-up until the 31-Aug-2019.
*Retained in PrEP program defined as <6 month lapse beyond expected refill date. Program re-enrollment required after 6 month lapse.
**Data sources: PrEP prescriptions, lab data, vital statistics, provider feedback.
†2 participants had PrEP medication supply within 30 days prior to diagnosis, 2 diagnosed >1 month without medication, and ††4 diagnosed >6 months without medication.

979 POPULATION-LEVEL EFFECTIVENESS OF PrEP AMONG MSM AND TRANSGENDER PERSONS WITH STI

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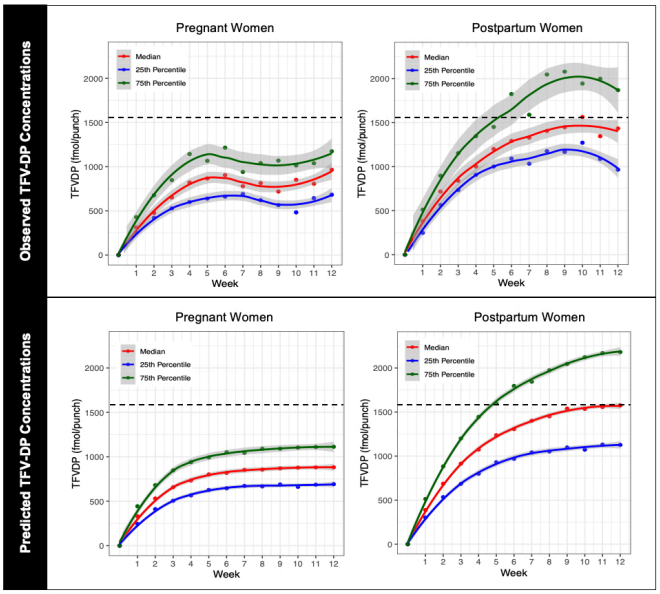
Background: HIV PrEP is highly efficacious, but its effectiveness may be limited by poor adherence or discontinuation. Few studies have evaluated PrEP effectiveness outside of specific clinics or healthcare organizations.
Methods: We conducted a retrospective cohort study using King County, Washington STI partner services (PS) interview data collected January 2014 to August 2018. During PS interviews, public health staff asked men who have sex with men (MSM) and transgender persons who have sex with men (TGSM) if they were taking PrEP. We used name, date of birth and sex to match STI PS data to public health HIV surveillance data to identify persons diagnosed with HIV after their interview. We calculated the incidence of HIV diagnoses per 100 person years in PrEP users and non-users and used Cox proportional hazard regression, adjusting for age and race/ethnicity, to assess the risk of HIV diagnosis based on past PrEP use. We included PrEP use status, race, Latinx ethnicity, age, and bacterial STI diagnoses in multivariate analysis. MSM and TGSM without an identified HIV diagnosis were administratively censored on August 31, 2018. We reviewed HIV PS interview records for PrEP users who were diagnosed with HIV to assess if they were taking PrEP at the time of their diagnosis.
Results: The median time from PS interview to HIV diagnosis or censoring was 14 months (IQR 6 to 23 months). Five (0.4%) of 1206 people who reported PrEP use at the time of their STI diagnoses and 97 (3%) of 2162 persons who were not using PrEP were diagnosed with HIV infection (p<0.001). HIV incidence was lower among PrEP users than nonusers (0.02 vs. 0.09 cases per 100 person-years, aHR 0.16, 95% CI 0.06 to 0.45). Other factors associated with incident HIV diagnosis included age <20 years (aHR 1.76, 95% CI 0.68 to 4.54), Black race (aHR 1.21, 95% CI 0.60 to 2.45), and Latinx ethnicity (aHR 2.13, 95% CI 1.30 to 3.51). All five PrEP users diagnosed with HIV after their STI PS interview reported discontinuing PrEP prior to their HIV diagnosis.
Conclusion: Based on current use in King County, PrEP is highly effective, reducing HIV incidence by 84% among MSM and transgender persons. Our findings highlight PrEP discontinuation as a key challenge limiting the effectiveness of PrEP, and the elevated risk of HIV among young and minority MSM and TGSM diagnosed with STI.

980LB TFV-DP IN DBS FOR PREGNANT/POSTPARTUM ADOLESCENT AND YOUNG WOMEN ON PrEP IN AFRICA

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Background: Pregnant/postpartum adolescent girls and young women (AGYW) in Africa are one of the populations at highest risk for HIV acquisition; yet, pharmacokinetic (PK) data for pre-exposure prophylaxis (PrEP) remains limited. Intracellular tenofovir-diphosphate (TFV-DP) concentration in red blood cells, measured via dried blood spots (DBS), has been used to monitor cumulative PrEP adherence in many settings.
Methods: The first phase of IMPAACT 2009 evaluated PK characteristics of daily oral PrEP (FTC 200mg/TDF 300mg) among pregnant/postpartum AGYW (16-24 years) in Malawi, South Africa, Uganda, and Zimbabwe. Daily FTC/TDF was administered under direct observation for 12 weeks in two groups: pregnant AGYW starting at 14-24 weeks gestation (pregnancy) or 6-12 weeks after delivery (postpartum). Weekly TFV-DP was measured from DBS using a validated liquid chromatography-tandem mass spectrometry assay. TFV-DP distributions were determined at 12 weeks and groups compared with the Wilcoxon test. Population PK models were fit to estimate half-life and steady state concentrations.
Results: From March to June 2019, we enrolled 20 pregnant (median gestational age: 18 wks) and 20 postpartum (median time after delivery: 7 wks) women at a median age of 20 years (IQR:19,22). Of 3360 doses, 3348 (>99%) were directly observed. TFV-DP accumulated with a half-life of 15.3 days (95%CI: 12.8,17.8) in pregnancy and 18.0 days (95%CI: 15.3,20.7) postpartum, with steady state achieved by 8-10 weeks in both groups. Median TFV-DP was 965 fmol/punch (IQR: 691,1166) in pregnancy vs 1406 fmol/punch (IQR: 1053,1859) postpartum (p=0.006). Predicted median TFV-DP was 890 fmol/punch (IQR: 704,1143) in pregnancy vs 1418 fmol/punch (IQR: 1179,2139) postpartum (Figure). Two fetal demises (unrelated to study agent), two

newborns <10%tile birthweight, and one preterm birth were recorded. No HIV transmissions occurred during follow-up.
Conclusion: Under conditions of near perfect adherence, TFV-DP in African AGYW was 31-37% lower in pregnancy than postpartum. With sequential measurements and a novel measure of cumulative drug exposure, these findings extend prior studies showing lower plasma TFV during pregnancy. There are few data correlating HIV protection and TFV-DP concentrations in women; however, our results suggest that strict adherence is needed during pregnancy. They also provide guidance for assessing PrEP adherence using TFV-DP levels in DBS for pregnant/postpartum African women.



The dashed horizontal line is the median TFV-DP steady state concentration in US men and non-pregnant, non-lactating women under directly observed therapy (1540 fmol/punch). Grey shading represents the 95% confidence interval for these estimates.

981 WITHDRAWN

982 WAXING AND WANING HIV RISK: DYNAMICS OF PrEP ELIGIBILITY IN RAKAI, UGANDA

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Background: PrEP is based on the presence of substantial HIV risk (SHR) behaviors making PrEP eligibility and retention dynamic. We used population-based data to describe longitudinal patterns of SHR of PrEP eligibility and identify factors associated with incidence, persistence and recurrence of PrEP eligibility.
Methods: Between August 2011 – June 2018, 4 surveys including SHR-focused questions were conducted by the Rakai Community Cohort Study among consenting adults aged 15-49 years. SHR was defined by the Uganda national PrEP eligibility as either reporting sexual intercourse with >1 partner of unknown HIV status, non-marital sex without a condom or having transactional sex. Recurrence of SHR was defined as the resumption of SHR after stopping SHR, while persistence of SHR meant SHR on >1 consecutive visit. Poisson and log-binomial regressions with generalized estimating equations and robust variance estimators were used to estimate adjusted incidence rate ratios (aIRRs) and prevalence rate ratios (aPRRs) for PreP eligibility with 95%CIs.
Results: 25,695 HIV-negative individuals participated in the cohort, including 13,010 participants with SHR assessment data at ≥ 2 visits (24,132 person-intervals). Overtime, prevalence of SHR increased from 20.1% to 25.2% (p<0.001), and incidence of SHR increased from 6.0/100pys to 7.7/100 pys (p<0.001). Recurrence of SHR was 27.4%. Persistence of SHR at 24, 36 and 48 months was 67.5%(95%CI=66-69), 46.9%(95%CI=45-49) and 26.0%(95%CI=24-28), respectively. Incidence of SHR was associated with male sex (aIRRs=1.27[95%CI=1.19-1.36]); never married vs married (aIRRs=3.04[95%CI=2.74-3.37]), previously married vs married (aIRRs=4.05[95%CI=3.70-4.43]); age 20-24 vs 15-29 (aIRR=1.71 [95%CI=1.55-1.87]), 25-29 (aIRR=1.29 [95%CI=1.13-1.47]), and 30-34 (aIRR=1.21[95%CI=1.05-1.39]). Persistence of SHR was associated with male sex (aPRRs=1.15[95%CI=1.08-1.23]); never married vs married (aPRRs=3.05[95%CI=2.77-3.36]), previously married vs married (aPRRs=2.62[95%CI=2.36-2.91]). Recurrence of SHR also associated with male sex (aIRRs=1.39[95%CI=1.14-1.71]), never married vs married (aPRRs=2.97[95%CI=2.37-3.73]), and previously married (aPRRs=2.81[95%CI=2.25-3.53]).
Conclusion: Persistence of SHR was modest in this population while incidence and recurrence of SHR were high. The overall prevalence of SHR steadily increased. PrEP programs in similar settings should expect short and repeated PrEP eligibility periods with turnover due to incidence and recurrence of SHR.

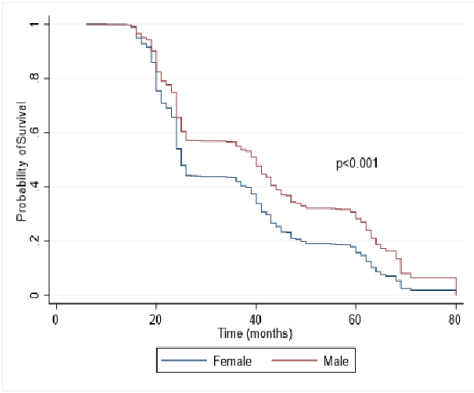


Figure1. Adjusted Cox proportional hazards regression of Stopping PrEP eligible Substantial Risk Behavior

983 IMPLEMENTATION OF MOBILE PrEP, STI, AND HIV PREVENTION SERVICES IN SOUTH FLORIDA

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Background: Men of color who have sex with men (MSM) and transgender women (TGW) of color are disproportionately affected by HIV. National testing guidelines state that sexually active MSM should have HIV testing annually, and persons at higher risk of acquisition may consider testing every 3-6 months. Little is known about HIV testing patterns of MSM and TGW of color. The THRIVE demonstration project promotes HIV care and prevention services through health department-led collaboratives at 7 sites in the United States. We used THRIVE client data to compare HIV testing patterns for MSM and TGW of color based on PrEP screening results.
Methods: Preliminary THRIVE data from 2016-2019 were used. Inclusion criteria were: 1. HIV-negative MSM or TGW of color, 2. Received ≥2 HIV tests, 3. At least 180 days follow-up time. We calculated median and interquartile ranges (IQR) for: days from first to last test, number of tests, and days between tests. We determined what proportion of persons had testing intervals of 90, 120, 180, and 365 days among persons screened for PrEP and found to have 1. PrEP indications and 2. No PrEP indications. Chi squared tests were used for statistical comparisons.
Results: For the 2490 MSM and TGW of color, 92% had PrEP indications. Overall, the median (IQR) days to last test was 335 (167-503); median number of tests 3 (2-5); and median days between tests 110 (73-183). Overall, cumulative percentages of persons tested were 36%, 55%, 74%, and 93% for intervals of at least 90, 120, 180, and 365 days respectively. For persons with PrEP indications, cumulative percentages were 37%, 58%, 77%, and 95% for the same intervals; cumulative percentages were 36%, 47%, 63%, and 87% for the same intervals for persons without PrEP indications. Proportion tested every 90 days did not differ significantly between groups; for all other testing intervals significantly more persons with PrEP indications were tested (p<0.05).
Conclusion: The majority of MSM and TGW of color with evidence of serial HIV testing are tested at least annually, however, persons without indications for PrEP were significantly less likely to receive annual testing. Similar proportions of MSM and TGW of color with and without PrEP indications were tested

every 90 days. Additional investigations are needed to understand the factors influencing HIV testing frequency among MSM and TGW of color.

Table. HIV testing patterns among MSM and TGW of color, by PrEP indications

MSM and TGW of color	Persons with ≥2 HIV tests							
	Total	Median days to last test (IQR)	Median number of tests (IQR)	Median days between tests (IQR)	N(%)* tested every 90 days	N(%)* tested every 120 days	N(%)* tested every 180 days	N(%)* tested every 365 days
Total	2490	335 (167-503)	3 (2-5)	110 (73-183)	993 (36)	1520 (55)	2052 (74)	2580 (93)
PrEP indications	2303	346 (179-510)	3 (2-6)	107 (73-170)	856 (37)	1327 (58)	1779 (77)	2179 (95)
No PrEP indications	187	241 (78-526)	2 (2-4)	133 (59-243)	68 (36)	88 (47)	118 (63)	162 (87)

* Testing interval columns are cumulative so that each subsequent column contains persons included in the column before

984 IMPLEMENTATION OF MOBILE PrEP, STI, AND HIV-PREVENTION SERVICES IN SOUTH FLORIDA

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Background: Pre-Exposure Prophylaxis (PrEP) can substantially reduce HIV incidence among those at risk for acquisition. To achieve population-level impact, effective dissemination of PrEP to priority groups in areas with a high incidence of HIV, such as black and Hispanic men who have sex with men (MSM) living in South Florida, is needed. To address multiple social, logistical, and structural barriers to PrEP uptake, we implemented PrEP/HIV and sexually transmitted infections (STI) services combined with cancer screening through the Sylvester Gamechanger vehicle. We describe demographics, utilization, and early retention in PrEP care during the first year of operation.

Methods: The mobile clinic was positioned at 4 sites in Miami with high HIV incidence with input from community stakeholders. Key program personnel were a medical provider, HIV/PrEP counselors, and a pharmacist. In addition to self-referrals, Prevention305 and Latino Salud, community-based organizations, developed focused patient recruitment through social media. All services were provided at no cost. Normative demographics, risk behavior, STIs, and early-maintenance-in-care data, were collected. Descriptive statistics were compiled using SPSS.

Results: From September 2018 to September 2019 services were provided to 429 clients. Of these, 266/429 (62%) sought PrEP. Of PrEP clients, 223 (83.8%) identified as Hispanic, 19 (7.1%) as non-Hispanic Black, 17 (6.4%) as non-Hispanic White, and 7 (2.6%) as other. 194/265 (73.2%) were foreign-born; 233/266 (87.6%) of PrEP clients identified as MSM (66.2% MSM only, and 21.4% MSMW). Ten (3.8%) PrEP-seeking clients were HIV positive at baseline. Of these, 2 were identified as acute/early infections. Among clients assessed for PrEP, an initial PrEP prescription was filled by 239/251 (95.2%). Of the 175 clients seen within the initial 6 months of operation, 129 (74%) completed a follow-up visit. Overall, 74/307 (24.1%) PrEP clients had positive STI results (gonorrhea, chlamydia, or syphilis) at baseline. STI treatment delivery on the mobile clinic began in August, 2019.

Conclusion: Implementation of HIV-PrEP prevention and STI services using a mobile clinic model is acceptable and effective in engaging Hispanic/Latino immigrant MSM at risk for HIV and STIs. Low-barrier-to-entry services delivered through a mobile clinic inclusive of other prevention services can be an effective method for engagement of priority populations with difficulty accessing traditional clinic settings.

985 PrEP USE APPROACHING 50% AMONG HIGH-RISK MSM IN WESTERN WASHINGTON

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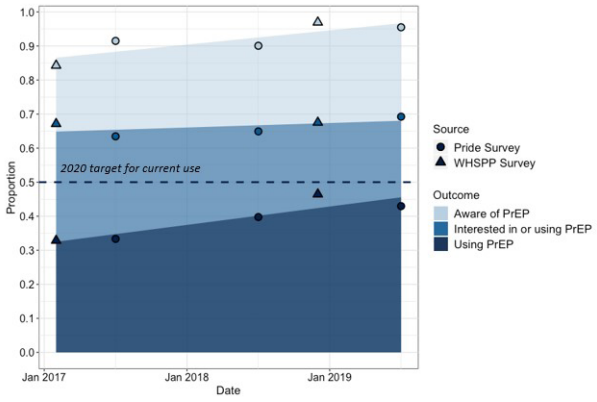
Background: Washington State and Public Health—Seattle & King County promote the use of HIV pre-exposure prophylaxis (PrEP) among persons at elevated risk for HIV and provide financial support to help cover PrEP-related costs. To monitor progress towards a target of 50% uptake among high-risk men who have sex with men (MSM) by 2020, we compared estimates from two ongoing surveys of Washington State MSM.

Methods: We analyzed data collected 2017-2019 from the Washington HIV/STI Prevention Project (WHSPP), a statewide online survey, and an annual paper-based survey administered to men attending the Seattle Pride Parade in June of each year. Samples from both surveys were restricted to cisgender males residing in King, Pierce, and Snohomish counties who reported sex with a man in the past 12 months (N=213-291 for Pride surveys and 463-726 for WHSPP). To adjust for differences in sample composition between the surveys, we used a raking procedure to standardize the samples by age, race/ethnicity, education, sexual orientation, and county. We classified respondents as high risk if they reported any of the following in the past year: bacterial STI diagnosis, use of methamphetamine or poppers, ≥10 male anal sex partners, or condomless anal sex with an HIV-positive or unknown-status partner. For each year, we calculated the proportion of high-risk men who reported awareness, interest, and current use of PrEP, and we used logistic regression to test differences by calendar time and survey source.

Results: After adjusting for demographic variables and calendar time, estimates from the Pride and WHSPP surveys were similar for all three outcomes (p=0.2-0.4). The proportion of high-risk MSM who had heard of PrEP increased over time (p<0.001) from 84% in 2017 to approximately 96% in 2019 (Figure 1). The proportion of men who reported use of PrEP or expressed interest in starting PrEP (a measure of total demand) remained stable over time at around 66% (p=0.7). Current use of PrEP increased from 33% in 2017 to 43-46% in 2019 (p<0.001).

Conclusion: Awareness of PrEP increased among high-risk MSM in western Washington State from 2017-2019, but did not lead to increases in demand. The proportion of high-risk men using PrEP increased, tracking well with local prevention targets. Although the representativeness of samples from both surveys is unknown, the concordance in estimates supports continued use of these low-cost methods to monitor trends and inform ongoing HIV prevention efforts.

Figure 1. Trends in PrEP awareness, interest, and use among high-risk Seattle-area men who have sex with men, 2017-2019



Shaded areas are defined using linear trend lines for awareness, interest, and use of PrEP, fitted to estimates from both surveys.

986 OPTIMIZING PrEP CASCADE OUTCOMES FOR SEXUAL HEALTH CLINIC NAVIGATION

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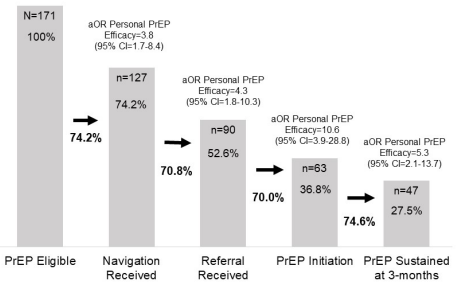
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Background: Sexual Health and STI clinics are increasingly integrating PrEP navigation services to identify, refer and link eligible patients to PrEP. Increasing the effectiveness of these programs requires optimizing each step of the PrEP cascade, i.e., acceptance of navigation and referral, PrEP initiation, and sustained PrEP use. Epidemiological data have focused almost exclusively on demographic predictors of cascade outcomes, which are not amenable to behavioral intervention. This implementation science study examined modifiable psychosocial predictors of cascade outcomes that can guide targeted intervention efforts.

Methods: Data were collected as part of an NIH-funded sub-study of a PrEP navigation program in 8 NYC public sexual health clinics. Between Feb 2017 and Aug 2018, we recruited 279 patients with program-specific indications for

PrEP navigation; this analysis includes participants who were PrEP-naïve and completed baseline and 3-month study visits.
Results: Of 171 patients (31% ≤ 25 years; 90% cis male; 57% Black or Latinx), 74% accepted navigation, 53% accepted PrEP referral, 37% initiated PrEP, and 27% were still on PrEP at 3-months. PrEP referral, initiation, or persistence were not associated with HIV risk behavior, belief in PrEP effectiveness, or desire for condomless sex. The strongest predictor of PrEP outcomes at every step of the cascade was a 6-item measure of personal PrEP efficacy (Fig. 1), including positive attitudes toward PrEP pills, self-efficacy for pill-taking, and confidence in PrEP's ability to work "for me." All cascade outcomes were positively associated with HIV worry; PrEP initiation and sustained use were negatively associated with medical mistrust. Perceived HIV risk was not associated with navigation acceptance, referral, or PrEP initiation, but was negatively associated with sustained PrEP use at 3-months (aOR=.97, 95% CI .95-.99).
Conclusion: These data are some of the first to identify specific, modifiable targets for psychosocial intervention to optimize PrEP cascade outcomes in the context of sexual health clinic navigation. In contrast to focusing on risk behavior, risk perception, or effectiveness, these data suggest the importance of messaging and counseling that enhances self-efficacy beliefs, promotes PrEP as an antidote to HIV worry, and builds trust. Findings can inform development of interventions to be tested in implementation science RCTs in public clinics.

Figure 1. PrEP Cascade and association with Personal PrEP Efficacy among NYC Sexual Health Clinic PrEP navigation patients seen between Feb 2017 and Aug 2018 (N=171)



Note: Percentages within each bar represent the proportion of the total sample (n=171); percentages between bars represent the proportion retained in each step of the cascade.

987 NONDAILY USE OF HIV PREEXPOSURE PROPHYLAXIS IN A LARGE ONLINE SAMPLE IN THE US

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Background: Event-driven dosing of HIV preexposure prophylaxis (PrEP) using a 2-1-1 strategy has been shown to be efficacious in reducing HIV risk for men who have sex with men (MSM). However, data on interest in and use of non-daily PrEP in the US are limited.
Methods: We developed a survey to assess interest in and experiences with PrEP, including non-daily use, among HIV-negative adults in the US. We distributed the survey nationally in May 2019 on geosocial networking sites commonly used by MSM. We used chi-square tests and t-tests to identify factors associated with interest in and use of non-daily PrEP.
Results: Our study sample included 9,697 respondents. Mean age was 43 years, 67% were non-Hispanic white, and 90% were MSM. Nearly all (96%) had heard of PrEP, 40% had ever used PrEP, and 33% had used PrEP in the last 6 months. Interest in non-daily PrEP was high (67%). A greater proportion of those interested in non-daily than daily PrEP were aged <30 years (21% vs 18%, P=0.013), had no graduate degree (76% vs 71%, P<0.001), had annual income <$80,000 (76% vs 73%, P=0.02), and were uninsured (11% vs. 9%, P<0.001). Of the 3232 who used PrEP in the past 6 months, only 5% used non-daily dosing. Non-daily dosing strategies included event-driven (49%), regular but not daily use (e.g., on days of the week starting with T or S; 24%), daily but only for short periods (e.g., on vacations; 19%), and other strategies (8%). Of the 85 using event-driven dosing, 65% used the 2-1-1 strategy; the remaining 35% used a variety of strategies, including daily dosing for a week before and after sex, 1 pill before and after sex, or 1 pill around the time of sex. A greater proportion of non-daily than daily users had annual income ≥$80,000 (36% vs 30%, P=0.04) and always planned sex in the past 6 months (21% vs 11%, P=0.007). Common reasons for non-daily use were not consistently engaging in sexual activity (59%), high cost of PrEP (49%), concerns about potential long-term side effects (39%), not engaging in sex perceived as high-risk for HIV (37%), and planning sex in advance (25%).
Conclusion: In this national sample, interest in non-daily PrEP was high, and 5% of recent PrEP users reported non-daily dosing. Given the use of non-daily strategies that have not been evaluated in clinical studies, there is an urgent need for US public health authorities to provide clear guidance for safe and effective non-daily dosing options.

988 EFFECTIVENESS OF PrEP NAVIGATION MODELS IN THE THRIVE DEMONSTRATION PROJECT

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[1]CDC, Atlanta, GA, USA

Background: HIV pre-exposure prophylaxis (PrEP) uptake has been suboptimal among populations with the highest rates of HIV diagnoses, including men who have sex with men (MSM) of color. Effective navigation models for PrEP clinical care can help persons at risk of acquiring HIV to initiate, adhere to, and persist with PrEP. PrEP providers currently lack evidence-based models for PrEP service navigation. The THRIVE demonstration project funded seven state health departments to develop collaboratives comprised of community-based organizations (CBOs) and clinical providers to implement comprehensive HIV prevention and care services for MSM of color. THRIVE used several different PrEP navigation models in the demonstration project.
Methods: We analyzed cohort data of 8,339 MSM of color enrolled in THRIVE from September 2015 through March 2019. Study locations included Alabama, Baltimore, Louisiana, New York City, Philadelphia, Virginia and Washington (DC). We estimated the number of MSM of color who were eligible for and linked to PrEP care. We explored possible navigation models based on the following navigation components common across all seven jurisdictions: navigator education (professional with a college or higher vs. peers from the community with no formal educational requirement) and source of navigation protocol development (health department or clinic/CBO); three navigation models were identified. We conducted multivariable regression analyses [risk ratio, 95% confidence intervals (CI)] to estimate the associations between type of PrEP navigation model and linkage to care.
Results: Among 4,999 MSM of color who were eligible for PrEP, 4,227 (84.6%) were linked to care. Our analyses identified three navigation models. We found that navigation models that combined professional and peer navigators with protocols designed by clinics/CBOs were more than 3 times as likely to link eligible clients to PrEP compared to navigation models that combined peer navigators with protocols designed by health departments (88.8% vs. 21.5%) (RR: 3.48, 95% CI=2.61–4.62).
Conclusion: Navigation models that included professional navigators and CBO-developed protocols were more effective for increasing linkage to PrEP healthcare services. Our analyses of interim data from the THRIVE demonstration project provide evidence to guide the development of PrEP navigation models that can be used in U.S. jurisdictions funded by the Ending the HIV Epidemic federal initiative.

Effectiveness of pre-exposure prophylaxis (PrEP) navigation models among men who have sex with men (MSM) of color, THRIVE Demonstration Project in seven selected jurisdictions, 2015-2019.

	Number of PrEP eligible patients	Number of patients linked to PrEP	% of persons linked to PrEP	RR	95% CI	p-value
Navigation Model						
Professional + Peer and CBO Protocol	3211	2850	88.8%	3.48	2.61 - 4.62	<0.001
Professional + Peer and HD Protocol	372	95	25.5%	Ref	n/a	n/a
Peer and HD Protocol	1416	305	21.5%	0.84	0.70 - 1.02	0.0752

PrEP = pre-exposure prophylaxis; MSM = men who have sex with men; RR = risk ratio; CI = confidence interval; CBO = community-based organization; HD = health department.

989 TURNING INTENT INTO ACTION: ASSESSING PrEP UPTAKE AT A PUBLIC STI CLINIC

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Background: Consistently taking pre-exposure prophylaxis (PrEP) reduces the risk of acquiring HIV by almost 90%. Washington, DC has a high incidence of HIV

(360 new cases in 2018) which disproportionately affects people of color (71.1% Black and 9.2% Latinx). The DC Health and Wellness Center began prescribing PrEP in 2016 to start and maintain men who have sex with men (MSM) and transgender women of color on PrEP at low or no cost to them. We assessed differences between patients on PrEP <1 month and those on ≥1 month.

Methods: Demographics and reasons for starting PrEP were collected in REDCap at initiation. Eligible patients received PrEP, scheduled a follow-up visit, and agreed to additional follow-ups every 3 months. REDCap data were merged with medical records to determine time on PrEP. Chart reviews were done to establish duration of therapy. Patients taking PrEP <1 month and ≥1 month were compared using chi-square analysis and multivariate logistic regression to explore the associations of race/ethnicity, age, gender identity, and insurance status.

Results: From August 2016 - December 2018, 530 people were prescribed PrEP; 81.7% were people of color (47.2% Black, 28.5% Latinx, and 6.0% other), 80.2% were MSM, 10.0% were cisgender women, and 3.6% were transgender women. Of these, 280 (52.8%) were still on PrEP at ≥1 month and 250 (47.2%) were not. Likelihood of being on PrEP ≥1 month increased with age (AOR: 1.02, 95% CI 1.00-1.04). Patients on PrEP ≥1 month were less likely to be transgender women (AOR: 0.089, 95% CI 0.019-0.41) or cisgender women (AOR: 0.21, 95% 0.095-0.46) compared to cisgender men. Those with private (AOR: 0.52, 95% CI 0.33-0.81) or public insurance (AOR: 0.24, 95% CI 0.14-0.40) were less likely to still be on PrEP at ≥1 month compared to those with no insurance.

Conclusion: This study shows that PrEP prescribing can successfully occur at a safety-net, public STI clinic with a high volume of persons of color and underinsured. The model of direct, immediate, and costless provision of initial medication with on-site enrollment in drug assistance programs could be responsible for increased uptake among uninsured individuals. The addition of a PrEP Case Manager to provide systematic appointment reminders, follow up for missed appointments, and linkage to additional services (e.g., gender-affirming therapy) might be beneficial, especially for youth, cisgender women, and transgender women. Reasons for stopping PrEP should routinely be collected and assessed.

990 DISCOVER: 96-WEEK FOLLOW-UP OF BLACK AND HISPANIC/LATINX STUDY PARTICIPANTS

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Background: In the US, Black and Hispanic/Latinx (H/Lx) men and transgender women who have sex with men (MSM, TGW) are disproportionately impacted by HIV and underutilize PrEP. Contributing factors include low access to and retention in care. Among 5,387 randomized participants in the DISCOVER study, noninferiority of F/TAF to F/TDF for HIV prevention was shown in MSM and TGW with signficant risk of HIV infection.

Methods: Using descriptive statistics, 96 week (W) follow-up data from study participants who confidentially self-identified as Black race or H/Lx ethnicity were analyzed for efficacy (HIV incidence, dried blood spot (DBS) adherence) and safety (renal biomarkers, serum lipids, bone mineral density).

Results: Of 5387 participants enrolled from 94 sites in North America and Europe, 474 (9%) identified as Black and 1318 (24%) identified as H/Lx. Fifty participants identified as both Black and H/Lx ethnicity and are included in both sub-populations. Through 96W, among Black or H/Lx participants, 11 individuals acquired HIV, incidence rate: 0.34 (95%CI 0.17-0.61). Two had suspected baseline HIV infection and the 9 remaining individuals (n=4 Black, n=5 H/Lx) had low or undetectable drug levels at diagnosis. The percent of Black participants lost to follow-up (LTFU) was 14.6 vs 7.1 among non-Black participants (p<0.001). The percent of Black participants with an adverse event (AE) leading to discontinuation was 2.3% vs 1.5% among non-Black participants (p=0.18). The percent of H/Lx participants LTFU was 8.7% vs 7.4% among non-H/Lx participants (p=0.14). The percent of H/Lx participants with an AE leading to study drug discontinuation was 0.8% vs 1.9% among non-H/Lx participants (p=0.004). While study drug adherence for the overall population was high, nonadherence was increased in Black vs non-Black participants: OR 2.4 (95%CI 1.2 to 4.8). Changes to eGFR, BMD, weight and lipids were similar in Black vs non-Black and H/Lx vs non-H/Lx participants (Table 1).

Conclusion: Through 96W, all Black or H/Lx participants who acquired HIV during follow-up had low or undetectable drug levels at diagnosis. Black vs non-Black participants were more likely to be LTFU and 2.4 times more likely to be nonadherent. The proportion of study drug discontinuations due to AEs was lower among H/Lx vs non-H/Lx participants. Overall, both F/TAF and F/TDF were efficacious, safe, and well tolerated in Black and H/Lx participants.

Table: 96W Safety Parameters of Black vs Non-Black and Hispanic/Latinx vs Non-Hispanic/Latinx Participants of the DISCOVER Study

	Black		Non-Black		Hispanic		Non-Hispanic	
Week 96	**F/TAF**	**F/TDF**	**F/TAF**	**F/TDF**	**F/TAF**	**F/TDF**	**F/TAF**	**F/TDF**
HIV Incidence/100PY (95%CI)	0.47 (0.06, 1.7)	0.72 (0.15, 2.1)	0.13 (0.05, 0.28)	0.26 (0.13, 0.45)	0.25 (0.05, 0.74)	0.24 (0.05, 0.69)	0.13 (0.04, 0.30)	0.32 (0.16, 0.56)
Median Change from Baseline eGFR (mL/min)	+0.1	-3.4	-0.6	-4.2	+0.3	-3.5	-0.6	-4.2
Mean % Change from Baseline Hip BMD	-0.1%	-1.6%	+0.7%	-1.0%	+0.8%	-1.5%	+0.6%	-0.9%
Mean % Change from Baseline Spine BMD	+1.8%	-0.8%	+0.9%	-1.4%	+0.7%	-1.6%	+1.0%	-1.3%
Median Change from Baseline Weight (kg)	+2.0	+0.9	+1.7	+0.5	+1.3	+0.5	+1.8	+0.5
Median Change from Baseline Total Cholesterol (mg/dL) [a,b,c]	-2	-11	-2	-13	-3	-13	-2	-13
Median Change from Baseline HDL (mg/dL) [a,b,c]	-3	-4	-1	-4	-1	-5	-1	-4
Median Change from Baseline Direct LDL (mg/dL) [a,b,c]	-2	-3	-1	-7	0	-8	-2	-6
Median Change from Baseline Triglycerides (mg/dL) [a,b,c]	9	-1	2	-4	1	-3	4	-5
Participants reporting any drug related treatment emergent AE (%)	17.9	24.8	20.9	23.6	24.3	26.5	19.5	22.8
Participants with AE leading to study drug discontinuation (%)	2.9	1.7	1.2	1.8	0.6	0.9	1.6	2.1
Participants lost to follow up (%)	17.1	12.0	7.5	6.7	9.3	8.2	8.1	6.8

a. Values are for fasted subjects
b. Excludes subjects who received lipid lowering agents during the treatment period
c. Includes only subjects with both baseline and Week 96 values

991 FACTORS ASSOCIATED WITH PrEP PERSISTENCE AND ADHERENCE AMONG MSM IN 4 US CITIES

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[1]CDC, Atlanta, GA, USA, [2]Los Angeles County Department of Public Health, Los Angeles, CA, USA, [3]Philadelphia Department of Public Health, Philadelphia, PA, USA, [4]Rutgers University, Newark, NJ, USA, [5]District of Columbia Department of Health, Washington, DC, USA, [6]George Washington University, Washington, DC, USA

Background: Pre-exposure prophylaxis (PrEP) persistence and adherence are critical to achieving national HIV prevention goals. While there is no gold standard for measuring PrEP persistence (continued use) and adherence (effective use), biological testing for tenofovir diphosphate (TFV-DP) and emtricitabine (FTC) is considered best practice. We conducted testing for PrEP among HIV-negative men who have sex with men (MSM) in 4 U.S. cities as part of 2017 National HIV Behavioral Surveillance.

Methods: MSM were recruited via venue-based sampling in Los Angeles, Philadelphia, San Francisco, and Washington DC. Eligible, consenting MSM completed a survey, HIV testing, and dried blood spot (DBS) collection. DBS were tested for tenofovir (TFV), FTC, and TFV-DP by liquid chromatography mass spectrometry. Our analysis was limited to HIV-negative MSM who had CDC-based PrEP indications and self-reported PrEP use in the past year. Persistence was defined as self-reporting PrEP use in the past 12 months and having any detectable TFV, FTC, or TFV-DP in DBS collected at the interview. Among those reporting past-month PrEP use, adherence was defined as TFV-DP ≥1250 fmol/punch or TFV-DP ≥700 fmol/punch (consistent with an average of 7 doses/week or 4-7 doses/week, respectively). Poisson regression with generalized estimating equations clustering by recruitment event and adjusting for city was used to assess associations between key characteristics and persistence and adherence.

Results: Overall, 81.2% (310/382) were persistently using PrEP based on biological testing. Persistence was significantly lower among MSM who were younger (p=0.03), had lower education (p<0.01), had public insurance (p=0.02), and had fewer male sex partners (p<0.01). Among MSM reporting past-month PrEP use, 66.2% (200/302) were adherent at 7 doses/week and 80.5% (243/302) were adherent at 4-7 doses/week. Adherence was significantly lower among MSM who were younger (all p<0.01), had less than high school education (p=0.02, p=0.04), were black race/ethnicity (p=0.04, p=0.01), had fewer male sex partners (p=0.03, p=0.05), and lived in Philadelphia (p<0.01, p=0.01).

Conclusion: Approximately 19% of PrEP-using MSM in the 4 cities had not persistently used PrEP. About 34% of MSM were not adherent at 7 doses/week and 20% were not adherent at 4-7 doses/week. Efforts to support PrEP persistence and adherence are needed for MSM and should include strategies tailored to age, education, race/ethnicity, insurance type, and city context.

Factors associated with PrEP persistence and adherence among men who have sex with men indicated for PrEP in 4 U.S. cities—National HIV Behavioral Surveillance, 2017

	PrEP Persistence[1] (N=382)			PrEP Adherence[2] (N=302)					
				7x/week[3]			4-7x/week[4]		
	No.	%	p[5]	No.	%	p[5]	No.	%	p[5]
Age (years)									
18-29	116	72.5	**0.03**	72	60.0	**<0.01**	88	73.3	**<0.01**
30-39	131	87.9	0.67	78	62.4	**<0.01**	100	80.0	**<0.01**
≥40	63	86.3	Ref	50	87.7	Ref	55	96.5	Ref
Race/ethnicity									
Black/African American	53	73.6	0.75	24	42.1	**0.04**	33	57.9	**0.01**
Hispanic/Latino[6]	79	79.0	0.96	47	61.0	0.05	61	79.2	0.06
White	135	86.5	Ref	95	76.0	Ref	109	87.2	Ref
Other	42	79.2	0.27	33	78.6	0.85	39	92.9	0.37
Education									
≤High school degree	40	69.0	**0.01**	19	45.2	**0.02**	26	61.9	**0.04**
Some college	59	68.6	**<0.01**	37	59.7	0.16	47	75.8	0.23
College degree or higher	211	88.7	Ref	144	72.7	Ref	170	85.9	Ref
Health insurance									
No health insurance	21	70.0	0.09	12	60.0	0.62	17	85.0	0.63
Public	61	70.1	**0.02**	37	57.8	0.82	45	70.3	0.71
Private	222	86.0	Ref	146	68.9	Ref	175	82.5	Ref
Other/multiple	5	83.3	0.94	4	80.0	0.41	5	100.0	<0.01
Number of male sex partners, past 12 months									
1-4	41	61.2	**<0.01**	20	45.5	**0.03**	29	65.9	0.05
5-9	52	73.2	**0.02**	33	63.5	0.98	38	73.1	0.38
≥10	217	88.9	Ref	147	71.4	Ref	176	85.4	Ref
City									
Los Angeles	74	84.1	0.71	54	72.0	0.91	62	82.7	0.58
Philadelphia	34	68.0	0.05	13	34.2	**<0.01**	21	55.3	**0.01**
San Francisco	122	85.3	Ref	87	71.3	Ref	106	86.9	Ref
Washington DC	80	79.2	0.23	46	68.7	0.71	54	80.6	0.41
Total[7]	310	81.2		200	66.2		243	80.5	

Abbreviations: x/week=doses/week, p=p-value, Ref=referent
[1]Among participants who reported using PrEP in the past 12 months, consented to dried blood spot (DBS) storage, and had valid test results. Persistence was defined as self-reporting PrEP use in the past 12 months and having any detected tenofovir (TFV), emtricitabine (FTC), or tenofovir diphosphate (TFV-DP) by liquid chromatography mass spectrometry in DBS.
[2]Among those who reported PrEP use in past month, consented to DBS storage, and had valid TFV-DP results.
[3]Detected TFV-DP at ≥1250 fmol/punch by liquid chromatography mass spectrometry in DBS.
[4]Detected TFV-DP at ≥700 fmol/punch by liquid chromatography mass spectrometry in DBS.
[5]P-values were calculated from Poisson regression models with generalized estimating equations accounting for clustering by venue recruitment event and adjusting for city.
[6]Hispanic/Latinos can be of any race.
[7]Numbers may not sum to total due to missing values.

992 HIV-1 INCIDENCE, PrEP UPTAKE, AND ADHERENCE AMONG KENYAN MSM

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Background: Data on HIV-1 incidence following programmatic pre-exposure prophylaxis (PrEP) uptake by men who have sex with men (MSM) in sub-Saharan Africa is not available. We assessed PrEP uptake and adherence, and HIV-1 incidence, in at-risk MSM with access to PrEP in coastal Kenya.
Methods: Since June 2017, at-risk MSM followed at monthly visits were offered daily PrEP with adherence and risk reduction counselling. At each visit, we assessed PrEP adherence, intention to continue, and HIV-1 status using rapid antibody tests. If symptoms of acute HIV-1 (e.g. fever) or risk criteria (e.g. receptive anal sex,) were met, X-pert RNA Qual testing was done. We determined tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots 6-12 months after PrEP initiation, and tenofovir (TFV) concentrations and genotypic drug resistance in plasma samples when HIV-1 was detected. HIV-1 incidence was assessed as per reported PrEP use, and population-averaged multivariable Poisson regression with robust standard errors was used to identify predictors of HIV-1 acquisition.
Results: Of 167 at-risk MSM, 162 (94.9%) were eligible for PrEP, 131 (80.9%) started it, and 57 (43.5%) reported PrEP use at study censoring, for a median follow-up time of 21.2 (interquartile range: 10.2–22.1) months. Nine MSM acquired HIV-1 [incidence rate: 3.9 (95% confidence interval (CI), 2.0–7.4) per 100 person-years (PY)]. Of these, 5 MSM reported PrEP use at the time of HIV-1 acquisition [incidence rate: 3.7 (95% CI, 1.5–8.8) per 100 PY] and 4 MSM had stopped or had never started PrEP [incidence rate: 4.2 (95% CI, 1.6–11.1) per 100 PY; figure]. Among 75 (57.3%) MSM who reported PrEP use, 11 (14.7%) had protective TFV-DP levels of ≥700 fmol/punch (≥4 tablets a week). Among the 5 MSM who acquired HIV-1 while reporting to take PrEP, only one had detectable but low TFV levels in plasma (66.0 ng/mL) and none had genotypic HIV-1 resistance. In multivariable analysis, no factors were significantly associated with HIV-1 acquisition.
Conclusion: HIV-1 incidence among at-risk MSM with access to programmatic PrEP was high and did not differ by reported PrEP use. Only one in seven MSM taking PrEP had protective tenofovir levels, and a substantial proportion of MSM stopped taking PrEP despite frequent risk reduction counselling. Strengthened PrEP adherence support is required among MSM in Kenya.

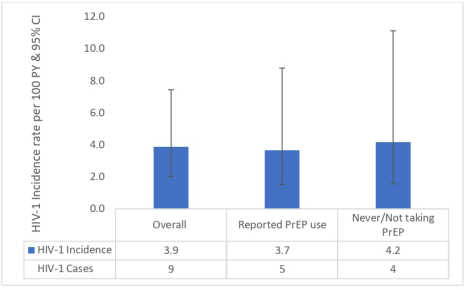
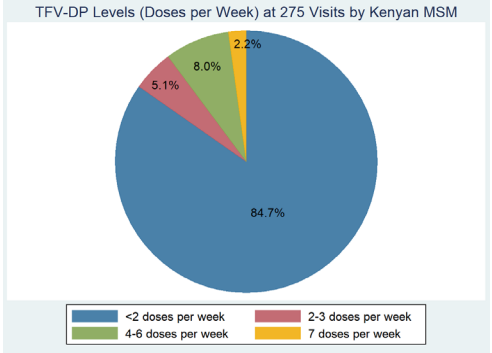


Figure. HIV-1 Incidence in MSM by reported PrEP use in Kenya, June 2017 – June 2019. PrEP, pre-exposure prophylaxis; PY, person-years; CI, confidence interval

993 HIGH REPORTED ADHERENCE BUT LOW PrEP LEVELS AMONG KENYAN MEN WHO HAVE SEX WITH MEN

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Background: Gay, bisexual, and other men who have sex with men (MSM) are at high risk of HIV acquisition in Kenya, where pre-exposure prophylaxis (PrEP) has recently become available. Our aim was to evaluate factors associated with tenofovir diphosphate (TFV-DP) detection and protective TFV-DP levels in a cohort of high-risk, HIV-negative MSM in Kisumu, Kenya.
Methods: HIV-negative MSM ≥18 years were enrolled if they reported recent unprotected anal sex, ≥3 male sex partners, sexually transmitted infection (STI), transactional sex, or injection drug use. All participants were offered PrEP at baseline, with adherence counselling at each visit. Follow-up occurred at week 2; months 1, 2 and 3; then quarterly for 1 year. Adherence was measured by visual analogue scale (VAS) and qualitative self-rating. Dried blood spots (DBS) were collected at months 3 and 9 for TFV-DP testing. Generalized estimating equations (GEE) with robust variance were used to detect associations with (1) TFV-DP detection and (2) protective TFV-DP levels (≥700 fmol/punch, compatible with ≥4 weekly doses).
Results: DBS were provided at 275 visits by 161 participants. At baseline, median age was 26, 46.6% reported unprotected anal sex, 86.5% reported >3 male partners, 9.8% reported a recent STI, 66.3% reported transactional sex, and 5.5% reported injection drug use. Median VAS adherence was 98% (IQR 90%-100%), and men reported taking PrEP "most" or "all of the time" at 89% of visits. DBS results showed no detectable TFV-DP at 178 visits (64.7%), and protective TFV-DP levels at only 28 visits (10.2%). In GEE analysis, age, education, occupation, sex with female partners, injection drug use, depressive symptoms, social support, and time were associated with one or both outcomes in bivariable analysis. Only time was associated with TFV-DP detection in multivariable analysis (adjusted odds ratio [aOR] 0.84, 95% confidence interval [CI] 0.78-0.90 per month). Increasing age (aOR 1.12, 95% CI 1.04-1.21), sex with a female partner in the past 3 months (aOR 3.98, 95% CI 1.33-11.9), and lower social support score (aOR 0.97, 95% CI 0.95-0.99) were associated with protective TFV-DP levels in multivariable analysis.
Conclusion: Despite high reported adherence, drug levels were undetectable in most participants, and only 10% had protective levels. These results suggest that PrEP adherence is not aligned with risk among GBMSM in Kenya, and that tailored interventions to address PrEP adherence in this population are urgently needed.



994 PREEXPOSURE PROPHYLAXIS CASCADE AMONG MEN WHO HAVE SEX WITH MEN IN ZIMBABWE

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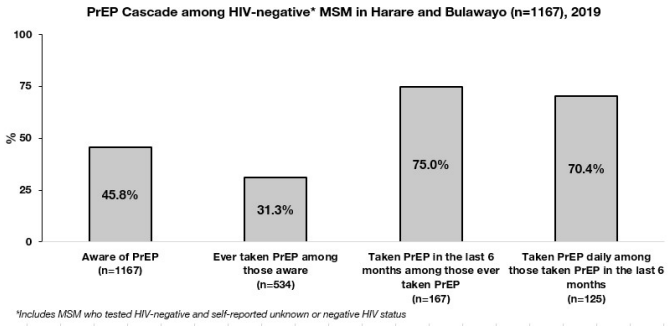
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Background: Pre-exposure prophylaxis (PrEP) for persons at high risk of acquiring HIV, including men who have sex with men (MSM), is increasingly being scaled-up in Zimbabwe, with goals to roll-out PrEP to all public facilities by 2020. We assessed gaps in PrEP awareness, uptake, and use among HIV-negative MSM in two cities of Zimbabwe.

Methods: We used respondent-driven sampling to recruit 1538 MSM to participate in a cross-sectional survey assessing HIV-related outcomes in Harare and Bulawayo, Zimbabwe (March–July 2019). MSM were eligible for the survey if they were born male, engaged in anal or oral sex with a man in the past 12 months, and were aged ≥18 years. Consenting participants completed a questionnaire and received HIV testing. The sample did not reach equilibrium and was treated as a convenience sample. Unweighted univariate analyses were restricted to MSM who self-reported negative/unknown HIV status that was confirmed via HIV testing.

Results: Overall, 75.9% (1167/1538) of all participants tested HIV negative and self-reported HIV-negative/unknown status (Harare, 75.9%; Bulawayo, 75.9%). Awareness of PrEP was 45.8% (534/1167; Harare, 57.8%; Bulawayo, 35.2%; Figure). Of those aware of PrEP, 31.3% (167/534) had ever taken PrEP (Harare, 32.7%; Bulawayo, 29.2%). Most (71.1% [261/367]) reporting never taking PrEP were interested in starting PrEP (Harare, 65.1%; Bulawayo, 79.4%). The top 3 reasons for never starting PrEP included not knowing where to access PrEP (24.8 [91/367]), fearing side effects (20.4% [75/367]), and not feeling at risk for HIV (19.6% [72/367]). Most (74.9% [125/167]) MSM who had ever used PrEP had taken it in the last 6 months (Harare, 73.8%; Bulawayo, 76.6%). Reasons for discontinuing PrEP included side effects (59.5% [25/42]), trust in partner (7.1% [3/42]), inability to access PrEP (4.8% [2/42]), concern about others finding out (2.4% [1/42]), or other reasons (26.2% [11/42]). Most PrEP users in the last 6 months reported taking PrEP daily (70.4% [88/125]).

Conclusion: Our findings highlight gaps in PrEP awareness and use among participants. Less than half of HIV-negative MSM were aware of PrEP, and awareness was lower in Bulawayo than Harare. Despite interest among participants in starting PrEP, uptake was low. To increase awareness and uptake, demand creation messaging could be strengthened by providing information on locations where PrEP is accessible, risk behaviors for HIV and PrEP eligibility, and side effects.



995 CASCADE TO TRICKLE: REASONS FOR SUBOPTIMAL PrEP USE AMONG AT-RISK US MSM (HPTN 078)

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Background: PrEP decreases HIV acquisition in men who have sex with men (MSM), yet it has been underutilized. Successful strategies to scale-up PrEP implementation will require an understanding of the salient factors associated with use.

Method : HPTN 078 screened 1305 MSM in Boston, Baltimore, Atlanta and Birmingham in 2018. The current analysis focuses on MSM who screened HIV-negative and were at risk for infection (according to CDC criteria). Participants reported sociodemographic and behavioral risk factors, as well as PrEP attitudes. Plasma tenofovir concentrations were determined for those who indicated they had used PrEP in the prior 12 months. Univariate and multivariable models were constructed to determine the factors associated with having heard of PrEP, having used PrEP in the prior 12 months, and having protective plasma tenofovir concentrations (>40 ng/mL).

Results: Of 382 HIV-negative MSM, 267 (70%) met CDC risk criteria for PrEP. Among the 267 at risk MSM, 21% were 18-24 and 39% were 25-35 years old; 42% were Black and 17% Latinx; 37% had a high school or less education; 21% did not have health insurance; 87% reported an income under $30,000 per year; 187 (72.5%) indicated that they had heard of PrEP. Among those who had heard of PrEP, 43 (23.1%) indicated that they used it in the past year, and among those who used it, 19 (57.6%) had protective blood concentrations. In the multivariable models, factors associated with having heard of PrEP included: younger age (p=0.001), being White (p<0.001), post-high school education (p=0.001). Correlates of having used PrEP included: being employed (p=0.025), living in Baltimore (p=0.012), having health insurance (p=0.040), self-perceived increased HIV risk (p<0.001), and not being concerned about side effects (p=0.023). Having protective PrEP drug concentrations was associated with not being concerned about side effects (p=0.007).

Conclusion: The majority (83%) of the 267 at-risk urban American MSM in this sample were not using PrEP. White race and higher education correlated with PrEP knowledge, but among the majority who had heard of it, economic factors and PrEP beliefs correlated with use and maintenance of protection. Interventions to increase PrEP knowledge, uptake, and optimal use will need to provide information, address socioeconomic challenges and risk perceptions.

996 SAFETY AND TOLERABILITY OF ONCE-DAILY BIC/FTC/TAF FOR POSTEXPOSURE PROPHYLAXIS

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Background: The use of antiretrovirals for post-exposure prophylaxis (PEP) is well-established, although completion rates with prior regimens have been suboptimal because of pill burden or side effects. The purpose of the current study has been to evaluate the single tablet regimen of of bictegravir, emtricitabine, tenofovir alafenamide (BIC/FTC/TAF) for PEP, administered daily for 28 days after a high risk exposure.

Methods: The analyses focused on a prospectively enrolled clinical cohort recruited through referrals from a busy medical department in a Boston community health center, specialized in HIV care, as well as from a community education campaign.

Results: Of the first 39 enrollees, the median age was 33 years (range 22-71), with 12.8% Black and 5.1% Latinx. Most (76.9%) were cisgender gay or bisexual men. Other participants included 3 heterosexual cisgender men, 1 transgender woman and 2 cisgender women. Most (76.9%) completed college +/- advanced degrees. Behaviors that led to PEP initiation included: receptive anal (49.7%), insertive anal (43.6%), receptive oral (15.4%), and insertive or receptive vaginal sex (7.7% for each). The most commonly reported adverse events were nausea +/- vomiting (12.8%), fatigue (10.3%), and diarrhea (10.3%). One participant noted mild gastrointestinal discomfort and another reported flatulence. All but one of the symptoms were grade 1; a grade 2 report of fatigue led to product discontinuation. The only lab abnormalities were elevated transaminases (N=2) and decreased creatinine clearance (N=1). These changes did not lead to product discontinuation, and reverted after regimen completion. Of the 39 fully evaluable participants, 92.3% completed the regimen as prescribed; 2 did not return for follow-up, and one participant discontinued prematurely. No HIV seroconversions have been detected in the study.

Conclusion: The fixed drug combination of bictegravir, emtricitabine, tenofovir alafenamide appears to be safe and well-tolerated when used as PEP, with occasional, mainly mild, gastrointestinal side effects, fatigue, and infrequent laboratory abnormalities. This favorable safety profile, and the high completion rates, suggest that BIC/FTC/TAF is a potential option for PEP.

997 HYPO-OSMOLAR RECTAL DOUCHE DELIVERED TFV DISTRIBUTES TFV DIFFERENTLY THAN ORAL PrEP

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Background: In spite of the PrEP with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) rollout, the rate of new HIV infections remains a major hurdle. In the US alone, the rate of new infections has shifted to predominantly men having sex with men in rural settings where access to PrEP can be an issue, in addition to cost and the need for adherence. As an alternative, we have developed an on demand PrEP approach using TFV-based hypo-osmolar (HOsm) rectal douches that are congruent with sexual behavior. Using stringent intrarectal repeated exposures of macaques to SHIV, this approach has delivered significantly better protective efficacy from virus acquisition compared to oral daily TDF and TDF/FTC PrEP. We therefore attempted to delineate the parameters that may dictate such improved efficacy and tested the safety of repeated TFV douching.

Methods: Sodium based HOsm intrarectal douches were compared to oral daily PrEP for their ability to promote uptake of TFV into the tissue and circulation.

Results: Analysis of HOsm formulation of TFV douche delivery demonstrated the presence of >14,000 fmol/mg TFV-DP at 3 hours 2500 fmol/mg TFV-DP in rectal tissues at 24 h post rectal douching, markedly higher than the ~200 fmol/mg steady state achieved by daily oral PrEP. TFV-DP levels in all other tissues analyzed including colonic lymph nodes draining the rectal mucosa were considerably lower, between 10-30 fmol/mg irrespective of anatomical location. Of note, while single oral TDF and HOsm rectal TDF achieved the same peak of plasma TFV, general AUC were higher for the oral delivered TDF. Rapidly repeated HOsm rectal douching (x5) using 30 vs 60 ml did not cause any detectable tissue or systemic toxicity. The single vs repeated HOsm rectal douching achieved similar TFV and TFV-DP levels in colorectal tissues, but plasma TFV levels were significantly higher for the repeated 60 ml dosing. Gel and bicarbonate formulations of rectal TDF douching did not markedly improve the pharmacokinetics of TFV or TFV-DP in tissues.

Conclusion: TFV HOsm douching showed high protection efficacy and appeared well tolerated even after multiple administrations within 30 minutes. The most salient parameter potentially associated with protection from rectal infection appeared to be the considerably higher levels of TFV-DP at the portal of entry but not in distal lymphoid tissues, suggesting that drug levels at that barrier are critical for preventing mucosal virus acquisition.

998 THE POTENTIAL FOR A RECTAL MICROBICIDE DOUCHE: FINDINGS FROM AN INTERNATIONAL SURVEY

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Background: Since many individuals who engage in receptive anal intercourse (RAI) regularly use cleansing rectal douches beforehand, an HIV-prevention douche could have high acceptability. Administration of tenofovir via a rectal douche results in faster and higher drug concentration in the rectal mucosa than oral administration. We aimed to describe behavioral aspects of rectal douching before RAI in different international settings to inform development of a behaviorally congruent tenofovir douche.

Methods: Using the social media app Grindr, we recruited individuals aged 18 or above, born male, who had engaged in RAI in the past three months. They completed an online survey about their rectal douching practices. The survey was available in English, Spanish, and French. Participants were recruited from: 1) the United States and its territories; 2) Latin America; 3) Africa. Data were analyzed using descriptive statistics.

Results: In total, 5,127 participants from 52 countries responded; 87% from the US, 10% from Latin America, and 3% from Africa. Among those who reported RAI, 80% in the US, 63% in Latin America, and 73% in Africa reported douching beforehand. Proportions who reported douching after RAI included 27% in the US, 37% in Latin America, and 59% in Africa. Most (90%) douched for cleanliness, though one-quarter of respondents in Latin America and Africa believed it might prevent infections. While half of US respondents used an enema bottle, reported use of this device was less common in other regions, with infrequent use in Africa (14%). Instead, a hose attached to a faucet was most popular in Latin America (51%) and Africa (45%), while a rubber bulb was used across all regions (39%). Tap water was the liquid preferred by 89% of respondents in all regions. Among those who did not douche, most had never thought about it (58%) or did not feel the need (28%). Finally, 98% of those who douched and 96% those who did not reported likelihood of using a rectal douche to prevent HIV transmission.

Conclusion: Findings from this international survey demonstrate a high prevalence of rectal douching associated with RAI and high likelihood of using a rectal microbicide douche to prevent HIV if one were available, even among those who do not currently douche. Ideally, an HIV-prevention douche should be adaptable to various devices, as enema bottles such as those used for douche administration in current clinical trials are not commonly used in regions outside of the US.

Table 1. Behavior and attitudes of respondents, by region

		US	Latin America	Africa
Behavior/Attitude	Sub-sample	Mean (SD) N[1] (Range)	Mean (SD) N[1] (Range)	Mean (SD) N[1] (Range)
Receptive anal intercourse (RAI) occasions, past 3 mos.	All respondents	8.22 (36.36) 4448 (0-1000)	6.95 (13.01) 528 (0-100)	4.17 (6.06) 151 (0-40)
Douching occasions before RAI	Respondents who report RAI	7.22 (27.09) 3365 (0-1000)	5.08 (10.80) 405 (0-90)	4.07 (6.53) 95 (0-40)
Douching occasions after RAI	Respondents who report RAI	1.61 (5.69) 3278 (0-100)	2.44 (7.77) 391 (0-90)	3.15 (6.15) 94 (0-40)
		N[1] (%)	N[1] (%)	N[1] (%)
Reasons for douching[2]	Respondents who douche	2685 (100%)	271 (100%)	78 (100%)
-I wanted to be clean		2606 (97%)	242 (89%)	66 (85%)
-I didn't want to smell		1736 (65%)	157 (58%)	29 (37%)
-Douching enhances sexual pleasure		641 (24%)	35 (13%)	17 (22%)
-Douching might prevent infections		271 (10%)	61 (23%)	19 (24%)
Device used[2]	Respondents who douche	2674 (100%)	268 (100%)	78 (100%)
-Enema bottle		1333 (50%)	76 (28%)	11 (14%)
-Rubber bulb		1148 (43%)	84 (31%)	33 (42%)
-Hose attached to faucet		856 (32%)	137 (51%)	35 (45%)
Liquid used[2]	Respondents who douche	2662 (100%)	268 (100%)	77 (100%)
-Tap water		2337 (88%)	241 (90%)	69 (90%)
-Commercial douche		678 (26%)	40 (15%)	6 (8%)
Would use rectal douche to prevent HIV transmission	Respondents who douche	2590 (100%)	259 (100%)	73 (100%)
-Definitely not		17 (<1%)	3 (1%)	3 (4%)
-Probably not		34 (1%)	1 (0.4%)	0 (0%)
-Probably yes		738 (29%)	53 (21%)	19 (26%)
-Definitely yes		1801 (70%)	202 (78%)	51 (70%)
Reasons for not douching[2]	Respondents who did not douche	592 (100%)	127 (100%)	18 (100%)
-Never thought about it		330 (56%)	78 (61%)	10 (56%)
-Might be harmful to health		83 (14%)	12 (9%)	4 (22%)
-Cramps/side effects		37 (6%)	3 (2%)	1 (6%)
-Don't feel any need		172 (29%)	34 (27%)	5 (28%)
Would use rectal douche to prevent HIV transmission	Respondents who did not douche	581 (100%)	126 (100%)	18 (100%)
-Definitely not		10 (2%)	0 (0%)	0 (0%)
-Probably not		21 (4%)	1 (1%)	0 (0%)
-Probably yes		210 (36%)	31 (24%)	5 (28%)
-Definitely yes		340 (59%)	94 (75%)	13 (72%)

[1] Total Ns are those among the subsample with non-missing data. [2] Multiple responses allowed.

999 A PHASE I TRIAL OF A RECTALLY ADMINISTERED GEL FORMULATED WITH THE NNRTI IQP-0528

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Background: There is an unmet need for the development of a dual-purpose topical microbicide, for rectal and vaginal use, as pre-exposure prophylaxis (PrEP) against HIV. A microbicide gel was formulated with IQP-0528, a potent non-nucleoside reverse transcriptase inhibitor (NNRTI). The primary objectives of this study were to assess local and systemic safety, and to evaluate single-dose pharmacokinetics (PK) and pharmacodynamics (PD) in plasma, and rectal and cervicovaginal (CV) tissue following rectal dosing of an IQP-0528 gel.

Methods: In this phase 1, open-label trial, 7 healthy participants (4 men and 3 women) received a 10 mL rectal dose of 1% IQP-0528 gel. Plasma sample collection was adaptively designed, with samples initially collected over 72 h (4 participants), and then over 48 h (3 participants). Rectal tissue (RT) biopsies were collected at baseline (5), 3-6 h post-dose (14), and 24-26 h post-dose (14). CV biopsies were collected at baseline (2), and 24-26 h post-dose (4). Biopsies were distributed for measurements of IQP-0528 concentration, and ex vivo HIV challenge assays.

Results: 4 adverse events (AEs) were experienced in 3 participants. None was Grade 3 or higher and 1 Grade 1 event was attributed to study product. All concentrations measured from plasma and CV tissue were below the limit of quantitation, indicating a lack of systemic exposure with no transfer to CV

tissue following rectal dosing. The median [IQR] IQP-0528 concentration in RT 3-6 h and 24-26 h post-dose was 4914 [2907, 5142] ng/mg and 5.4 [3.5, 7.5] ng/mg, respectively, with a median [IQR] half-life of 2.24 [2.23, 2.32] h. In RT, the median [IQR] cumulative p24 3-6 h post-dose (0.1 [0.0, 0.3] pg/mg) was reduced relative to that at baseline (38.4 [22.0, 63.7] pg/mg; $p = 0.0277$), and 24-26 h post-dose (53.1 [6.6, 144.8] pg/mg; $p = 0.0350$). The median [IQR] IC_{50} determined was 47.4 [3.4, 183.0] ng/mg. In CV biopsy explants, p24 was not significantly different at baseline versus 24-26 h post-dose ($p = 1.0000$).
Conclusion: The IQP-0528 gel was found to be safe and well tolerated. Despite the short IQP-0528 half-life in RT, concentrations remained well above the in vitro IC_{90} of 146 ng/mL within 3-6 h post-dosing. RT PD indicated that cumulative p24 reductions are significantly associated with greater IQP-0528 (Fig. 1). The offset of IQP-0528 accumulation by its short half-life in RT indicates that this gel may be better suited for episodic use. Furthermore, dual protection is not offered from single-compartment dosing.

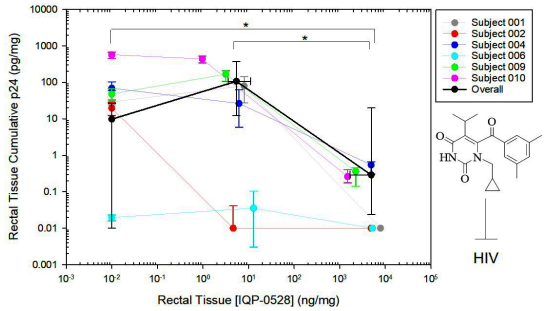
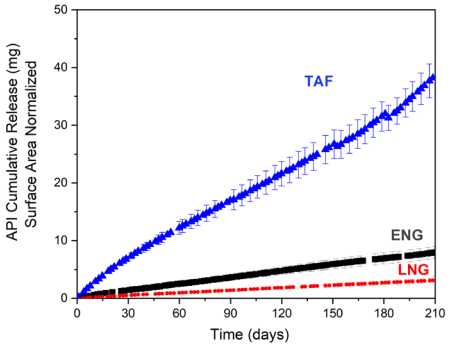


Figure 1. Cumulative p24 measured from *ex vivo* explant challenge assays versus determined IQP-0528 concentration in rectal tissue. * indicates $p < 0.05$ by Wilcoxon Signed Rank test.

1000 BIODEGRADABLE IMPLANT FOR DELIVERY OF ANTIRETROVIRAL (ARV) AND HORMONAL CONTRACEPTIVE

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Background: Women worldwide confront two frequently concurrent reproductive health challenges: the need for contraception and protection from sexually transmitted infections, including HIV. Multipurpose prevention technologies (MPTs) that simultaneously prevent unintended pregnancy and HIV could address these challenges with one product. Here, we are developing a long-acting (LA) subcutaneously administered and biodegradable implant system that provides sustained delivery of hormone and antiretroviral (ARV) with zero-order release kinetics.
Methods: Polycaprolactone (PCL) tubes were extruded and filled with various formulations and enclosed by heat sealing. In-vitro release from devices (in PBS, pH 7.4 at 37˚C) was monitored over 7 months using UV-vis spectroscopy or HPLC. Devices were transferred to fresh buffer three times per week to maintain sink conditions.
Results: We selected two well-characterized progestins, levonorgestrel (LNG) and etonogestrel (ENG), as well as one ARV, tenofovir alafenamide (TAF), for MPT indication. We formulated these active pharmaceutical ingredients (APIs) with several excipients and identified the lead excipients that support the targeted release kinetics, requisite dosing and long-term stability of the APIs. We achieved sustained delivery of LNG, ENG and TAF with zero-order release kinetics for 7 months (Figure 1) and high stability of APIs. Devices with LNG formulation demonstrated linear release kinetics at approximately 30 mg/day, and LNG inside the device core displayed >98% stability after 7 months of in-vitro release. ENG formulations exhibited zero-order release kinetics at approximately 35 mg/day and maintained a purity of >99% after 7 months in-vitro. We also demonstrated sustained release of TAF at 180 mg/day with a purity of >93% at the 6-month timepoint. This MPT system is amenable to administration of two implants in-line with a single trocar or as a single segmented implant that houses different drug formulations in each compartment.
Conclusion: We developed a LA MPT implant system for sustained delivery of TAF, LNG and ENG with zero-order kinetics that maintains in-vitro stability of the APIs. We are currently evaluating this implant system in preclinical animal studies to correlate in-vitro and in-vivo results. This MPT platform offers the potential to address the unmet need for dual protection against unintended pregnancy and HIV infection in resource-limited areas.



1001 WITHDRAWN

1002 HIV-1 DRUG RESISTANCE IN THE DISCOVER PREEXPOSURE PROPHYLAXIS TRIAL

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Background: The DISCOVER study is an ongoing randomized, double blind study of pre-exposure prophylaxis (PrEP) using daily FTC/TAF (F/TAF; Descovy; DVY) or FTC/TDF (F/TDF; Truvada; TVD) in men or transgender women who have sex with men. Of the 5,335 randomized participants, 23 participants (0.4%) became infected with HIV-1 through 96 weeks on study. The infected participants from the DISCOVER study were evaluated with both standard and ultrasensitive sequencing and the overall resistance data and analysis are presented here.
Methods: Plasma samples from participants who became HIV-1 infected and had a viral load of > 400 copies/mL were tested with the Monogram GenoSure™ MG assay, using Sanger sequencing to analyze the protease (PR) and reverse transcriptase (RT) genes for any known resistance mutations (at ≥20% of the viral population). Identification of minor variants was evaluated using ultrasensitive resistance testing (at ≥1% of the viral population) on all available plasma samples using unique molecular identifiers with next generation sequencing (UMI-NGS) to analyze RT codons 63-131 and 152-211 (University of Pittsburgh).
Results: By standard sequencing, 4/20 HIV positive participants tested had M184V, all in the F/TDF group and all with suspected baseline infection; 2 of these 4 also had M184I present. Six participants had additional mutations conferring resistance to non-study drugs including NRTI, NNRTI, and PI, which were presumed to be transmitted.
By UMI-NGS, 22/23 HIV infected participants had samples available and 20/22 were successfully analyzed. The four participants with M184V each had M184I also detected; K65R was detected in 1 participant at very low levels. One participant on F/TAF had the M184V mutation present at 2%. Two out of 3 participants with samples that had viral loads < 400 copies/mL were successfully tested and neither had resistance to study drugs.
Conclusion: Using standard sequencing, M184V was detected in 4 participants, all in the F/TDF arm. Using ultrasensitive UMI-NGS testing, similar results were observed, with the addition of one participant with M184V in the F/TAF arm and one participant with possible low level K65R in the F/TDF arm. Overall, drug resistance in the DISCOVER study was most commonly seen in participants with suspected baseline infections and in only 1 individual who became infected while on study.

1003 PrEP SEROCONVERSION-SEGMENTAL HAIR ANALYSIS FOR UNRAVELING TIMING OF VIRAL RESISTANCE

Brentton T. Lowery[1], Hideaki Okochi[2], Karen Kuncze[2], Nhi Phung[2], Cheryl McDonald[3], Matthew A. Spinelli[2], Anthony Mills[1], Patricia A. Defechereux[2], Kathryn Jee[2], Peter L. Anderson[4], Robert M. Grant[2], Monica Gandhi[2]

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Background: Failure on PrEP with emtricitabine (FTC)/tenofovir (TFV) disoproxil fumarate (TDF) can occur from poor adherence or acquisition of resistant virus. Here, we describe a case of seroconversion on PrEP with resistant virus but 100% self-reported adherence, with objective adherence metrics providing clues to the timing of viral resistance.

Methods: History was obtained from patient and records. PrEP adherence was assessed via self-report, TFV-diphosphate (TFV-DP) levels in dried blood spots (DBS) collected at seroconversion, and measuring TFV/FTC levels with segmental hair analysis. Genotypic resistance was evaluated.

Results: A 44 year-old Latino MSM started daily FTC/TDF on 12/15/17 after a non-reactive HIV antibody (Ab) and confirmatory test on 12/14/17. He reported 100% adherence to FTC/TDF since PrEP initiation with zero missed doses. HIV antigen (Ag)/Ab test was negative x 4 in 2018, 1/15/19, 4/9/19, but indeterminate on 6/10/19. HIV RNA level was 146,000 cps/ml on 6/17/2019 and 2-drug PrEP was switched to 3-drug ART (BIC/TAF/FTC) that day. Viral genotyping 6/17/19 showed an M184V and a TAM (K70N) mutation in the reverse transcriptase (RT) gene, with no TDF-associated mutations or significant mutations in the protease or integrase genes. DBS collected on 6/17/2019 showed a TFV-DP level of 1683 fmol/punch, consistent with high (7 doses/wk) adherence over the past ~6 weeks. A hair sample (~4 cm) was collected that day and, to evaluate adherence over preceding months, segmental analysis of TFV/FTC levels was performed in 1 cm segments from the scalp. Hair drug levels were consistent with high PrEP adherence over the preceding 2 months, but lower PrEP adherence (<4 doses/wk) from ~mid-Feb to ~mid April 2019 when he reported 4 new partners (Figure).

Conclusion: Seroconversion on PrEP can result from poor adherence or the acquisition of drug-resistant virus. However, since continuing two-drug PrEP in the face of HIV infection can lead to the emergence of new RT mutations, determining whether resistance was acquired or emerged requires timed objective adherence metrics. This patient had good adherence 6 weeks prior to seroconversion per DBS and proximal hair data, but segmental hair analysis revealed inadequate adherence 3 months prior to seroconversion, making subsequent development of M184V from consistent FTC/TDF use with active HIV infection epidemiologically most likely. Objective adherence metrics that look back over time can help unravel the etiology of PrEP failures.

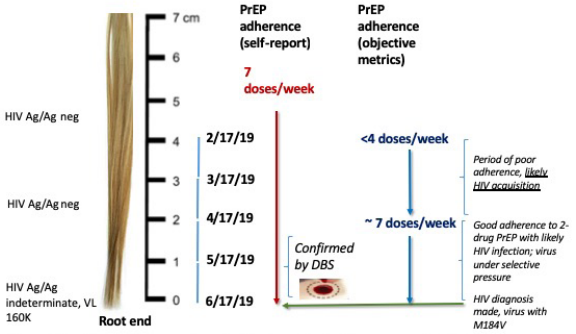


Figure: Illustration of adherence patterns by objective metrics in this case, unraveling that 2-drug PrEP continued after period of low protection (with low adherence) and likely HIV acquisition, putting virus under selective pressure for emergence of M184V by diagnosis

1004 RENAL IMPAIRMENT IN A PREEXPOSURE PROPHYLAXIS IMPLEMENTATION COHORT IN AUSTRALIA

Hamish McManus[1], Douglas Drak[2], Jack E. Heron[2], Tobias Vickers[1], Stefanie Vaccher[1], Iryna Zablotska[3], Rebecca J. Guy[1], Benjamin Bavinton[1], Fengyi Jin[1], Andrew E. Grulich[1], Mark Bloch[4], Catherine C. O'Connor[2], David Gracey[2], for the EPIC Study

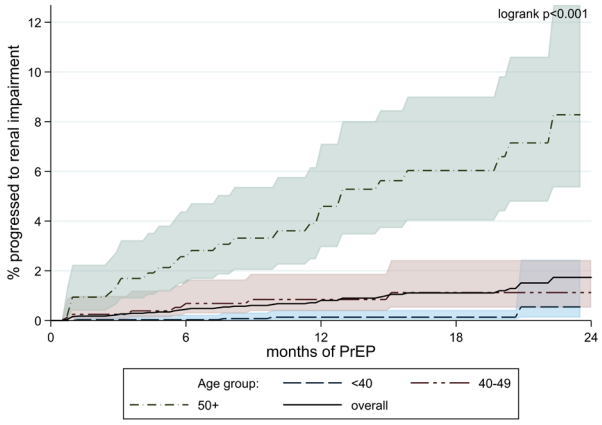
[1]University of New South Wales, Sydney, NSW, Australia, [2]University of Sydney, Camperdown, NSW, Australia, [3]University of Sydney, Westmead, NSW, Australia, [4]Holdsworth House Medical Practice, Sydney, NSW, Australia

Background: Co-formulated tenofovir disoproxil fumarate/emtricitabine is prescribed as pre-exposure prophylaxis (PrEP) to prevent HIV infection. Prior studies have found low incidence of new renal impairment in people taking PrEP but have been restricted to clinical trial settings. We sought to quantify rates of renal impairment in a large prospective cohort of participants taking PrEP as part of a population-level implementation study in Australia.

Methods: Participants enrolled in the EPIC-NSW study with baseline eGFR≥60 ml/min/1.73m$_2$, more than one PrEP dispensing visit between 1 March 2016 and 30 April 2018, and no recorded history of prior PrEP were included. Patients without eGFR monitoring during this period were excluded. Risk of renal impairment (defined as average eGFR of two consecutive tests <60) was estimated using the Kaplan-Meier method. Cox proportional hazards models stratified by study site were used to compare risk factors including baseline eGFR (60-90, ≥90), age (<40, 40-49, ≥50), sex, recreational drug use, and HBV and HCV infection status. Time-updated PrEP medication possession ratio (MPR) was included as a binary independent covariate (<0.95, ≥0.95). Significant covariates ($p<0.05$) were included in a multivariate model.

Results: Of 9,596 participants dispensed PrEP, 4,514 met the inclusion criteria for this analysis. Most were aged <50 (88%), male (99%), and had baseline eGFR ≥90 (76%). Baseline eGFR<90 was observed in 55% of participants aged ≥50 compared to 20% aged <50 ($p<0.001$). The observed rate of renal impairment was 8.0/1,000 person-years (95%CI: 5.86-10.99) over 4,859 person-years follow-up, with two-year cumulative risk of 1.7% (95%CI: 1.11-2.70) (Figure 1). Renal impairment was highest in patients aged ≥50 at 44.7/1,000 person-years (95%CI: 30.65-65.16) and two-year cumulative risk of 8.3% (95%CI: 5.35-12.69). The rate of renal impairment was also increased in participants with baseline eGFR<90 (32.0/1,000 person-years [95%CI: 23.20-44.20]) and with MPR≥0.95 (11.2/1,000 person-years, [95%CI: 7.95-15.72]). A multivariate model showed increased risk associated with age ≥50 compared to <40 (HR: 12.9 [95%CI: 4.31-38.58], $p<0.001$) and baseline eGFR <90 (HR: 25.6 [95%CI: 5.99-109.18], $p<0.001$) after adjustment for MPR (HR: 2.3 [95%CI: 0.96-5.68], $p=0.060$).

Conclusion: In a large real-world PrEP cohort, risk of renal impairment increased over two years of PrEP, with older patients and those with pre-existing renal dysfunction at significantly higher risk.



1005 DEVELOPMENT OF A PrEP EQUITY INDEX TO SET LOCAL TARGETS FOR PREP COVERAGE

Julie Myers[1], Sarah L. Braunstein[1], Zoe R. Edelstein[1], Alexis Rivera[1], Njideka Motanya[1], Oni J. Blackstock[1]

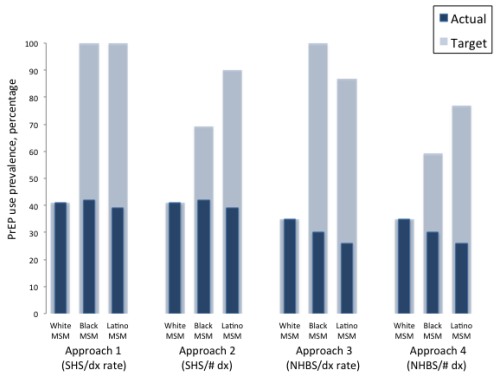
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Background: Scaling up PrEP is a priority in ending the HIV epidemic plans, yet progress remains inequitable. Indicators are needed to drive PrEP programming, guide resource allocation, and quantify inequities. We developed a PrEP equity index (PEI) to support local target development for PrEP coverage among MSM, **focusing on racial equity.** Methods:

To calculate the PEI, we first estimated PrEP coverage using a PrEP-to-need ratio, where the numerator was prevalence of PrEP use in the past 6-months (derived either from the Sexual Health Survey (SHS) among NYC MSM aged 18-40, 2018, or the National HIV Behavioral Surveillance (NHBS) study among NYC MSM, 2017) and the denominator was epidemiologic need (derived either from HIV diagnosis rate per 100,000 for men ages 13-59 from NYC HIV surveillance data and US Census data, or the number of new diagnoses among MSM, both for 2017), each stratified by race/ethnicity (Black, Latino, White). We then calculated the PEI by dividing the PrEP coverage for white MSM by that for Black and Latino MSM. To set targets for Black and Latino MSM, we then multiplied the PEI by the PrEP use prevalence for each group, effectively quantifying the improvement in PrEP coverage needed to approximate the PrEP coverage of White MSM (with a maximum of 100%).

Results: PrEP use prevalence was 40% and 31% using SHS 2018 and NHBS 2017, respectively, and neither set of estimates differed significantly by race/ethnicity. Numbers of new HIV diagnoses for Black, Latino, and White MSM were 396, 515, and 234, respectively; HIV diagnosis rates for Black, Latino, and White men ages 13-59 were 105, 77, and 31/100,000, respectively. PEI varied markedly for Black and Latino MSM regardless of approach used (Black MSM: 1.7-3.9; Latino MSM: 2.3-3.3). Targets for Black MSM (range: 59%-100%) and Latino MSM (range: 77%-100%) varied by approach used to define PEI (figure), but would require substantial increases in current PrEP use prevalence to be met (Black MSM: 65-295% increase; Latino MSM: 131-235% increase).
Conclusion: Applying a newly developed equity index to set local PrEP targets dramatically illustrates inequity in PrEP coverage for Black and Latino MSM, likely driven by both inequities in PrEP access and the large differential HIV burden in these populations. These findings illustrate the distance needed to travel to move beyond equality towards equity and should motivate intensive efforts to address racial disparities in PrEP scale-up.

Figure. Targets for PrEP coverage among Black and Latino MSM in NYC derived from a novel PrEP Equity Index.



Dx, diagnosis; MSM, men who have sex with men; NHBS, National HIV Behavioral Surveillance; NYC, New York City; PrEP, pre-exposure prophylaxis; SHS, Sexual Health Survey

1006 IMPLEMENTATION OF ON-DEMAND PrEP IN A LARGE INTEGRATED HEALTH CARE SYSTEM

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Background: Data describing real-world implementation of on-demand (2-1-1) HIV preexposure prophylaxis (PrEP) are limited. In this study, we report on the experiences of early 2-1-1 adopters in Kaiser Permanente San Francisco (KPSF).
Methods: KPSF started offering 2-1-1 PrEP in February, 2019. We abstracted data from the electronic health record, including demographics, reasons for selecting 2-1-1, and self-reported challenges, adherence, and persistence. These were collected by clinicians at baseline and at follow-up visits using standardized notes. We examined data descriptively and, for those with 3-month follow-up data, we used Fisher's exact tests to compare demographics between those who did and did not continue using 2-1-1 PrEP.
Results: As of August 2019, there were 2338 active PrEP patients in KPSF, with 251 (11%) using 2-1-1 PrEP. At baseline, median age of individuals using 2-1-1 was 43 (range 18-78); most were white (57%), MSM (99%), and had previously used daily PrEP (76%). In total, 179 patients (71%) had 3-month follow-up data available at the time of analysis. Of these, 23 patients (13%) reported challenges with using 2-1-1 PrEP, including difficulty planning sex in advance, adherence to the dosing schedule, and side effects. Ninety patients (50%) used 2-1-1 PrEP as their sole dosing regimen in the last 3 months; 35 (20%) opted to stay on daily PrEP despite their initial interest in 2-1-1 dosing; 34 (19%) used a combination of 2-1-1 and daily dosing; 4 (2%) used a different intermittent dosing regimen; and 16 (9%) had discontinued PrEP, primarily because of loss of insurance or change in sexual risk. We found no differences in use of 2-1-1 PrEP at the 3-month follow-up by age or race/ethnicity (P>0.05). Of the 90 who reported using only 2-1-1 PrEP at the 3-month follow-up, the majority (90%) cited infrequent sex as their reason for opting against a daily regimen. Only 3 (3%) individuals using 2-1-1 PrEP reported missed doses at their last sexual encounter, and none had started postexposure prophylaxis.
Conclusion: Our findings suggest that 2-1-1 PrEP is a desirable alternative for many patients. While missed 2-1-1 doses were infrequent in our setting, many individuals changed back to a daily dosing strategy or transitioned between daily and 2-1-1 dosing. With potential scale-up of 2-1-1 PrEP in the U.S., resources to support patients as they transition between dosing regimens are needed, as well as interventions to support the optimal use of 2-1-1 PrEP.

1007 USE OF HIV PREDICTION MODEL TO EVALUATE PrEP COVERAGE IN A LARGE HEALTH CARE SYSTEM

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Background: Monitoring progress in scale-up of HIV preexposure prophylaxis (PrEP) requires tools for identifying populations who may benefit from PrEP. Our objective was to evaluate PrEP coverage and disparities in use among people at high risk of HIV acquisition in a large healthcare system, using a validated prediction model to estimate HIV risk.
Methods: Our study population was all adult members of Kaiser Permanente Northern California (KPNC) as of January 1, 2018, excluding those with a prior HIV diagnosis as documented in the KPNC HIV registry. Using an HIV risk prediction model we previously developed and validated in our setting, we generated an HIV risk score for each member based on historical electronic health record data. We then used pharmacy fill data to assess recent PrEP use during January 1, 2018–June 30, 2019, and ever PrEP use during all enrollment history, by HIV risk score strata. Among members with very high risk scores (i.e., 3-year risk of incident HIV diagnosis ≥1.0%), we used chi-square tests to compare recent and ever PrEP use by demographic characteristics.
Results: Among 3,281,965 members, recent PrEP use ranged from 0.02% to 40.4%, and ever PrEP use from 0.02% to 51.4%, among those with low and very high risk scores, respectively (Table). Of the 8,840 with very high risk scores, mean age was 38 years, 97.7% were male, 19.1% were Black, and 18.6% were Hispanic. Recent PrEP use among those with very high risk scores was higher among males than females (41.2% vs. 7.3%), higher among those aged 30-49 than 18-29 (44.8% vs. 33.8%), higher among those in the highest quintile of neighborhood-level socioeconomic status compared with the lowest (45.3% vs. 32.9%), and higher among Asian (50.8%), White (47.9%), and Hispanic members (42.4%) than Black members (14.1%; P<0.001 for all comparisons). Demographic differences were similar for ever PrEP use.
Conclusion: HIV risk prediction models can be used to monitor progress toward PrEP scale-up and equity goals in healthcare settings. Of those identified by our model as being at very high risk of HIV acquisition, nearly 60% had not recently used PrEP and there were substantial disparities in use. Efforts are needed to increase PrEP uptake in insured populations, particularly among females, younger age groups, those with lower socioeconomic status, and Black individuals.

Table. Recent and ever PrEP use by HIV risk score, Kaiser Permanente Northern California

		PrEP use, n (%)	
	N	Recent[a]	Ever[b]
HIV risk score[c]	3,281,965	6,733 (0.2)	8,311 (0.3)
Low	2,827,373	533 (0.02)	589 (0.02)
Moderate	402,923	1,066 (0.3)	1,223 (0.3)
High	42,829	1,564 (3.7)	1,955 (4.6)
Very high	8,840	3,570 (40.4)	4,544 (51.4)

[a]Recent PrEP use was defined as any PrEP fill during January 1, 2018–June 30, 2019. [b]Ever PrEP use was defined as any PrEP fill during all available enrollment history. [c]HIV risk scores were generated using a previously validated prediction model (Marcus et al., *Lancet HIV* 2019). Scores were categorized as a 3-year risk of incident HIV diagnosis of low (<0.05%), moderate (0.05% to <0.2%), high (0.2% to <1.0%), or very high (≥1.0%).

1008 POPULATION-BASED ESTIMATES OF PrEP ACCESS-TO-NEED IN OREGON, 2012-2016

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Background: PrEP is an important HIV prevention modality. Population-based metrics of PrEP uptake and access are critical to the evaluation of public health efforts to increase PrEP use.
Methods: Using the Oregon All Payers All Claims administrative dataset, we determined the number of unique individuals at least 16 years of age starting

PrEP, defined as at least one prescription of >30 days of Truvada, each year from 2012-2016. People with HIV or hepatitis B were excluded. We created two metrics of PrEP access in 2016: the number of individuals starting PrEP per 100K population and the number of individuals with a PrEP prescription in each of the four quarters of 2016 per 100K population (i.e., prevalent users). Using public health surveillance data, we created three metrics of PrEP need in 2016: the number of HIV diagnoses per 100K population; the number early syphilis and gonorrhea diagnoses per 100K population; and the number of acute or chronic hepatitis C diagnoses among patients aged 16-30 years per 100K population. We calculated six metrics of PrEP access-to-need by dividing each of the access measures by the need measures.

Results: The number of individuals with a new PrEP prescription increased from 8 in 2012 to 571 in 2016. Most new PrEP users were men, aged 25-34 years, identified as white, lived in an urban area, had commercial insurance, and had an internal medicine PrEP prescriber. In 2016, there were 17.2 PrEP starts and 9.9 individuals with a PrEP prescription in all four quarters of 2016 per 100K population. There were 6.7 HIV cases, 136.0 early syphilis and gonorrhea cases, and 109.1 acute and chronic hepatitis C cases per 100K population. Per HIV diagnosis, there were 2.6 PrEP starts and 1.5 prevalent users. However, there were 0.13 PrEP starts and 0.07 prevalent users per early syphilis and gonorrhea diagnosis and 0.16 PrEP starts and 0.09 prevalent users per hepatitis C diagnosis. Women, people aged 16-24, people of color, and people in rural areas experienced lower PrEP access-to-need.

Conclusion: Access metrics based on prevalent users (a measure of longer-term adherence to PrEP), STI diagnoses (a measure of HIV acquisition risk), and HCV diagnoses among those less than 30 years of age (a measure of need among people who inject drugs) may provide a more complete assessment of PrEP access-to-need than those based on PrEP starts and HIV diagnoses.

Table. PrEP access to PrEP need by selected characteristics, Oregon, 2016.

	PrEP starts per HIV diagnosis	PrEP starts per STI diagnosis	PrEP starts per HCV diagnosis[a]	Prevalent users per HIV diagnosis	Prevalent users per STI diagnosis	Prevalent users per HCV diagnosis[a]
Overall	2.6	0.13	0.16	1.5	0.07	0.09
Sex/gender						
Men	2.7	0.18	0.28	1.6	0.11	0.17
Women	1.4	0.02	0.02	0.4	0.01	0.01
Age						
16-24	2.1	0.05		0.7	0.02	
25-34	3.4	0.14		1.6	0.06	
35-44	2.3	0.17		1.6	0.11	
45-54	2.2	0.23		1.8	0.19	
55+	1.8	0.25		1.3	0.18	
Race/ethnicity[b]						
Hispanic, anyrace	0.3	0.02	0.12	0.1	0.01	0.03
Non-Hispanic white	0.8	0.04	0.05	0.6	0.03	0.04
Non-Hispanic black	0.7	0.02	0.27	0.3	0.01	0.11
American Indian/Alaskan Native	0.5	0.03	0.05	0	0	0
Asian	0.6	0.06	0.16	0.2	0.02	0.06
Native Hawaiian/Pacific Islander	0	0	0	0	0	0
Region						
Portland metro area	3.5	0.17	0.33	2.1	0.10	0.19
Balance of state	1.2	0.06	0.05	0.6	0.03	0.03

PrEP, pre-exposure prophylaxis; HCV, hepatitis C virus; STI, sexually transmitted infection (includes early syphilis and gonorrhea).

[a]Among people aged 16-30 years.

[b]Based on 27% of sample with complete race/ethnicity data.

1009 STUDY SUGGESTS PrEP ACCESS ISSUE: DISPARITY IN PRIOR AUTHORIZATIONS ACROSS US REGIONS

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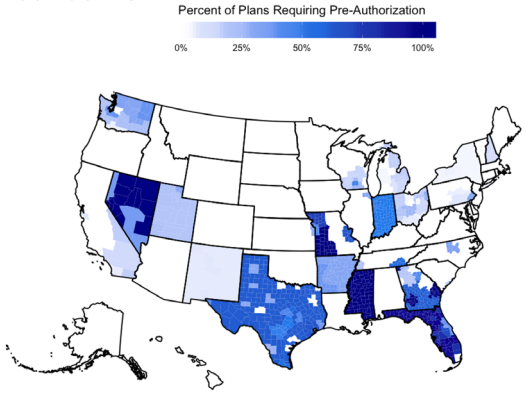
Background: With the goal of ending the HIV epidemic in the United States, access to HIV Pre-exposure Prophylaxis (PrEP) is essential to curb new HIV infections. There has been differential regional uptake of PrEP with the South lagging behind. We explore a potential systemic barrier: prior authorization (PA) requirements. This study explores differential PA for PrEP across geography and insurance characteristics.

Methods: The design was a cross-sectional study of all individual Qualified Health Plans (QHPs) offered in the 2019 Affordable Care Act Marketplace. QHP PA requirement for combined tenofovir disoproxil fumarate and emtricitabine (PrEP) was our primary outcome. Log binomial regression was used to estimate the association between region and PA requirement, and assess whether other plan characteristics (national issuer, high deductible, PrEP cost sharing structure, PrEP specialty drug tier status, plan level, rating area urbanicity, and rating area competition) may explain regional disparities in PA.

Results: 16,853 QHPs were analyzed (18% Northeast, 20% West, 25% Midwest, and 37% South). Overall, 19% of plans required PA for PrEP. Compared to plans in the Northeast, a plan in the South was 15.9 (95% Confidence Interval (95% CI), 12.6-20.1) times as likely to require PA whereas the Midwest and West were 5.7 (95% CI, 4.5-7.3) and 2.7 (95% CI, 2.0-3.5) times as likely, respectively. Figure 1 demonstrates QHPs' PA rate for PrEP by rating area. National issuers were more common in the South (Risk Ratio [RR] 1.9, 95% CI, 1.7-2.2) and were more likely to require PAs (RR 3.3, 95% CI, 3.1-3.6). This may mediate part of the high PA rate in the South, but it does not completely explain the disparity. QHP factors that shift drug costs to consumer, such as co-insurance cost sharing, specialty drug tiering, catastrophic level plans, were associated with lower likelihood of PA, but these characteristics were unlikely to explain regional disparities.

Conclusion: QHPs in the South are 16 times as likely to require PrEP PA. PA reduces the chance of obtaining a prescribed medication. High PA rates are a possible barrier to PrEP access in the South, which is the region with the most new HIV diagnoses. Due to PrEP's USPSTF Grade A rating, QHPs must start offering PrEP without cost-sharing starting in 2021. However, there is no regulation on QHPs' use of PA for PrEP. We have the tools to end the HIV epidemic, and we will also need robust health policies to end the HIV epidemic.

Figure 1. Percent of Individual Qualified Health Plans that Require Prior Authorization for Combined Tenofovir Disoproxil Fumarate and Emtricitabine (HIV Pre-exposure Prophylaxis) by Rating Area, 2019



1010 FACTORS ASSOCIATED WITH LOSS TO RETENTION AMONG FREE AND FEE-BASED PrEP IN THAILAND

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Background: Pre-exposure prophylaxis (PrEP) is highly effective in preventing HIV acquisition. PrEP is currently available in Thailand for free through demonstration projects, while some healthcare settings provide fee-based services. This study aims to look at retention in the two largest PrEP programs in Thailand; PrEP-15, a fee-based service available at the Thai Red Cross Anonymous Clinic (TRCAC) and Princess PrEP, a free service at the TRCAC and at 9 community clinics in 6 provinces with high HIV burden.

Methods: Self-reported demographic and risk behavior data was collected from January 2016-July 2019. Retention was determined if the client came back for a scheduled visit and measured at months 1, 3, 6, 9, and 12 after PrEP initiation. Multivariable linear regression was used to observe factors associated with loss to follow up at one month and one year after enrollment.

Results: A total of 5,687 clients were provided with PrEP, 66.6% through Princess PrEP. 80% were men who have sex with men, 9.5% transgender women, 21.2% had education lower than bachelor's degree, 72.3% reported inconsistent condom use, and 6.8% used amphetamine.Retention rates in PrEP-15 were 45.1%, 37.3%, 31.5%, 28.3%, and 25.2%, and in Princess PrEP were 65.4%, 56%, 48.2%, 44.5%, and 39.9% at month 1, 3 ,6, 9, and 12, respectively. In the multivariable analysis, factors associated with loss to follow up after month 1 were having an education lower than bachelor's degree (adjusted odds ratio -aOR:1.56; 95% confidence interval -CI 1.32-1.84, p<0.001), clients aged less than 20 years (aOR:1.76; 95%CI 1.2-2.59, p<0.05), inconsistent condom use (aOR:1.31; 95%CI 1.1-1.55, p<0.05), reporting sex work (aOR:1.66; 95% CI

1.37-2.02, p<0.001), and clients who paid for PrEP (aOR:2.48; 95%CI 2.06-3.0, p<0.001). Factors associated with loss to follow at month 12 were clients aged less than 20 years (aOR:2.02; 95%CI 1.1-3.67, p<0.05), and clients who paid for PrEP (aOR:1.47; 95%CI 1.18-1.84, p<0.05).

Conclusion: Retention rates in free PrEP program where higher than in fee-based PrEP. PrEP should be available under universal health coverage to retain clients in care. Interventions tailored to support adolescents and clients with education less than bachelor's degree should be concise and promote PrEP as a health empowering tool should also be proritized to address this finding.

1011 COSTS OF PROVIDING PREEXPOSURE PROPHYLAXIS FOR HIV PREVENTION IN US HEALTH CENTERS

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Background: Pre-exposure prophylaxis (PrEP) with daily tenofovir disoproxil fumarate/emtricitabine is effective in preventing HIV acquisition, and is a major component of the new initiative to End the HIV Epidemic in the United States. The Centers for Disease Control and Prevention (CDC) recommends health care providers consider offering PrEP for people at substantial risk of acquiring HIV, but information on the costs associated with PrEP implementation is limited. We assess health care utilization and costs of PrEP implementation at two federally qualified health centers.

Methods: The Sustainable Health Center Implementation PrEP Pilot (SHIPP) Study is an observational cohort of persons receiving daily oral PrEP at five participating health centers. We assessed health care utilization and costs of providing PrEP from the health care provider's perspective for one year for a subset of patients in each of two centers, Howard Brown Health, Chicago, IL (2016-2018) and Whitman-Walker Health, Washington, DC (2015-2017). The clinics followed CDC guidelines for PrEP provision, including regular visits with providers and ongoing laboratory monitoring. Using clinic billing records and Current Procedural Terminology (CPT) coding, we retrospectively extracted the frequency and costs (in 2017 $US) of PrEP clinic visits and frequency of laboratory screening. We used the Centers for Medicare and Medicaid Services national payment rates to estimate the costs of laboratory services. Incorporating the differences in medical record keeping and available databases between the two sites, we abstracted PrEP-related health care utilization and cost data electronically in Chicago (n=482) and manually in Washington, DC (n=56).

Results: The average annual number of PrEP clinic visits and associated laboratory screens per patient was 5.1 visits and 22.3 screens in Chicago, and 5.4 visits and 25.5 screens in Washington, DC (Table). The average annual cost per patient was $607 for clinic visits and $986 for laboratory screens in Chicago; and $923 for clinic visits and $1,033 for laboratory screens in Washington, DC. The average total cost per patient was $1,593 (95% CI: $1,552–$1,634) and $1,956 (95% CI: $1,444–$2,469) in Chicago and Washington, DC, respectively.

Conclusion: Our analysis provides the first estimates of the implementation costs of PrEP provision in the United States, and the results inform health care providers in planning and scaling up PrEP implementation.

Table. Annual service utilization and program cost of providing pre-exposure prophylaxis (PrEP) for HIV prevention.

	Service Utilization		Program Cost (in 2017 $US)	
	Total	Mean (95% CI)	Total	Mean (95% CI)
Chicago, IL (n=482)				
Office visits	2,476	5.1 (5.0–5.3)	292,619	607 (577–637)
Laboratory screens	10,737	22.3 (8.1–36.4)	475,374	986 (975–997)
Total	13,213	27.4 (13.1–41.7)	767,994	1,593 (1,552–1,634)
Washington, DC (n=56)				
Office visits	300	5.4 (4.0–6.8)	51,677	923 (681–1,165)
Laboratory screens	1,428	25.5 (18.8–32.2)	57,876	1,033 (763–1,304)
Total	1,728	30.9 (22.8–38.9)	109,553	1,956 (1,444–2,469)

1012 THIRD-PARTY PAYER AND PATIENT OUT-OF-POCKET COSTS FOR PrEP: UNITED STATES, 2017

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Background: Pre-exposure prophylaxis (PrEP) with daily tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is an effective HIV prevention tool. While the cost of PrEP is high, information about how the costs are distributed across payers is limited. We estimated average third-party payer and out-of-pocket (OOP) costs of PrEP by third-party payer type using a national pharmacy database.

Methods: Using a previously validated algorithm to distinguish TDF/FTC prescription as PrEP prescriptions in the IQVIA Longitudinal Prescriptions database, we compiled nationwide PrEP prescriptions from the year 2017. We further excluded prescriptions paid for by AIDS Drug Assistance Programs since these prescriptions were for HIV-positive patients. We classified third-party payers as commercial, Medicaid, Medicare, Gilead's Medication Assistance Program (MAP), or other. We compared the mean cost for 30 pills and total number of pills prescribed for each third-party payer by state.

Results: In 2017, 28.0 million pills of TDF/FTC for PrEP were prescribed to 146,064 patients in the United States. The total annual cost of PrEP was $1.59 billion of which $1.51 billion (94.8%) were paid by third party payers and $83 million (5.2%) were OOP costs paid by patients. Among the $1.51 billion paid by third party payers, $1.21 billion (80.2%) were paid by commercial insurance, $0.15 billion (9.9%) by Medicaid, $35 million (2.3%) by Medicare, and $68 million (4.5%) by Gilead's MAP. Mean third-party payer costs were $1,622 for 30 pills for commercial insurance, $1,653 for Medicare, and $1,596 for Medicaid (p<0.001). The mean cost for Medicaid per 30 pills varied by state (range $1,411 to $1,795 for 30 pills, p<0.001 for mean state costs being equal) (Table 1). Mean OOP costs were $101 for 30 pills for commercial insurance compared to $72 for Medicare and $4 for Medicaid (p<0.001).

Conclusion: Commercial insurers cover most PrEP prescriptions costs. The mean cost to Medicaid for 30 pills varied by state. OOP costs were lower for public insurance programs compared to commercial insurance. The pharmacy database could not account for 340B, Medicare, or Medicaid rebates and may overestimate the overall cost of TDF/FTC for PrEP to the healthcare system.

Table 1. Quintiles of Medicaid cost for PrEP by state, United States 2017

Quintile	States*	Mean Payment Range per 30 Pills
1	AK, GA, IA, MA, MD, NY, SC, UT, VA, VT	$1,411 - $1,557
2	CO, DC, FL, MI, ND, NJ, OH, OR, WA, WV	$1,558 - $1,591
3	AL, AR, CA, IN, MO, MT, NC, NE, NV, PA	$1,594 - $1,622
4	AZ, CT, HI, ID, KS, KY, LA, NH, RI	$1,623 - $1,667
5	DE, IL, ME, MN, MS, NM, OK, TN, TX, WI	$1,673 - $1,795

**PrEP prescriptions paid by Medicaid were not included in the database for South Dakota or Wyoming.*

1013 SOCIAL MEDIA INFLUENCERS ENHANCE RECRUITMENT OF YOUNG THAI MSM INTO PrEP INTERVENTION

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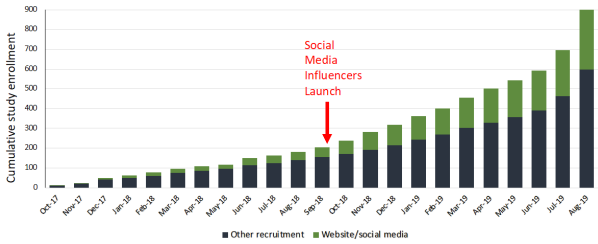
Background: Engagement of HIV at-risk young persons who might benefit from PrEP is an urgent prevention priority. Young male sex workers (MSW) aged 18-26 in Bangkok, and Pattaya, Thailand, are at very high risk for HIV acquisition and have had low rates of PrEP use. COPE is an NIH funded Thai-US collaborative effectiveness and cost effectiveness intervention for young Thai MSW recruited through venue, street, and community outreach; HIV VCT referral; and a web-based portal

Methods: Eligible Thai MSW selected a prevention package with or without daily oral Truvada for PrEP and could stop or start PrEP at any time. SMS messaging was used to support adherence and collect weekly PrEP use data. Enrollment in the first 12 mos averaged 17/month—too slow to meet study aims. Of these recruits, 23.0% reported learning of the project through social media. We then implemented a social media influencers (SMI) campaign with a community partner, APCOM. Short, (< 1 minute) scenario-based videos were developed with MSW-specific content and were promoted by hired SMI with combined reach to over 5 million Thai LGBTQ followers. We also expanded recruitment sites to 3 community partner locations convenient for MSW. We used a Poisson interrupted time-series analysis (ITSA) to estimate the impact of SMI on monthly recruitment, including coefficients to capture change in intercept and change in slope. We excluded the last 2 months of recruitment due to high enrollment prior to cessation

Results: SMI intervention was implemented in September 2018, with serial boosts across multiple social media platforms through August 2019 and led to 17,393 website views. The impact SMI on study recruitment and initiation of PrEP was immediate and sustained.(Figure). From campaign launch to close of enrollment in August, 2019, we enrolled 63.3 men/month, for a total N =

900. Among later recruits, 36.4% reported learning of the study through social media. The majority of MSW, 75%, chose a package with Truvada for PrEP. The ITSA showed an 82% increase in monthly recruitment following the start of SMI promotion (95% CI = 31%, 154%; p < .001).
Conclusion: Social media is a key platform for health messaging and outreach. SMI further extend this reach by serving as credible advocates with high relatability and followings within target communities. The success of the COPE campaign confirms the use of SMI to increase engagement and enrollment for at-risk individuals marginalized from traditional health structures.

Figure. Cumulative study enrollment of young MSW in Bangkok and Pattaya, Thailand: The COPE4YMSM project.



1014 PrEP NONADHERENCE, WHITE COAT DOSING, AND HIV RISK AMONG A HIGH-RISK COHORT OF MSM

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Background: Therapeutic drug monitoring is critical to interpretation of PrEP trials as a biomarker of adherence and correlate of protection. Perceived expectations from providers or study staff may lead individuals to participate in "white coat dosing" (WCD), or increased adherence to study products just prior to a study visit. As little is known about WCD, this analysis seeks to explore factors associated with this practice.
Methods: This is a secondary analysis of PATH-PrEP, an open label study evaluating TDF/FTC PrEP for MSM at high risk for HIV acquisition at two sites in Los Angeles, California. Study participants received daily oral TDF/FTC for 48 weeks. Adherence was assessed using TFV-DP and FTC-TP in dried blood spots (DBS) and TFV in plasma. TFV concentrations were measured at weeks 4, 12, 24, 36, and 48. WCD was defined as TFV-DP < 350fmol/punch on DBS and either or both FTC-TP > 0.1pmol/punch or plasma TFV > 40ng/mL at the same time point. Optimal and sub-optimal levels were defined as TFV-DP ≥ 700fmol/punch and < 700fmol/punch on DBS, respectively. CASI assessed sexual behaviors and STI screening occurred at each visit. Generalized structural equation modeling with multinomial logit compared optimal with 1) sub-optimal and 2) WCD at study visits, adjusting for demographics, incident syphilis, and risk behaviors in last 30 days: condomless anal intercourse with multiple partners, exchange sex, and discussing HIV serostatus before intercourse.
Results: Between April 2014 and July 2016, 300 MSM were enrolled. 281 MSM had at least one follow-up visit and were included in the analysis. Median age was 34 (range 20-69) and 53.2% were White, 26.8% Latino, and 8.0% Black. Optimal drug levels were detected at 1,118 (89.2%) visits, sub-optimal at 122 (9.7%) and WCD at 14 (1.1%). Compared to visits with optimal levels, incident syphilis was associated with WCD. Individuals with sub-optimal and WCD had lower odds of discussing HIV serostatus before intercourse, compared to optimal levels (Table).
Conclusion: Individuals who participate in WCD demonstrate behavioral and STI-associated risk for HIV acquisition. Sub-optimal chronic use of PrEP with WCD in the setting of ongoing condomless sex is a precarious clinical scenario in which HIV protection may be limited, and post-infection WCD carries high rates of selection for resistant viral variants, particularly M184V/I.

Table: Adjusted odds ratios of factors associated with sub-optimal drug levels and white coat dosing among a cohort of men who have sex with men using PrEP[jj]

	Sub-Optimal Levels		White Coat Dosing	
	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age	0.95 (0.91-0.98)	**0.007**	0.98 (0.91-1.06)	0.66
Race/Ethnicity				
White/Caucasian	Ref	--	Ref	--
Black/African American	5.88 (1.87-18.46)	**0.002**	5.75 (0.72-46.09)	0.1
Latino/Hispanic	0.92 (0.37-2.25)	0.85	0.68 (0.10-4.57)	0.69
Other	0.72 (0.21-2.43)	0.59	0.62 (0.04-9.03)	0.72
CAI[++] with multiple partners[j]				
No	Ref	--	Ref	--
Yes	0.72 (0.41-1.28)	0.27	0.79 (0.22-2.90)	0.72
Exchange sex[j]				
No	Ref	--	Ref	--
Yes	2.46 (0.79-7.69)	0.12	2.16 (0.17-27.23)	0.55
Incident syphilis[*]				
No	Ref	--	Ref	--
Yes	1.00 (0.23-4.37)	1.00	9.51 (1.30-69.38)	**0.026**
Discussed HIV serostatus[j+]				
Always	Ref	--	Ref	--
Not always	2.50 (1.40-4.46)	**0.002**	4.85 (1.09-21.60)	**0.039**

[++]Condomless anal intercourse; [+]before intercourse; [j]last 30 days; p-values <0.05 in bold
[*]Incident syphilis was screened at each study visit and defined as positive rapid plasma regain (RPR) titer with positive *Treponema pallidum* particle agglutination assay (TPPA) confirmation (if previous titer negative) and/or 4-fold increase in RPR from historical titers
Note: plasma TFV levels were not obtained on week 48, therefore white coat dosing was defined using DBS levels only
[jj]Calculated using mixed-effects generalized structural equation model with multinomial logit comparing optimal with 1) sub-optimal levels and 2) white coat dosing at study visits, controlling for all predictors listed in table

Keywords: pre-exposure prophylaxis, white coat dosing, PrEP adherence, MSM

1015 IMPACT OF THE "CHARISMA" INTERVENTION PILOT ON PARTNER DISCLOSURE, IPV, AND ADHERENCE

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Background: Biomedical, female-initiated HIV prevention methods can help address disproportionately high HIV rates among women in sub-Saharan Africa, but male partner resistance and intimate partner violence (IPV) may decrease effective use.
Methods: To promote consistent use of the dapivirine vaginal ring, we pilot tested the CHARISMA relationship counseling intervention with women enrolled at the Wits RHI (WRHI) site (Johannesburg) of the multisite open-label MTN-025/HOPE trial. Lay counselors used a 42-item tool with 5 subscales to tailor counseling at enrolment, followed by a booster at Month 1 and follow-up (FU) checks at Months 3 and 6. Though not fully-powered, we evaluated potential impact by comparing indicators of ring disclosure to partners, partner clinic attendance, incident social harms (SH) and IPV, and biomarkers of ring adherence at WRHI vs. 3 comparator sites using multivariable regression models. Comparator clinical sites were purposively selected as those most similar to WRHI for baseline characteristics identified a priori.
Results: At WRHI, 95 (95%) of HOPE participants enrolled into CHARISMA. Mean age was 30, 36.8% lived with a partner, and 85.3% received his financial support. During FU, CHARISMA participants reported: partner disclosure at 72.7% visits; 4.3% partners attending the research clinic; 1 partner-related SH; and 9.5% experiencing IPV. The mean level of dapivirine released was 3.4mg (SD 1.56), suggesting moderate adherence. In adjusted regression models (Table 1), partner clinic attendance was lower at all comparator sites; and significantly so at Site A (aRR 0.12, 95% CI 0.00-0.98). Sites B and C had lower levels of dapivirine released (less adherent), but this was not significant. Site B women were more likely to report partner disclosure at FU visits (aRR 1.12, 95% CI 1.00-1.25). The risk of IPV report during FU was significantly lower at Site A (aRR 0.20, 95% CI 0.04-0.98).
Conclusion: CHARISMA participants had high IPV but were nevertheless able to adhere to ring use, and more CHARISMA male partners came to the research clinic vs. comparators. CHARISMA taught women skills to decide on levels of disclosure; therefore it is difficult to interpret differences in partner disclosure with other sites. Similarly, CHARISMA heightened awareness of abuse, possibly increasing IPV reports. Testing CHARISMA under fully-powered controlled conditions will improve understanding of its impact on women's relationships and ability to use female-initiated HIV prevention methods.

Table 1. Key outcomes of CHARISMA pilot study, comparing Wits RHI to 3 comparison sites

Outcomes	n		Comparator Sites			CHARISMA site
			Site A	Site B	Site C	Wits RHI
Disclosure of ring use to partners[1]	1482 visits among 394 participants	%	67.20	84.41	82.28	72.73
		RR	0.95	1.12	1.09	Ref
		95% CI	0.83 – 1.08	1.00 – 1.25	0.98 – 1.21	
Partner research clinic attendance[2]	394 participants	%	0.00	1.28	0.78	4.3
		aRR	0.12	0.31	0.11	Ref
		95% CI	0.00 – 0.98	0.01 – 2.95	0.00 – 1.17	
Any IPV[3]	400 participants	%	7.14	10.00	1.55	9.47
		aRR	0.62	0.91	0.20	Ref
		95% CI	0.24 – 1.58	0.40-2.09	0.04 – 0.98	
Social Harms[4]	404 participants	%	3.06	1.25	0.76	1.04
		aIRR	2.02	0.6	0.78	Ref
		95% CI	0.16-105.11	0.01-49.63	0.01-59.62	
Ring adherence[5]	1955 visits among 374 participants	mean level of dapivirine (SD)	3.26 (1.58)	3.09 (1.51)	3.12 (1.39)	3.37 (1.56)
		aβ	0	-0.25	-0.11	Ref
		95% CI	-0.36-0.35	-0.62-0.11	-0.43-0.20	

[1] GEE Poisson model with robust standard errors (SE) adjusted for baseline partner awareness, age, and time in study. There was no meaningful change in the point estimates after additional adjustment for baseline measures of cohabitation, financial support, age difference with partner, baseline IPV, education, whether she earns an income, partner HIV status, or transactional sex.
[2] Exact Poisson models adjusting for age, time in study, and baseline measures of cohabitation with partner and financial support from partner, and restricting the model to women who ever reported a primary partner during follow-up. There was no additional change when adjusting for baseline clinic attendance so I did not include that in the model.
[3] Poisson model with robust SE adjusting for age, time in study, and baseline measures of any IPV, cohabitation with partner, financial support from partner, and transactional sex
[4] Exact Poisson models with offset for time in study and adjusting for age, baseline partnership status (cohabiting with partner, or not cohabiting with partner), and baseline partner awareness of ring, as well as restricting the models to women who never reported a primary partner during the study
[5] GEE linear regression with robust SE, adjusting for age, time in study. There was no meaningful change in the point estimates after additional adjustment for baseline measures of education level, any IPV, earning any income, having a primary partner, cohabiting with primary partner, primary partner financial support, age difference with primary partner, primary partner HIV status, primary partner being new in the past 3 months, and engaging in transactional sex.

1016 REDUCED RELIANCE ON SEX WORK: RESULTS OF AN INTERVENTION FOR YOUNG WOMEN IN TANZANIA

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Background: In sub-Saharan Africa, adolescent girls and young women (AGYW) account for 25% of new HIV infections. Gender, age, and economic disparities are drivers of HIV infection. To address these factors, the PEPFAR-funded "DREAMS" program employs a holistic approach to reduce HIV incidence among AGYW, including an economic-strengthening group intervention of starting a business. We evaluated the effect of these interventions on HIV risk and vulnerability of AGYW in Tanzania.
Methods: We recruited a prospective cohort of AGYW from DREAMS communities and measured changes in economic situation and vulnerability to HIV. DREAMS interventions targeted seven districts that included urban, semi-urban, and rural communities identified as uniquely vulnerable for AGYW due to their situation along transit corridors, in major urban centers, or in proximity to mining activities. Eligible participants for the DREAMS program and the cohort were sexually-active, out-of-school AGYW aged 15-24 years. Data were collected from May 2017 to February 2019. We used conditional logistic regression to examine significant changes in HIV risk and vulnerability from baseline to 12 months in association with program interventions. A key outcome was dependence upon sex work as primary source of income.
Results: We enrolled 778 AGYW, and 598 (77%) completed follow-up (70 were lost to follow-up, 59 moved, 49 dropped, and 2 died). The economic-strengthening group intervention reduced dependence on sex work as primary income source (OR=0.55, $p<0.05$). The effect was particularly strong among those whose business was established by the end of follow-up (OR=0.33, $p<0.05$). In the cohort as a whole, AGYW reported significantly increased food security, adult support, planning for the future, self-esteem, and condom self-efficacy. No negative effects on sexual health and well-being were observed.
Conclusion: Economic strengthening interventions offer alternative livelihoods to AGYW who previously relied on sex work. As HIV prevention strategies advance worldwide, protection of AGYW lags behind. Our study supports economic strengthening as a promising tool in the struggle to keep AGYW AIDS-free.

1017 TRANSPREP: SOCIAL NETWORK–BASED PrEP ADHERENCE FOR TRANSGENDER WOMEN IN LIMA, PERU

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Background: While pre-exposure prophylaxis (PrEP) is an effective HIV prevention method, uptake remains poor among transgender women (TW). We conducted a pilot randomized controlled trial of a social network-based intervention to promote PrEP adherence among Peruvian TW.
Methods: From September, 2017-July, 2018, we screened 172 TW from three geographic areas of Lima, Peru. Screening visits were conducted to: assess HIV serostatus; introduce PrEP as a prevention strategy; and discuss PrEP adherence. We enrolled 89 HIV-uninfected TW into 6 groups based on pre-existing social network clusters. Clusters were randomized on a 1:1 basis to standard of care (n=44) or the TransPrEP intervention (n=45). Groups assigned to TransPrEP attended 4 weekly introductory workshops (to discuss principles of and barriers to PrEP adherence, and to construct and support group adherence goals). Biweekly maintenance workshops reviewed adherence strategies, discussed participants' experiences taking PrEP, and encouraged network cohesion. Adherence was evaluated through self-report and by measurement of tenofovir (TFV) levels in hair. Intent-to-treat analyses compared intervention versus control conditions at baseline and 3-month follow-up.
Results: Participants' mean age was 26.9 years (range 18-58), with 76.5% using feminizing hormones. At 3-month follow-up, we evaluated 40 TW and obtained 21 hair samples. Though no statistically significant differences were observed in ITT analysis, a higher proportion of participants in the TransPrEP arm reported taking "Most" or "All" TDF-FTC doses in the prior 30 days (90.5% [19/21] versus 73.4% [14/19]). In hair sample analysis, 36.4% (4/11) of participants in TransPrEP and 10.0% (1/10) in the control arm had TFV levels >0.023 ng/mg (consistent with taking >4 doses per week) while 81.8% (9/11) and 40.0% (4/10), respectively, had any detectable amount of TFV in their hair. Participants in the intervention arm described the workshops as "helpful," "enjoyable," and "comfortable," settings to discuss HIV prevention.
Conclusion: Pilot assessment of our network-based intervention showed improvements in PrEP adherence among TW in Peru according to both biological and behavioral adherence markers but did not achieve statistical significance. Mixed-methods data identified potential modifications to improve participant involvement and retention. Additional research to assess the TransPrEP intervention with a larger sample is needed.

1018 PrEP CONTINUUM OF CARE AMONG MSM AND TGW OF COLOR IN THE THRIVE DEMONSTRATION PROJECT

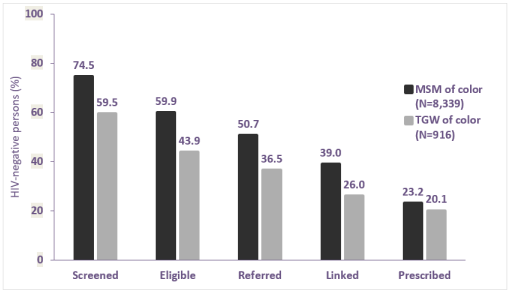
Kashif Iqbal[1], Weiming Zhu[1], Kenneth L. Dominguez[1], Mary Tanner[1], Kirk D. Henny[1], Karen W. Hoover[1]
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Background: Pre-exposure prophylaxis (PrEP) reduces the risk of HIV acquisition when taken daily as prescribed. Access to and uptake of PrEP have been suboptimal among populations with the highest rates of HIV diagnoses, including men of color who have sex with men (MSM of color) and transgender women (TGW) of color. The THRIVE demonstration project funded seven U.S. health departments to lead community collaboratives that consisted of community-based organizations and clinical providers to implement comprehensive HIV prevention and care services for MSM and TGW of color. In this analysis, we estimated the PrEP care continuum among MSM and TGW in the THRIVE demonstration project.
Methods: We analyzed data collected from a cohort of 10,422 HIV-negative MSM and 1,009 TGW enrolled in THRIVE from September 2015 through March 2019. We estimated the proportions who were included at each step in the PrEP care continuum: screened, eligible, referred, linked, and prescribed PrEP, stratified by age and race and ethnicity. For both MSM and TGW, we used multivariable logistic regression models to estimate the associations of being linked, referred, and prescribed PrEP among persons who were eligible for PrEP, by race/ethnicity and age group (aged <30 and >30 years).
Results: Among HIV-negative MSM and TGW in THRIVE, 8,339 (80.0%) were MSM of color and 916 (90.8%) TGW of color. At each step of the continuum, there were significantly larger proportion of MSM of color compared to TGW of color (Figure). In the multivariate model, among MSM eligible for PrEP, there were similar proportions of white MSM and MSM of color who were referred (77.8% and 84.6%, p=0.50) and linked (44.1% and 65.0%, p=0.62), but fewer MSM of color were prescribed PrEP than white MSM (40.0% and 38.9%) ($p<0.05$). In addition, among MSM of color, a smaller proportion of men aged

<30 years were prescribed PrEP compared to men aged >30 years (35.2% and 43.1%) (p<0.05).

Conclusion: The THRIVE demonstration project expanded access to PrEP services for MSM and TGW of color, however challenges exist in prescribing PrEP to younger MSM of color. Increased use of interventions that support PrEP uptake among MSM and TGW of color are needed to improve the PrEP care continuum for these populations. Further investigation is needed to understand reasons that MSM of color were prescribed PrEP after referral and linkage to PrEP less frequently than white MSM.

Figure: PrEP care continuum among MSM and TGW of color enrolled in THRIVE,



1019 PrEP INDICATION AND CARE CONTINUUM AMONG TRANSGENDER WOMEN IN THE UNITED STATES

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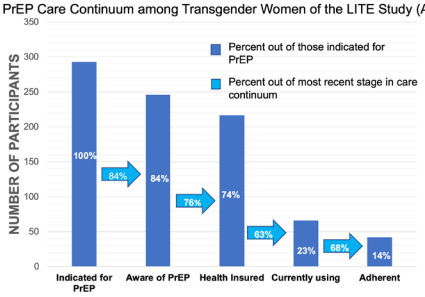
Background: U.S. transgender women (TGW) have a disproportionate burden of HIV, with an estimated prevalence of 28%. Pre-exposure prophylaxis (PrEP) is effective in preventing HIV acquisition among adherent users. However, the PrEP care continuum among TGW as well as factors associated with high risk for HIV and subsequent PrEP indication (e.g. condomless anal sex, high sex partner number, having an STI, etc.) are not well understood.

Methods: The LITE study is a multi-site cohort enrolling TGW across six cities in the southern and eastern U.S. Upon screening, participants underwent HIV/STI testing and completed a socio-behavioral survey in which they reported experiences with PrEP. We identified factors associated with PrEP indication using prevalence ratios from a multivariate Poisson regression with robust variance. We also calculated descriptive statistics to depict the PrEP care continuum.

Results: As of April 2019, there were 751 participants not living with HIV at baseline. Among this group, 293 (39%) met PrEP indication based on the following: had a laboratory confirmed STI, recent partner who was known to be living with HIV, reported recent sex work, and/or recent condomless anal sex. Participants who were Non-Hispanic Black [ref: Non-Hispanic White, PR: 1.98, p=<0.0001] or had self-perceived low risk of HIV [ref: no risk, PR: 2.09, p=0.012], medium risk of HIV [ref: no risk, PR: 3.33, p<0.001], or high risk of HIV [ref: no risk, PR: 3.81, p<0.0001,] were more likely to be indicated for PrEP. Having some college education or above was associated with being less likely to be PrEP indicated [ref: high school education or less, PR: 0.79, p=0.04]. Ultimately, among those indicated for PrEP, 42 (14%) were currently using and adherent to PrEP (Figure 1). Eighty-four percent of those indicated were aware of PrEP, 76% of those aware of PrEP had health insurance, 63% of those insured were taking PrEP, and 68% of PrEP users reported 100% adherence within the prior 7 days of the survey (14% among all who were indicated for PrEP).

Conclusion: Over a third of TGW not living with HIV at baseline were indicated for PrEP. Although most PrEP users were adherent, overall uptake and adherence among those PrEP indicated were low. Improving uptake and adherence among TGW warrants further investigation, particularly with respect to development of culturally appropriate strategies to increase uptake and adherence among Black TGW for whom PrEP indication is higher.

Figure 1. PrEP Care Continuum among Transgender Women of the LITE Study (April 2019)



1020 DISCOVER: NO EFFECT OF HORMONES ON F/TAF OR F/TDF PK, EFFICACY & SAFETY IN TRANSWOMEN

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Background: Emtricitabine (F), tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) do not have relevant drug interactions with low-dose hormones used for contraception. The current analysis explored PK as well as efficacy and safety of transwomen receiving either F/TAF or F/TDF in the DISCOVER trial, the majority of whom were taking high-dose, gender-affirming, hormonal therapy.

Methods: Overall, 74 transwomen at risk of HIV were randomized 1:1 to receive blinded F/TAF or F/TDF once daily in DISCOVER. Efficacy and safety results are summarized. TFV-DP and FTC-TP PBMC trough levels (C_{tau}; defined as 20 to 28 hours postdose) were evaluated at steady-state (W4) and compared between transwomen taking high-dose hormones concomitantly with F/TAF (N=17) and a randomly pre-selected, representative group of MSM randomized to F/TAF not using high-dose hormones (N=161) using geometric least squares mean (GLSM) ratios and 90% confidence intervals (CIs). Comparisons were made using a lack of PK alteration boundary of 50 to 200% to identify potentially clinically relevant differences. Levels of TFV-DP and FTC-TP with F/TDF in transwomen on high-dose hormones (N=10) were compared descriptively to levels in MSM randomized to F/TDF (N=155) due to a smaller sample size.

Results: No transwomen acquired HIV. Transwomen had similar numerical improvements in dipstick proteinuria and markers of tubular proteinuria as MSM. No transwomen developed clinically significant proteinuria (UPCR>200 mg/g). There were no differences between F/TAF and F/TDF in change from baseline in weight or eGFR in transwomen. GLSM ratios and 90% CIs for comparisons of PBMC TFV-DP and FTC-TP levels with F/TAF between transwomen taking high-dose hormones and MSM were within the 50 to 200% boundary, indicating no clinically significant interaction. In transwomen taking F/TDF and high-dose hormones, TFV-DP and FTC-TP levels were comparable to MSM, suggesting no interaction (Table).

Conclusion: The absence of infections suggests that both F/TAF and F/TDF were effective for HIV prevention in transwomen. Both F/TAF and F/TDF were safe and well-tolerated in transwomen and MSM. No clinically meaningful differences in PBMC TFV-DP and FTC-TP levels with F/TAF or F/TDF were observed between transwomen taking high-dose hormone therapy and MSM, suggesting that both F/TAF and F/TDF are effective and safe options for PrEP in transwomen on gender-affirming, high-dose hormone therapy.

Table. Comparisons of Safety Parameters and PBMC TFV-DP and FTC-TP with F/TAF and F/TDF Between Transwomen and MSM

PK Parameter Geometric Mean (CV%) F/TAF 200/25 mg	Transwomen on High-dose Hormones[a] (N=17)		MSM (N=161)		GLSM Ratio% (90% CI)	
TFV-DP C_{tau} [fmol/10^6 cells]	366 (144)		407 (157)		89.9 (54.0, 150)	
FTC-TP C_{tau} [fmol/10^6 cells]	5,856 (114)		7,268 (102)[b]		80.6 (53.8, 121)	
PK Parameter Geometric Mean (CV%) F/TDF 200/300 mg	**Transwomen on High-dose Hormones[a] (N=10)**		**MSM (N=155)**		**GLSM Ratio% (90% CI)**	
TFV-DP C_{tau} [fmol/10^6 cells]	82.4 (76)		74.0 (235)		N/A	
FTC-TP C_{tau} [fmol/10^6 cells]	9,160 (80)		6,710 (92)[c]		N/A	
	Transwomen (N=74)		MSM (N=5313)		P-value for F/TAF vs. F/TDF	
Safety Parameters	F/TAF(n=45)	F/TDF(n=29)	F/TAF(n=2649)	F/TDF(n=2664)	Transwomen	MSM
Urine β2M/Cr (mg/g)[d]	2.2	13.3	-10.9	15.4	0.93	<0.001
Urine RBP/Cr (mg/g)[d]	-8.7	-4.1	0.3	20.1	0.69	<0.001
eGFR[e] (Cockcroft-Gault; ml/min)	-4.0	-1.3	1.8	-2.3	0.71	<0.001
Dipstick Proteinuria[f]	28.8%	33.3%	21.1%	24.2%	0.82	0.008
Body Weight[g]	1.6 (1.0)	1.9 (1.4)	1.3(1.0)	0.0(0.0)	0.81 (0.75)	<0.001 (<0.001)

CV= Coefficient of Variation; GLSM= Geometric Least Squares Mean; N/A= not applicable
a Participants on high-dose hormones defined as those taking estrogens (e.g., conjugated estrogens, estradiol cypionate, estradiol valerate, etc), or progestogens (medroxyprogesterone, etc)
b N=155
c N=150
d median percent change from baseline
e median change from baseline
f percentage with treatment emergent dipstick proteinuria
g median percent change from baseline (change in kg)

1021 ASSOCIATIONS BETWEEN HORMONE USE, PrEP USE, AND STIGMA IN US TRANSGENDER WOMEN

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Background: The association between hormone therapy and PrEP use among transgender women is unclear. Qualitative research suggests that hormone use may facilitate PrEP use for some, while others may prioritize hormone therapy or have concerns about hormone-PrEP interactions.

Methods: We analyzed data (collected March-May 2019) from 330 sexually active transgender women aged ≥15 years who resided in the US. We used bivariate multinomial regression to estimate the association between self-reported past-year hormone use (i.e., no hormone use, provider-prescribed hormone use, and non-prescription hormone use) with past-year PrEP use. We used Chi-squared ($\chi 2$) tests to compare past-year sexual practices (i.e., condomless anal intercourse [CAI], condomless vaginal intercourse [CVI], and transactional sex) and past-year healthcare engagement across the provider-prescribed and non-prescription groups.

Results: Median age was 24 (IQR: 20,31) and 72.7% (240/330) of the sample was White, non-Hispanic. 104 (31.5%) participants reported no hormone use while 190/330 (57.6%) reported provider-prescribed and 35/330 (10.6%) reported non-prescription hormone use. 22 participants (6.66%) used PrEP. 115 individuals (34.85%) reported CAI, 128 (38.79%) CVI, and 29 (8.79%) engaging in transactional sex. 303 (91.8%) reported a past-year healthcare provider visit. Compared to no hormone use individuals, provider-prescribed participants had 10.78 times the odds (95% CI 1.42-81.94), and non-prescription participants had 9.65 times the odds (95% CI 0.97-96.09) of having used PrEP. There were no differences in PrEP use across the provider-prescribed and non-prescription groups. Among hormone-users (n=226),non-prescription individuals were more likely to have engaged in CAI ($\chi 2$=5.89, p=0.015) and transactional sex ($\chi 2$=15.31, p<0.001), while provider-prescribed individuals were more likely to have visited a health care provider ($\chi 2$=5.91, p=0.015).

Conclusion: Integrated hormone therapy and PrEP provision strategies may support health care engagement for individuals in the provider prescribed group who may not be taking PrEP and for encourage individuals in the non-prescription group who may be engaged in PrEP care to use provider-prescribed hormones.

1022 HIGH PrEP ADHERENCE AND PERSISTENCE IN A NATURALISTIC COHORT OF TRANSGENDER WOMEN

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Background: Transgender women (TGW) are a highest priority population for HIV prevention intervention, but there are limited data on PrEP uptake and adherence among TGW in naturalistic, real-world settings. FIRED-UP is an NIH cohort study of 150 TGW (100 on PrEP; 50 not on PrEP) designed to examine rates and correlates of PrEP uptake, adherence, and persistence among TGW receiving care at a community-based health center (CBHC).

Methods: Between Dec 2018 and Sep 2019, we enrolled 150 TGW (55% ≤ 29 years; 25% White; 66% publicly insured). TGW in the PrEP cohort (n = 100) had been taking daily oral PrEP for at least 3 months (range 4 to 54 months; median =17.5 months); TGW in the non-PrEP cohort had never taken PrEP. Across both arms, 85% were taking feminizing hormones (49 % injection, 39% pill; 6% patch, 6% combination), 70% were taking spironolactone, and 66% had received one or more gender-affirming surgery. All were receiving gender-affirming care at the CBHC. We collected survey and EMR data at enrollment and 3-months, and measured PrEP adherence with a urine TFV assay at 3-months (n = 45).

Results: The PrEP and non-PrEP cohorts did not differ by demographics, medical mistrust or PrEP-related attitudes (e.g., beliefs about hormone interactions). Among TGW not taking PrEP, 56% reported that they had never talked to a doctor about PrEP, and 58% reported that the reason they were not taking PrEP was because it had not been offered or prescribed. A higher percentage of TGW in the PrEP cohort had a CDC indication for PrEP (82%) compared to those in the non-PrEP cohort (47%, p < .001); however, PrEP indication was not associated with talking to a provider about PrEP. Among TGW in the PrEP cohort, a high percentage reported two or fewer missed pills in the past 30 days at baseline (61%) and 3M (74%), and 75% reported "always/almost always" taking PrEP as prescribed at both time points. Self-reported adherence was consistent with urine TFV levels, with 70% of TGW at >1000ng/ml. PrEP adherence did not differ by hormone use, PrEP-related attitudes, substance use, housing insecurity, or insurance status.

Conclusion: TGW who are engaged in care can successfully uptake and adhere to PrEP. Research should focus on interventions to enhance patient-provider communication about PrEP for TGW, and adherence support for TGW should be provided consistent with findings on adherence across priority populations and medications

1023 HIV PREVENTION AND DRUG-USER HEALTH CARE ON SITE AT A SYRINGE -EXCHANGE PROGRAM

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Background: Syringe exchange programs (SEPs) serve populations who are high risk for acquiring HIV and other infectious diseases. Adherence to offsite healthcare referrals is low. We describe a novel partnership between an academic medical center and an SEP to deliver low barrier healthcare to people who use drugs (PWUD) onsite at an SEP.

Methods: A Montefiore Medical Center clinic was opened within the drop-in center of a local SEP on February, 11, 2019. In this setting clients are able to access clean syringes, laundry, showers, group education, and psychosocial counseling. We conducted a retrospective chart review of patients seen at the drop-in center clinic from 2/11/2019-5/29/2019 using the electronic medical record. Sexual risk factors for HIV were defined: multiple sex partners, unprotected sex, sex worker, STD in the last 12 months, and/or sexual partners who are anonymous, HIV+, or currently injecting drugs.

Results: A total of 118 patients were seen by a provider during the study period. The mean age was 43 (IQR 17). The majority f patients were female (53%) and Hispanic (44%) or non-Hispanic Black (32%). 30% of patients were homeless. 61% of patients had ever injected drugs and 61% of patients also had one or more sexual risk factors for HIV. The most common current substances used were heroin (50%) and crack/cocaine (44%). The primary reason for a patient's first visit to the clinic was for buprenorphine treatment (32%), followed by PrEP (20%), hepatitis C treatment (20%), and PEP (8%). Of those who initiated buprenorphine treatment, 50% were retained in treatment at 90 days. 27% of patients who initiated PrEP were retained in treatment at 90 days. Of the 8 patients who received PEP, 3 initiated PrEP afterward. Of the 22 patients who were HCV positive, 20 (91%) were evaluated for treatment and had fibrosis staging, 10 (50%) initiated treatment.

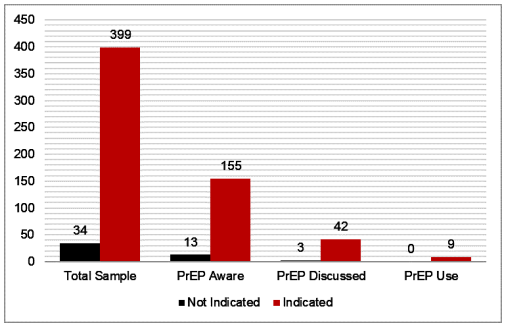
Conclusion: Through a novel SEP-academic medical center partnership, PWUD received well-established HIV-prevention services (buprenorphine and PrEP/PEP), as well as HCV treatment on-site at an SEP, demonstrating the feasibility of such initiatives. Rates of retention in buprenorphine treatment are comparable to retention rates at other low-barrier programs. PrEP retention was slightly lower than reported in other populations, but few studies have evaluated PrEP engagement among PWUD. Low barrier care delivered onsite at an SEP should

be further explored to improve access to care and HIV and HCV prevention for PWUD who may otherwise never receive them.

1024 HIGH PREVALENCE OF PrEP INDICATION IN PEOPLE WHO INJECT DRUGS IN BOSTON, MA, 2018

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Background: PrEP is recommended for HIV prevention in people who inject drugs (PWID) in the US. In Massachusetts, increasing prevalence of injection drug use has contributed to outbreaks of HIV, potentially identifying missed opportunities for PrEP. Understanding PrEP need, knowledge, and use among PWID will help inform and evaluate PrEP as an HIV prevention tool.
Methods: We used the 2018 National HIV Behavioral Surveillance (NHBS) data from PWID in Boston, MA. Eligible participants were ≥18 years old, reported past year injection drug use, lived in the Boston Metropolitan statistical area, could complete the interview in English or Spanish, and consented to be interviewed. Based on US Preventive Services Task Force (USPSTF) guidelines, we estimated the proportions of PWID with PrEP indication by types of HIV acquisition risk: injection risks only (i.e., sharing syringes or injection equipment), sexual risks only (i.e., past-year sexually transmitted infections, being in serodiscordant relationships, or inconsistently using condoms with known MSM or PWID), and overlapping injection and sexual risks. We then evaluated PrEP awareness, conversations with healthcare providers about PrEP, and actual (self-reported) PrEP use among those with and without PrEP indications.
Results: Overall, among 433 HIV-uninfected PWID, 399 (92%) had PrEP indication based on USPSTF guidelines as follows: 298 (69%) were indicated for injection risks only, 3 (<1%) were indicated for sexual risks only, and 98 (23%) were indicated for both injection and sexual risks. As shown in Figure 1, among the 399 PWID with PrEP indication, 155 (39%) had PrEP awareness, 42 (11%) had discussed PrEP with a healthcare provider, and 9 (2%) had used PrEP in the last year.
Conclusion: The majority of PWID in the Boston 2018 NHBS had PrEP indication based on current guidelines. Although most PWID were indicated for PrEP due to high risk injection-related behaviors, nearly a quarter also reported high risk sexual behaviors. PrEP awareness was suboptimal, conversations about PrEP with providers were uncommon, and PrEP use was extremely low. These findings highlight important areas for clinical and community-based interventions to improve PrEP uptake among PWID.



1025 PROPHYLACTIC EFFECT OF PrEP AGAINST HBV INFECTION AMONG MSM

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Background: Universal HBV vaccination had not been available in Japan until 2016 and men who have sex with men (MSM) are still vulnerable to hepatitis B virus (HBV) infection. Thus, we evaluated incidence of HBV infection and prophylactic effect of pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF/FTC) against HBV infection among a non HIV-infected MSM cohort, sexual health clinic (SHC) in Tokyo.
Methods: MSM over 16 years old were included in SHC cohort. Participants were examined for HIV infection, syphilis (quantitative RPR/TPHA), pharyngeal and rectal Chlamydia trachomatis and Neisseria gonorrhoeae infections, and HBs antigen/antibody and HBc antibody, HCV antibody and HAV IgG antibody every 3 months. Entry criteria of the study were HBc antibody negative (< 1.0 S/CO CLIA method) and HIV negative at the study enrollment. TDF/FTC for PrEP were provided for free via an official program of daily PrEP or purchased via internet for its generic drug at their own expense. The definition of HBV infection was positive conversion of HBc antibody or HBs antigen during follow-up period. The participants were followed between January 2018 and September 2019 and incidence rate of HBV infection were evaluated. Participants who acquired HBV infection or HIV infection were censored. Use of vaccination of HBV were defined as self-report of their experience of HBV vaccination or HBs antibody >= 10 mIU/ml (CLIA method). The cox proportional hazards regression analysis was used to evaluate prophylactic effect of PrEP against HBV infection and other factors including HBV vaccination. Factors with statistically significance (p<0.05) and the use of HBV vaccination as a known preventive factor against HBV infection were entered into multivariate analysis.
Results: 827 MSM were included in the cohort as of September 2019. Of 827 MSM, 25 and 211 MSM were excluded from the study due to HIV infection and HBc antibody positivity at the enrollment, respectively. 591 (148 were PrEP+ and 443 were PrEP-) were followed every 3 months with 419.8 person-years [mean age (SD), 34.5 years (9.3)]. The incidence rate of HBV infection was 3.57 cases per 100 person-years (15 HBV infections, one in the PrEP+ group and 14 in the PrEP- group, Log Rank test p=0.012,). The table identified the preventive and risk factors estimated by the cox hazard analysis which showed significant prophylactic effect of PrEP against HBV infection.
Conclusion: PrEP is a good indication especially for non-responders to HBV vaccination among MSM.

Table. Results of uni- and multivariate analysis to estimate prophylactic effect of PrEP and other factors against HBV infection

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	p value	Hazard ratio	95% confidence interval	p value
Age, years	0.987	0.931-1.046	0.650			
PrEP use	0.114	0.015-0.873	0.037	0.123	0.016-0.948	0.044
HBV vaccination	0.505	0.161-1.588	0.242	0.627	0.198-1.981	0.426
HIRI-MSM score[1]	1.038	0.965-1.116	0.320			
CT and/or NG[2]	2.744	0.976-7.713	0.056			
Previous syphilis	2.259	0.873-7.501	0.087			
Active syphilis	1.629	0.214-12.415	0.638			

1. HIRI-MSM score; HIV incidence Risk score for men who have sex with men
2. CT; *Chlamydia Trachomatis*, NG; *Neisseria Gonorrhoeae*

1026 AV AND HBV VACCINATION COVERAGE AND ACCEPTABILITY AMONG MSM ON PrEP

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Background: Sexually transmitted viral hepatitis have a rising incidence in MSM. During the ANRS IPERGAY PrEP trial (NCT 01473472), vaccination against HAV and HBV was offered free of charge to non-immune participants. We assessed baseline immune status, vaccine acceptability and efficacy in IPERGAY participants.
Methods: All subjects included in the IPERGAY blind and/or open phases were studied. HAV and HBV immune status were assessed at baseline and after vaccination. Anti-HAV IgGs and anti-HBs antibodies (Abs) were analyzed on available samples taken 1 to 3 months after each vaccine dose and on the latest available sample. The vaccination scheme was analyzed in subjects with a follow-up >6 months after receiving the 1st vaccine dose. Vaccination was considered incomplete when the last dose was not administered (3rd if HBV, 2nd if HAV). Subjects who started vaccination before trial initiation were excluded from acceptability and efficacy analyses. Sociodemographic factors associated with baseline immune status were explored by univariate analysis.
Results: A total of 429 subjects were analyzed. Two subjects were excluded because of isolated anti-HBc Abs at baseline. The median follow-up was 2.2 years (IQR 1.6-2.9). Absence of anti-HAV IgG at baseline (50%, 215/427) was associated with younger age (p=0.0001) and tobacco use (p=0.02). HBV

immunization after infection and vaccination was noted for 12% (50/427) and 67% (287/427) of subjects, respectively. Absence of prior HBV immunization (21%, 90/427) was associated with tobacco use (p=0.05). Among HAV non-immune subjects, 96% (207/215) received ≥1 dose of HAV vaccine and 91% (172/189) received a complete scheme. Among HBV non-immune subjects, 98% (88/90) received ≥1 dose of HBV vaccine and 79% (58/73) received a complete scheme. Among subjects with complete scheme, anti-HAV IgG and anti-HBs Abs were detected on last available sample in 93% (148/159) and 80% (44/55) respectively. Among subjects with incomplete scheme, anti-HAV IgG and anti-HBs Abs were detected on last available sample in 80% (12/15) and 36% (5/14) respectively. After the 1st dose of HBV vaccine 63% (37/59) of subjects developed anti-HBs Abs.

Conclusion: The acceptability and efficacy of HAV and HBV vaccination were high in the IPERGAY population. High receptivity to prevention messages and free of charge vaccination may have favored the acceptability. Physicians must consider HAV and HBV vaccination in subjects receiving PrEP.

1027 HIGH PrEP ADHERENCE BASED ON TFV-DP LEVELS IN THAI 15-19-YEAR-OLD MSM AND TRANSWOMEN

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Background: Thailand initiated the first regional pre-exposure prophylaxis (PrEP) program in 2014, which has reached 10,000 PrEP users, including adolescents. Our objective was to assess 6-month adherence to oral tenofovir-diphosphate/emtricitabine (TDF/FTC) PrEP among adolescent men who have sex with men (MSM) and transgender women (TGW) in Bangkok.

Methods: MSM and TGW aged 15-19 years were provided free daily TDF/FTC with condoms funded by the Princess PrEP demonstration project and CIPHER program at youth-friendly clinics. Monthly contact was via clinic visits (months 0, 1, 3, 6) or telephone calls (months 2, 4, 5) after PrEP initiation. Clients were counselled on PrEP adherence and behavioral risk reduction. Self-reported sexual risk behaviors including sex acts and condom use were recorded. Dried blood spots (DBS) were collected for quantification of TFV-DP levels at months 3 and 6 using a validated LC-MS/MS assay. Behavioral risk data were summarized into 3-month blocks to assess HIV protection (PrEP and/or 100% condom use). TFV-DP levels of <100, ≥100-349, ≥350-699 and ≥700 were taken to be 'not protective', 'partly protective', 'protective' and 'highly protective' respectively against HIV.

Results: Between March 2018 and June 2019, 148 MSM (74%) and 52 TGW (26%) were initiated on PrEP. Twenty-two percent had a sexually transmitted infection at enrollment. Median (IQR) sex acts per 3-month block was 8 (4-14). Retention at months 3 and 6 was 86% and 75%, respectively. There were 199 DBS samples collected (123 and 76 at months 3 and 6 respectively). TFV-DP levels were ≥700, ≥350-699, 100-349 and <100 fmol/punch in 47%, 17%, 20% and 16%, respectively. Among 199 risk periods, 46% were protected by PrEP only, (12% and 34% of samples with TFV-DP levels of ≥350-699 and ≥700 fmol/punch, respectively), 15% were protected by PrEP and condom use, 11% were protected by condoms alone, and 28% remained at risk of HIV acquisition. Of the 76 adolescents who completed the study, 66% were protected at month 3, and of these, 37/50 (74%) remained protected at month 6 (see table 1). There were 8 adolescents (11%) whose adherence improved and 13 (17%) whom declined when comparing the first and second periods of PrEP use. No seroconversions occurred in this study.

Conclusion: Youth-friendly clinics and monthly follow-up in adolescent MSM and TGW provided a 72% HIV risk reduction by either 'protective' TFV-DP levels and / or 100% condom use. PrEP rollout should be encouraged in adolescent MSM and TGW.

Table 1: TFV-DP level comparison between months 3 and 6 of PrEP follow-up

TFV-DP level at month 3	TFV-DP level at month 6 n (% of total, 95% CIs)		Total
	<350 fmol/punch	≥350 fmol/punch	
<350 fmol/punch	18 (23.7, 14.1 – 33.3)	8 (10.5, 3.6 – 17.4)	26 (34.2, 23.5 – 44.9)
≥350 fmol/punch	13 (17.1, 8.6 – 25.4)	37 (48.7, 37.5 – 59.9)	50 (65.8, 55.1 – 76.5)
Total	31 (40.8 29.8 – 51.8)	45 (59.2, 48.2 – 70.2)	76 (100)

1028 DRUG LEVELS, ADHERENCE, AND RISKS FOR LOW ADHERENCE IN THE DISCOVER PrEP STUDY

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Background: In over 8,700 person-years (PY) follow up in the DISCOVER PrEP trial, the HIV incidence rates in the emtricitabine/tenofovir alafenamide (F/TAF) and emtricitabine/tenofovir disoproxil fumarate (F/TDF) arms were 0.16 and 0.34/100 PY, demonstrating noninferiority for HIV prevention. Study investigators and site staff provided comprehensive adherence support to study participants at all visits.

Methods: 5,387 men who have sex with men (MSM) and transgender women (TGW) at high HIV risk were randomized 1:1 to receive blinded once daily F/TAF or F/TDF. At all visits, adherence was assessed by self-report on a confidential questionnaire and also by pill count. Dried blood spot analyses of tenofovir diphosphate (TFV-DP) in red blood cells (RBCs) were assessed in a randomly selected subset of 10% participants, and in any participant who acquired HIV; peripheral blood mononuclear cell (PBMC) TFV-DP levels were assessed at W4 in the same subset. Adherence support included adherence counseling at each visit, personal communications from site staff as needed, optional text messaging daily, and email updates periodically.

Results: 17 of the 22 HIV infections diagnosed in DISCOVER occurred while on study; 5/22 were suspected baseline infections. Of the 17 HIV infections that occurred on study, 6/17 occurred in the F/TAF arm and 11/17 occurred in the F/TDF arm. In 15 of the 17 on study HIV infections, DBS testing demonstrated that participants had undetectable or low TFV-DP levels in RBCs. By univariate logistical regression analysis, 5 baseline variables were significantly associated with low adherence by DBS (see Table); 2/5 were selected by multivariate stepwise analysis (asterisks). In both arms, adherence of at least 95% was >80% by self-report and was 69% by pill count. In the F/TAF and F/TDF arms respectively, 86-96% and 84-93% of participants were using at least 4 tablets/week, as measured by TFV-DP levels in RBCs. Levels of TFV-DP in PBMCs strongly correlated with tablets per week adherence TFV-DP levels in RBCs.

Conclusion: DISCOVER participants had very high adherence and very low HIV incidence rates. TFV-DP levels in RBCs were significantly lower in those with low adherence. The most important risk factor for acquisition of HIV on study was low adherence. Not using PrEP at baseline, black race, US residence, age below 25, and less than 4 years of college were significant risks for having low adherence to study drugs.

Table. Odds ratios of risk factors associated with nonadherence (DBS), univariate logistical regression

Baseline Variable	Comparison	Odds Ratio Estimate (95% CI)
Using F/TDF for PrEP at baseline	No vs Yes	2.91 (1.14, 7.44)
Race	Black vs Nonblack	2.37 (1.17, 4.79)
Region*	US vs. Ex-US	2.27 (1.28, 4.0)
Age	< 25 vs >= 25	2.22 (1.07, 4.6)
Highest Level of Education*	< 4 Year vs >= 4 Year College	2.17 (1.29, 3.65)
Recreational Drug Use	No vs Yes	1.54 (0.92, 2.59)
Ethnicity	Hispanic vs Non-Hispanic	1.53 (0.89, 2.66)
Diagnosis of Rectal Gonorrhea, Rectal Chlamydia or Syphilis (within 6 mos. prior to screening)	No vs Yes	1.45 (0.79, 2.66)
Binge Alcohol Use	Never Have vs Have >= 6 Drinks on One Occasion	1.44 (0.87, 2.39)
Number of Condomless Anal Sex Partners (within 3 mos. prior to screening)	<= 3 vs > 3	1.37 (0.75, 2.52)
Circumcision Status	No vs Yes	0.95 (0.57, 1.61)

1029 COMPARISON OF TFV-DP AND WISEPILL ADHERENCE AMONG YOUNG KENYAN WOMEN USING PrEP

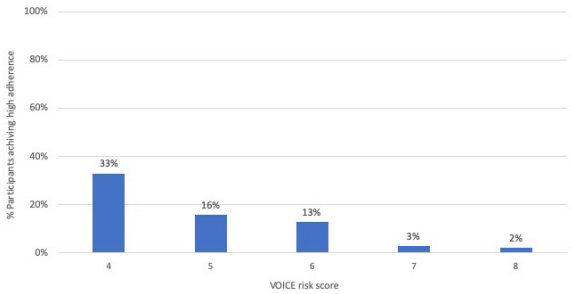
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Background: Understanding PrEP use and related barriers is dependent on good measures of PrEP adherence. We compared electronic monitoring with tenofovir-diphosphate (TFV-DP) assessed from dried blood spots (DBS) to assess consistency of both measures in a cohort of young women taking PrEP.
Methods: Participants were 18-24 year old women at high risk (by VOICE risk score) for HIV in Thika and Kisumu, Kenya. Participants were encouraged to take PrEP for at least the initial 6 months with study visits at 1 month, 3 months, and then quarterly for 24 months. The primary adherence measure was a real-time electronic monitor (Wisepill), while a random sample (15%) of DBS collected from non-pregnant participants receiving PrEP was also tested for TFV-DP. Adherence was categorized as high (>85% or 6+ doses/week; >1,050 fmol/punch), moderate (57-85% or 4-5 doses/week; 700-1,050 fmol/punch), and low (<57% or <4 doses/week; <700 fmol/punch) for electronic monitoring and DBS, respectively. Descriptive comparisons were made between DBS and corresponding Wisepill openings over the prior 30 days.
Results: DBS results from 39 samples (representing 36 women) over the first 12 months of follow-up were available. Overall concordance between electronically monitored and DBS adherence was moderate at 59%. Of the 21 participants with low electronically monitored adherence (<4 doses/week), almost all (n=20) had TFV-DP<700 fmol/punch, with an average of 128 fmol/punch. Of the 11 with moderate electronically monitored adherence (4-5 doses/week), 4 (10%) had TFV-DP ≥700 fmol/punch and an average of 559 fmol/punch. Of the 7 participants with high electronically monitored adherence (≥6 doses per week), only 1 had the expected TFV-DP ≥1050 fmol/punch, with an average of 577 fmol/punch. Notably, among women with high electronically monitored adherence, average TFV-DP was 526 fmol/punch when hemoglobin was <11 g/dL versus 616 fmol/punch when hemoglobin was >11 g/dL.
Conclusion: Overall, these findings show moderate consistency between both adherence measures, although the established TFV-DP thresholds may be high in this African population, especially among those with lower hemoglobin level. We found no evidence that women were taking PrEP by DBS without concurrent dosing by electronic monitoring; however, overreporting by electronic monitoring is possible. Additional studies are warranted to fully characterize both adherence measures for young women who are an important key population for HIV prevention.

1030 HIV RISK AND OBJECTIVELY MEASURED PrEP ADHERENCE IN YOUNG KENYAN WOMEN

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Background: Pre-exposure prophylaxis (PrEP) is a highly effective means for preventing HIV acquisition. However, use among young women has generally been suboptimal and poorly characterized. We present objectively measured adherence and associated socio-behavioral factors among a cohort of young women.
Methods: Participants were 18-24 year old women at high risk for HIV in Thika and Kisumu, Kenya. High risk was defined as a VOICE risk score >4; points (pts) were given for age <25 (2 pts), being single or not living with a primary sexual partner (2 pts), lacking financial or material support from a sexual partner (1 pt), a sexual partner having or potentially having other partners (2 pts), and alcohol use (1 pt). Participants were encouraged to take PrEP for at least 6 months and then counseled on continued use based on their preferences and HIV risk. Study visits occurred at 1 month, 3 months, and then quarterly for 24 months. Adherence was measured with a real-time electronic monitor (Wisepill) and summarized descriptively. Baseline predictors of high adherence were assessed by multivariable logistic regression analysis.
Results: A total of 347 women have been followed for 461 person-years (as of June 2019; study to end early 2020). At 1, 3, and 6 months of desired PrEP use, 35%, 14%, and 7% of participants took an average of 6 doses per week, respectively, while 50%, 24%, and 15% took an average of 5 doses per week. The only baseline factor significantly associated with high adherence (an average of 6 doses per week) over 6 months was the VOICE risk score: OR 0.53 (95% CI 0.33, 0.85) for each additional point (figure). Non-significant factors included in the model were age, number of current sexual partners, concern about PrEP, prior medication use, and intimate partner violence. Findings were similar when high adherence was defined as an average of 5 doses per week.
Conclusion: Objectively measured PrEP adherence likely to be sufficient for protection against HIV was seen in a minority of participants and declined with time. Higher baseline HIV risk was associated with lower adherence in the first 6 months of use. These findings suggest limited prevention-effective adherence, although future analyses will assess the alignment of risk and adherence over time. Similar assessments in other PrEP cohorts may be useful for program evaluation; novel approaches are needed to help young women understand risk and the means to achieve effective HIV prevention.



1031 USING A MOBILE APP AND DRIED BLOT SPOTS TO ASSESS ADHERENCE TO EVENT-DRIVEN PrEP

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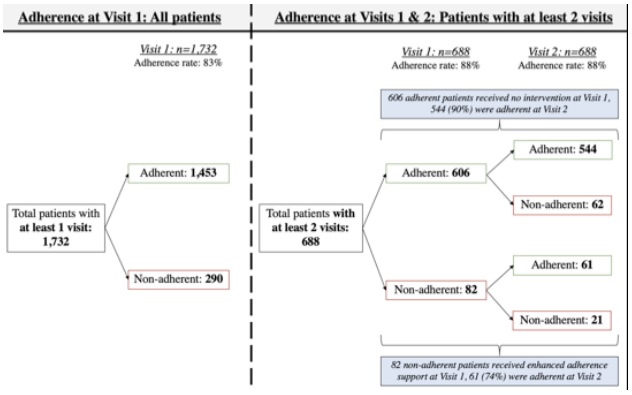
Background: Both daily and event-driven (i.e. before and after sex) pre-exposure prophylaxis (PrEP) regimens are effective against HIV acquisition. However, information about adherence to event-driven PrEP is scarce and predominantly based on self-reported data collected at 3-month intervals. We used a mobile-based diary application and intracellular tenofovir diphosphate (TFV-DP) levels to assess adherence among event-driven PrEP users participating in the Amsterdam PrEP demonstration project (AMPrEP) in the Netherlands.
Methods: Participants could choose and switch between daily and event-driven PrEP regimens. Participants used a mobile application to record their sexual behaviour and pill use on a daily basis. We studied adherence by assessing (1) the number of condomless anal sex (CAS) acts covered by PrEP using data collected by the mobile application and (2) the correlation between TFV-DP concentrations (measured in dried blood spot (DBS) samples taken at the 3, 6 or 9, and 12 and 24 month visits; lower level of detection 12.5 fmol/punch) and CAS, and between TFV-DP concentrations and self-reported pill use. Good adherence was defined as at least one tablet before a CAS act and one tablet within 48 hours of that CAS act.
Results: Between September 2015 and February 2019, 139 of 376 (37.0%) AMPrEP participants used event-driven PrEP for at least 3 months. In this period, a total of 6,583 CAS acts were reported in the mobile application during event-driven PrEP use, of which 5,518 (83.8%) were covered by good PrEP adherence. Good PrEP adherence was more common around CAS acts with known (93.0%) and unknown (90.4%) casual partners, than with a steady partner (56.2%; p<0.001). Median TFV-DP concentration was 528 fmol/punch (IQR 232-900; levels ≥700 fmol/punch are correlated with use of at least 4 pills per week in the preceding 6 weeks) and higher TFV-DP concentration was associated with the number of self-reported CAS acts (β=0.15, 95% CI 0.11-0.19) and with the number of pills taken (β=0.08, 95% CI 0.06-0.09) in the 6 weeks before the DBS.
Conclusion: In our PrEP demonstration study, the majority of reported CAS acts were covered by PrEP. Self-reported adherence to event-driven PrEP was very

high for CAS acts with unknown and known casual sex partners, suggesting that MSM use event-driven PrEP when they are most at risk for HIV. Observed TDF levels in event-driven PrEP users are lower than those reported from studies among daily users.

1032 USE OF A TENOFOVIR URINE TEST TO IMPROVE PrEP ADHERENCE AND PREDICT NON-RETENTION

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Background: Daily pre-exposure prophylaxis (PrEP) effectively prevents new HIV infections. Poor adherence and retention are pervasive, undermining PrEP's utility. Objective adherence monitoring (OAM) tools that identify non-adherent patients and drive behavioral change are urgently needed. A Liquid Chromatography Mass Spectrometry (LC-MS/MS) urine test for Tenofovir (TFV), a component of PrEP, was used clinically to identify non-adherent patients and target support services. Adherence data were analyzed to describe the association between recent adherence, missed visits, and loss to follow up (LTFU).
Methods: Urine samples were collected from PrEP patients at 16 clinics in the US during routine visits. The LC-MS/MS test detected recent non-adherence (no dose in 48 hours) versus recent adherence (a dose in the last 6 days). Non-adherent patients received adherence support, per clinics' standards of care. We assessed results from patients who attended ≥2 visits and analyzed follow-up test results to determine if non-adherent patients had repeat non-adherence or improved adherence at their next visit. Clinic visits were recorded based on dates of adherence testing. Missed visits were defined as a gap in care of >120 days since the last visit. LTFU was defined as a gap in care of >180 days since the last visit with no future visit. Rates of missed visits and LTFU were calculated based on patients' adherence status at the previous visits.
Results: 688 patients received urine screening and targeted adherence support at ≥2 visits. At Visit 1, 606 (88%) were adherent. Of the 606 adherent patients at Visit 1, 544 (88%) remained adherent at Visit 2. Of the 82 non-adherent patients at Visit 1, 61 (74%) were adherent at their next visit. Non-adherence was associated with missed visits and LTFU. Non-adherent patients were 70% more likely to miss their next visit and 114% more likely to be LTFU than adherent patients. Individuals who were initially non-adherent but became adherent had a similar chance of missing a visit or LTFU as patients with two adherent results in a row (25% vs 25%, 9% vs 8%, respectively).
Conclusion: Use of OAM coupled with targeted support for non-adherent individuals was associated with increased adherence. OAM also proved to be an invaluable tool to predict future non-retention and demonstrated the potential to reduce non-retention. This evidence indicates that OAM can be a key tool to identify and improve behavioral determinants of PrEP efficacy.



1033 DETERMINANTS OF HIV PREEXPOSURE PROPHYLAXIS INITIATION IN WOMEN AT HIGH RISK FOR HIV

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Background: Determinants of HIV Pre-Exposure Prophylaxis (PrEP) initiation in U.S. women at risk for HIV are poorly understood. We sought to identify barriers and facilitators of PrEP initiation among women at high risk for HIV in a high prevalence community. We hypothesized that there would be significant demographic, behavioral, and psychosocial barriers to PrEP initiation.
Methods: We offered an anonymous, validated survey to women presenting for care in a hospital-based family planning clinic and a government sexual health clinic in Washington, DC. We measured socio-demographics, HIV behavioral risk factors, knowledge, attitudes, norms, and self-efficacy regarding PrEP initiation. We used chi-squared and Fisher's exact tests for categorical variables, t-tests for continuous variables, and Mann-Whitney U test for ordinal variables. This analysis included women at high risk for HIV acquisition (i.e. ≥3 reported behavioral risk factors).
Results: 1118 women completed the survey; 32.4% (N = 362) were categorized as high risk for HIV acquisition. Of women at high risk, mean age was 27. The majority were Black (71.6%), single (88.5%), had completed ≥ high school/GED (94.6%), and reported household incomes <$25,000 (51.5%). 13.4% (n=48) were committed to starting PrEP in the next 12 months. Although specific behavioral risk factors for HIV were not associated with uptake intention, composite number of reported risk factors for HIV was positively associated (r=0.18, p<0.01). 8.7% perceived moderate-high risk of HIV acquisition in the next 12 months and 15.7% moderate-high lifetime risk. Perceived risk was not associated with intention to initiate PrEP. Age, race, marital status, income, distance from clinics, insurance status, transportation, housing, illicit drug use, and prior knowledge of PrEP were not associated with uptake intention. Prior discussion about PrEP with a medical provider was associated with intention to initiate. Attitudes toward PrEP, perceptions of norms (injunctive and descriptive) and efficacy, were positively associated with uptake intention (Table 1).
Conclusion: Demographic factors, behavioral risks, and perceived risk were not associated with intention to initiate PrEP among women at high risk for HIV. Psychosocial factors and healthcare provider support, however, were positively associated with intention to initiate PrEP. Our findings have important implications for PrEP messaging and development of interventions that center on the role of providers and social networks in the destigmatization and provision of PrEP.

Table 1: Differences in attitudes, norms, and efficacy beliefs between women at high risk for HIV acquisition with low/no intention to initiate PrEP vs. high intention

Global Measures • Attitudes, Norms, & Efficacy	No/Low Intention to Initiate PrEP Mean (SD)	 Median (10-90%)	High Intention to Initiate PrEP Mean (SD)	 Median (10-90%)	P value†
Global Measure: Attitude (PrEP daily to prevent HIV is a good thing)‡					
• PrEP is a safe way to prevent HIV infection. ‡	3.98(1.04)	4 (3, 5)	4.70(0.62)	5 (4, 5)	<.01
• PrEP is an effective tool to prevent HIV infection. ‡	4.03(0.97)	4 (3, 5)	4.64(0.82)	5 (3, 5)	<.01
• Using daily PrEP would make me feel in control of my health. ‡	3.77(1.14)	4 (2, 5)	4.79(0.55)	5 (4, 5)	<.01
Global Measure: Injunctive Norms (Thinking about the people who are important to you, would they support your using PrEP?) ‡					
• Doctor~	6.17(4.10)	8(0, 10)	9.18(2.07)	10(6, 10)	<.01
• Main sex partner~	4.64(4.41)	4(0, 10)	8.05(3.19)	10(3, 10)	<.01
• Mother~	3.95(4.74)	3(0, 10)	5.88(4.42)	8(0, 10)	.02
• Best Friend~	4.29(4.20)	4(0, 10)	6.95(3.67)	10(2, 10)	<.01
Global Measure: Descriptive Norms (Thinking about people who are similar to you, how likely would they be to use PrEP?) ‡					
• People would shame me if they learned that I was taking PrEP‡	1.99(1.18)	1 (1, 4)	1.51(1.06)	1 (1, 3)	<.01
Global Measure: Efficacy (If I really wanted to, I could use PrEP daily) ‡					
• If I really wanted to, I could remember to take the pill every day ‡	4.00(1.12)	4(2, 5)	4.66(0.73)	5(4, 5)	<.01
• If I really wanted to, I could take the pill every day, even if it gave me a stomach ache ‡	2.93(1.28)	3 (1, 5)	4.19(1.17)	5 (2, 5)	<.01
• I could use PrEP, even if my main partner didn't want me to‡	4.28(1.02)	5 (3, 5)	4.68(0.78)	5 (3, 5)	<.01

‡ The measure indicates the level of agreement (from 1-5) for this question. A higher score indicates stronger agreement.
~The measure (ranging from -10 to +10) indicates the impact of the individual's support on the surveyee, measured by multiplying the level of importance (1 to 5) by the level of support (-2 to +2). † The p-value to detect the difference was based on Mann-Whitney U Test.

1034 PRENATAL PrEP EXPOSURE AND LONGITUDINAL BIRTH OUTCOMES IN KENYA

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Background: PrEP is recommended for use among pregnant and breastfeeding women at risk for acquiring HIV by the World Health Organization and Kenyan Ministry of Health. As PrEP implementation continues, accruing data on birth outcomes following prenatal PrEP exposure remains important.
Methods: PrEP Implementation for Mothers in Antenatal Care (PrIMA) is a cluster randomized trial in Western Kenya (NCT03070600) evaluating different strategies for providing PrEP counseling to women attending antenatal care. Women enrolled in PrIMA are followed through 9 months postpartum whether or not they elect to use PrEP. Women were identified as PrEP-exposed during pregnancy if they were prescribed PrEP at any antenatal study visits. Birth outcomes including, miscarriage (≤20 week gestation), stillbirth (>20 week gestation), gestational age at birth, birth weight, birth length, and congenital malformations are collected on all participants at six-weeks postpartum. Low birthweight (LBW) was defined as birthweight <2.5 kg among term infants, and small-for-gestational age (SGA) as below the 10th percentile for birthweight at gestational age at birth. The proportion of births with miscarriage, stillbirth, preterm birth, congenital malformations, LBW, SGA, gestational age at birth, birthweight, and birth length were compared by PrEP exposure status using generalized estimating equations (GEE) with a binomial link or a gaussian link. Analyses were repeated adjusting for partner HIV status, maternal age, and syphilis status.
Results: As of September 2019, 4,445 women had enrolled during pregnancy and 3,882 had delivered; 654 (17%) used PrEP at any time during pregnancy and had delivered. Median gestational age at enrollment was 25 weeks (IQR: 20, 30) in the PrEP unexposed group and 24 weeks (IQR: 20, 28) in the PrEP exposed group. Compared to women who did not use PrEP, PrEP-exposed women were more likely to report having a partner who was known to be HIV-positive (61% v 33%) or a partner of unknown status (43% v 30%), and reported more HIV risk factors (p≤0.001 for all). Compared to PrEP-unexposed infants, there was no difference in miscarriage (0.5% for both, p: 0.41), stillbirth (3.3% v 2.2%, p: 0.98), preterm birth (17.2% v 17.6%, p: 0.67), birthweight (3.4kg for both, p: 0.51), or birth length (52 v 51cm, p: 0.99).
Conclusion: In this large longitudinal study, we found no significant differences in birth outcomes by prenatal PrEP exposure status.

TABLE 1. PARTICIPANT CHARACTERISTICS AND BIRTH OUTCOMES BY PREP EXPOSURE STATUS

		N (%) or Median (IQR)				
		PrEP Unexposed (n=3,228)	PrEP Exposed (n=654)	p-value		
Participant Characteristics						
Age (years), mean (SD)		23.8 (18.8)	25.4 (6.7)	0.034		
Partner HIV Status	HIV Negative	1975 (61.2%)	216 (33.0%)	<0.001		
	HIV Positive	41 (1.3%)	119 (18.2%)			
	No Current Partner	252 (7.8%)	39 (6.0%)			
	Unknown	951 (29.5%)	278 (42.5%)			
Gestational Age at Enrollment, median (IQR)		25.0 (20.0, 30.0)	24.0 (20.0, 28.0)	0.099		
HIV Risk Factors						
Lifetime number of sexual partners, median (IQR)		2.0 (2.0, 3.0)	3.0 (2.0, 4.0)	<0.001		
Syphilis Test Results	Negative	3148 (97.5%)	621 (95.0%)	0.001		
	Positive	26 (0.8%)	15 (2.3%)			
	Not done	54 (1.7%)	18 (2.8%)			
Engaged in sex in exchange of money or other favors?		46 (1.4%)	23 (3.5%)	<0.001		
Diagnosed with or treated for an STI?		66 (2.0%)	36 (5.5%)	<0.001		
Forced to have sex against your will?		167 (5.2%)	59 (9.0%)	<0.001		
HITS Score >=6		213 (6.6%)	102 (15.7%)	<0.001		
Physically assaulted including assault by your sex partner?		178 (5.5%)	63 (9.7%)	<0.001		
	PrEP Unexposed	PrEP Exposed	OR or Coeff* (95% CI)	p-value	Adjusted OR or Coeff~ (95% CI)	p-value
Birth Outcomes						
Miscarriage, n (%)	14 (0.5)	3 (0.5)	1.05 (0.28, 3.97)	0.94	1.79 (0.45, 7.08)	0.41
Stillbirth, n (%)	70 (2.2)	21 (3.3)	1.49 (0.92, 2.40)	0.10	0.99 (0.51, 1.93)	0.98
Gestational age at birth (weeks), median (IQR)	38 (37, 40)	38 (37, 40)	-0.17 (-0.67, 0.33)	0.48	-0.13 (-0.74, 0.48)	0.66
Preterm Birth, n (%)	536 (17.2)	113 (17.6)	1.04 (0.80, 1.35)	0.76	0.93 (0.66, 1.31)	0.67
Congenital Malformation, n (%)	11 (0.35)	2 (0.31)	0.88 (0.17, 4.51)	0.88	--	--
Birthweight (kg), median (IQR)	3.4 (3.0, 3.7)	3.4 (3.0, 3.7)	-0.005 (-0.088, 0.078)	0.90	0.051 (-0.11, 0.21)	0.51
Low Birth Weight (<2.5 kg) n (%)	30 (1.2)	6 (1.2)	0.81 (0.34, 1.92)	0.64	0.53 (0.17, 1.65)	0.27
Small for Gestational Age, n (%)	114 (3.7)	24 (3.7)	0.83 (0.47, 1.48)	0.54	0.76 (0.36, 1.63)	0.48
Birth length (cm), median (IQR)	51 (50, 54)	52 (50, 54)	0.33 (-0.99, 1.64)	0.61	0.014 (-1.92, 1.95)	0.99

*Odds Ratio for binary outcomes and coefficient for continuous variables ~Adjusted for maternal age, partner HIV status (negative or positive/unknown), syphilis status

1035 WOMEN ARE LESS LIKELY TO BE TESTED FOR HIV OR OFFERED PrEP AT TIME OF STI DIAGNOSIS

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Background: Ending the HIV epidemic requires implementation of comprehensive HIV prevention services (CHPS), including identification, testing, and linkage to care of at-risk individuals across diverse healthcare settings. Missed opportunities for CHPS remain common. Sexually transmitted infections (STI) are significant biomarkers of HIV risk and should trigger pre-exposure prophylaxis discussion. We reviewed STI testing practices outside of sexual health clinics at our center to identify opportunities for improvement in the provision of CHPS.
Methods: An electronic sexual health dashboard was used to identify patients with a positive bacterial STI test between January 1, 2019 and June 30, 2019 at 3 hospitals affiliated with an academic medical center in northern Manhattan. We excluded patients seen in our sexual health clinics. 690 patient encounters (PE) in 658 unique patients were reviewed to assess HIV testing, completeness of screening for STI, and HIV prevention discussions.
Results: Patients were predominantly female (65%); median age was 24 (range 18-85). Positive tests occurred in 50 inpatient and outpatient locations; the most frequent were the family planning clinic (25%) and the three emergency rooms (27%). The most common test performed was a genitourinary (GU) gonorrhea/chlamydia nucleic acid amplification test (46% of all tests ordered). Multi-site testing was rarely performed (7.9% of PE) and was more frequent in men than women (22% vs. 0.45%, OR 62.5, 95% CI 15.1-263.2). Of 41 individuals with positive extra-genital tests, GU was positive only in 24% of cases. Of all individuals with a positive STI test, 65%, 9% and 13% had concurrent, >12 months, or no HIV testing, respectively. Women were more likely to be inadequately screened for HIV (17% vs. 25%, OR 0.61, 95% CI 0.41-0.91). Documentation of PrEP discussion was rare (6.8% of PE) compared with safe sex (45%) and condoms (50%). PrEP was discussed almost exclusively with men compared to women (17% vs. 1.3%, OR 15.03, 95% CI 6.28-35.97).
Conclusion: In a cohort of patients with positive bacterial STI testing, gaps in CHPS exist. HIV screening, multi-site STI screening, and discussion of PrEP were particularly infrequent among women. Interventions to increase proper implementation of HIV prevention services must include improved HIV testing and provision of comprehensive sexual health services in all care settings and with all patients.

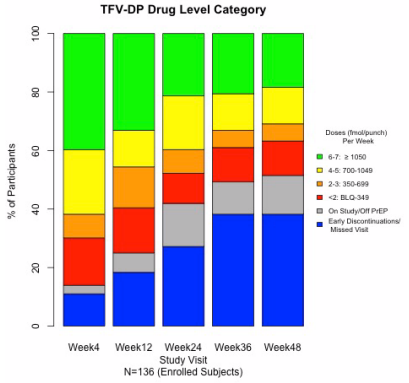
	Male	Female	Odds Ratio (Female Reference)	95% Confidence Interval (95% CI)	
Test Sent					
GC/CT-Genitourinary NAAT	95.04%	98.66%	0.26	0.10	0.70
GC/CT-Extragenital NAAT	22.17%	0.45%	62.50	15.11	263.16
HIV	73.97%	57.81%	2.07	1.47	2.92
RPR	50.83%	30.58%	2.35	1.70	3.24
HIV Prevention Discussion Documented					
Safe Sex	53.31%	41.29%	1.62	1.18	2.22
Condoms	53.72%	49.33%	1.19	0.87	1.63
PrEP	16.94%	1.34%	15.03	6.28	35.97
None	35.54%	45.98%	0.65	0.47	0.89
HIV Screening					
Inadequate (never screened or screened over 1 year ago)	16.94%	25.00%	0.61	0.41	0.91
Within 1 year	8.26%	15.18%	0.5	0.30	0.85
Within 1 week	74.79%	59.82%	1.99	1.41	2.82

1036 RESULTS FROM A PrEP DEMONSTRATION PROJECT FOR AT-RISK CISGENDER WOMEN IN THE US

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Background: Data on TDF/FTC PrEP use by cisgender women have largely been from Africa. We report the primary results from the first US demonstration project of oral PrEP among at-risk cisgender women.
Methods: Adherence Enhancement Guided by Individualized Texting and Drug Levels (AEGiS) was a 48-week PrEP demonstration project in cisgender women ≥18 years old at-risk for HIV conducted at 5 Southern California sites. Adherence was supported using two-way text messaging (Individualized Texting for Adherence Behavior; ITAB) and titrated adherence counseling based on rapid-turnaround tenofovir diphosphate (TFV-DP) concentrations. Study visits occurred at baseline, week 4, week 12, then quarterly through week 48. Demographics were collected with computer surveys. Outcomes included PrEP adherence, retention and persistence. Adherence was assessed by quantifying TFV-DP concentrations in dried blood spots. Concentrations ≥1050 fmol/punch were considered protective, suggesting ≥6 doses on average per week. Self-reported PrEP adherence was determined by the proportion of participants responding positively to daily iTAB text prompts over 30 days prior to study visits.
Results: Between 6/2016 and 10/2018, 136 ciswomen enrolled with mean age 40 (SD 11); 38% were non-Hispanic (NH) Black and 19% Latina. Over 48 weeks,

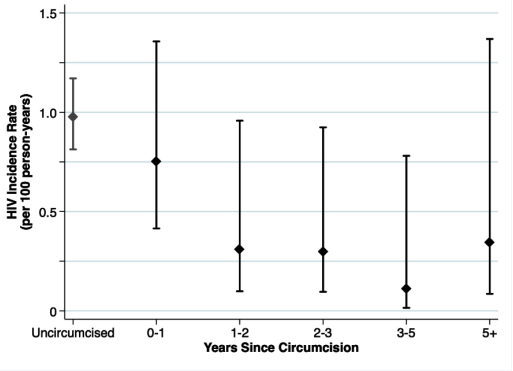
84 (62%) participants were retained and 62 (74%) remained on PrEP. Over one-third (12/31) of those on study but off PrEP discontinued TDF/FTC due to self-reported side effects; one led to study discontinuation. Of 120 participants with drug concentrations measured, 67 (56%) had at least one protective concentration; 22 (18%) had consistently protective drug concentrations across all available study visits attended. For all visits, women with protective TFV-DP were more likely to have a higher proportion of positive iTAB responses compared to those with TFV-DP<1050 fmol/punch ($p<0.05$ at all visits except week 24). There were no incident HIV infections and 4 incident bacterial STIs.
Conclusion: Cisgender women in a PrEP demonstration project had mixed adherence and retention; many had non-protective TFV-DP concentrations and over 25% were lost to follow up. US PrEP programs may need to consider offering prevention alternatives for women who discontinue or struggle with PrEP adherence. In particular, integrating PrEP delivery within other valued medical or social services may promote and augment HIV prevention efforts.



1037 LONG-TERM EFFECTIVENESS OF VOLUNTARY MEDICAL MALE CIRCUMCISION FOR HIV PREVENTION

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Background: While the efficacy of male circumcision for HIV prevention was demonstrated in clinical trials, evidence on the long-term effectiveness of post-childhood circumcision through voluntary medical male circumcision (VMMC) programs in sub-Saharan Africa is limited. We assessed effectiveness of VMMC in preventing HIV acquisition in a President's Emergency Plan for AIDS Relief (PEFAR) funded program in the Rakai region of Uganda using longitudinal data from the Rakai Community Cohort study (RCCS).
Methods: A cohort of initially uncircumcised HIV-uninfected men in the RCCS were followed between 2009 and 2016 in 30 communities during scale-up of VMMC programs. Self-reported data on circumcision status was collected and rapid HIV tests were done at five surveys conducted every 18 months. Incident HIV infection was estimated to occur at the midpoint of the inter-survey interval. Multivariable Poisson regression with generalized estimating equations was used to estimate adjusted incident rate ratios (IRR) and 95% confidence intervals (CI) of HIV acquisition in circumcised versus uncircumcised men adjusting for sociodemographic characteristics and sexual behaviors.
Results: 3,916 non-Muslim men were followed for 17,088 person-years over 9,469 study visits. There were 1,338 newly reported VMMCs (10.79/100py) and 138 incident HIV infections (0.81/100py) observed. At baseline, men adopting circumcision were significantly younger and more likely to have never initiated sex, consistently use condoms, and to be unmarried compared to uncircumcised men. Over the study period, the median age of men adopting circumcision declined from 28 years (interquartile range [IQR]:21-35) to 22 years (IQR:18-29; p-trend < 0.001). Overall, HIV incidence was 0.40/100 person-years (py) among circumcised men compared to 0.98/100 py among uncircumcised men (unadjusted IRR=0.4; 95% CI 0.25-0.66; adjusted IRR=0.47; 95% CI: 0.28-0.78). The effectiveness of circumcision for HIV prevention was sustained with increasing time from surgery (Figure) and was similar across age groups and calendar time.
Conclusion: A VMMC service program was highly effective in preventing HIV acquisition. The effectiveness of VMMC in this observational study is consistent with efficacy in clinical trials and support current recommendations that VMMC is a key component of combination HIV interventions and central to efforts to reduce HIV incidence.



1038 "STYLISH MAN" CLUSTER RCT TO INCREASE MALE CIRCUMCISION FOR ADULT MEN ≥19, UGANDA

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Background: There is need to increase acceptance of voluntary medical male circumcision (VMMC) among men ≥19 years who are at highest risk of incident HIV, but who are under-represented in VMMC programs in sub-Saharan Africa.
Methods: Between 2015-2018, we conducted a community cluster randomized trial (5 clusters per arm) to assess community promotion of voluntary medical male circumcision mobilization using a de-medicalized messaging intervention (the "Stylish Man".) In the intervention arm, VMMC was provided via mobile camps alongside a 3-4 day "Stylish Man Event" (infotainment, games, testimonials by satisfied adopters and their partners, "red carpet" VMMC services for men >19 years, messages stressing VMMC as an adult lifestyle choice rather than just a health service), compared to control arm services provided via standard mobile VMMC camps of the same duration. The primary endpoint was the number and proportion of men aged >19 accepting VMMC services, and the population prevalence/incidence of VMMC among non-Muslim men ≥ 19 in three population-based Rakai Community Cohort Study surveys during the trial. Differentials between intervention and control arms were estimated using rate ratios (RR) and 95% confidence intervals (CI).
Results: The number of men accepting VMMC in the intervention arm (5,992) was higher than in the control arm (4,394); also, the numbers and proportions of acceptors aged >19 was higher in the intervention (n=2,083, 34.8%, than the control arm (n=752, 17.1%, RR= 1.96, 95%CI 1.82-2.11); and the differential was statistically significant in all cluster pairs. The population prevalence of VMMC in men >19 increased over time in both arms and was significantly higher in the intervention compared to the control arm during the first follow up (RR=1.11, 95%CI 1.05-1.18.) The incidence of VMMC was also higher in the intervention arm during the first inter-survey interval (RR=1.71, 95%CI 1.43-2.06), but not at later time points.
Conclusion: Community mobilization/de-medicalized promotion increased VMMC uptake in men aged >19, as reflected in service statistics. Population-level VMMC prevalence in men >19 was initially higher in the intervention arm, but VMMC rates increased in both arms over time and the differential between arms was not sustained. Programs should consider demedicalized approaches to increase VMMC among older men.

1039 SEX AND THE PENILE MICROBIOME: POTENTIAL SHARING OF HIV RISK–ASSOCIATED ANAEROBES

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Background: Anaerobes in the genital microbiome have been associated with HIV acquisition in both men and women. Prevotella bivia and Dialister micraerophilus are associated with HIV risk and genital inflammation in both men and women despite major differences in vaginal and penile microbiome composition. Little is known regarding the potential transmission of HIV-associated anaerobes, particularly the directionality of transmission.
Methods: We characterized sub-preputial microbiota in uncircumcised HIV negative males, including non-sexually active adolescents (aged 15-17 yrs, N=95) and sexually active adult men (mean age 22 yrs, N=47) in Rakai, Uganda. Sub-preputial swabs were collected into 1% BSA in PBS with protease inhibitor. Total bacterial density was measured by qPCR and proportional and absolute abundance of penile bacteria was characterized by sequencing of the 16S rRNA V3V6 region. Overall penile microbiome composition was compared by PerMANOVA test. Prevalence and abundance of penile bacteria were compared by Chi-square test and Wilcoxon rank-sum test, respectively.
Results: Penile microbiome composition differed significantly between sexually active and non-sexually active uncircumcised males in both proportion and absolute abundances (PerMANOVA p<0.001 in both). However, the total bacterial density was similar in both groups. Non-sexually active adolescents had high abundances of anaerobic penile bacteria, including many Prevotella and Dialister species; however, the two species associated with HIV risk and inflammation—P. bivia and D. micraerophilus—were significantly less prevalent and abundant in non-sexually active adolescents, in contrast to sexually active men (Chi2 and Wilcoxon p<0.05 for both organisms). Peptostreptococcus anaerobius, associated with HIV risk in men, was also less prevalent and abundant in non-sexually active adolescents (Chi2 and Wilcoxon p<0.05). Other anaerobes—including Porphyromonas and Murdochiella—were more abundant in non-sexually active adolescents than sexually-active men.
Conclusion: Prior to initiation of sexual activity, the uncircumcised penile microbiome is dominated by anaerobic bacteria, but the specific species associated with HIV risk and genital inflammation are conspicuously rare. These data suggest that seroconversion-associated anaerobes may originate in the vaginal microbiome, which once when transmitted to penile microbiome could spur foreskin inflammation and colonize the penile microbiome.

1040 PREVALENCE AND INCIDENCE OF STIs DURING PREGNANCY IN SOUTH AFRICA

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Background: Global estimates of the prevalence of sexually transmitted infections (STIs) remain high with approximately one million new infections per day. STIs increase HIV acquisition and perinatal transmission risk. Syndromic management for STIs is standard of care in South Africa. We evaluated the incidence and prevalence of STIs in pregnancy in Tshwane District and Cape Town, South Africa.
Methods: We conducted two observational prospective studies of pregnant women enrolled while attending their first antenatal clinic (ANC) visit in Cape Town and Tshwane District. We interviewed women ≥18 years and tested them at first ANC visit for Chlamydia trachomatis (CT), Neisseria gonorrhoea (NG) and Trichomonas vaginalis (TV) using Xpert® assays (Cepheid, USA) as well as at the first postnatal visit. We evaluated the prevalence of STI at first ANC visit and factors associated using logistic regression model. We estimated the incidence of STI and factors associated with time to incident STI using Poisson regression model.
Results: We enrolled 669 pregnant women, 427 HIV-infected (64%) from Tshwane District and 242 (36%) from Cape Town (107 HIV-infected and 135 HIV-uninfected). At enrolment, median age was 30 years (IQR 26-34 years) and median gestational age was 18 weeks (IQR 13-23 weeks). Almost all women reported having vaginal sex in pregnancy (89%). At baseline the overall prevalence of any STI was 37% (n=250). The most common infection was CT (26%) followed by TV (18%), then NG (6%). Overall 11% (n=72) were infected with >1 STI, and 1% (n=7) had all 3 STI infections. Reporting symptoms was not associated with having an STI, 76% participants (n=190) had asymptomatic STI infection. STI infection at baseline was associated with younger maternal age (aOR=0.96, 95% CI=0.92-0.98), gestational age at booking (aOR=1.02, 95% CI=1.00-1.05), single relationship (aOR=1.58, 95% CI=1.13-2.21) and HIV status (aOR=1.91, 95% CI=1.07-3.39) adjusting for site and education. Of the 419 participants who were not infected with an STI at baseline, 21 had an incident STI during follow-up, with mean follow-up time of 81 days. The total incidence rate was 15 infections per 100 women-years (95% CI=9–23)
Conclusion: Our study shows high prevalence and incidence of STIs in pregnancy, demonstrating the need for STI screening and treatment in ANC to prevent infant STI and HIV transmission. More research is needed on how to move from syndromic management of STIs in South Africa which misses asymptomatic cases

Table 1: Factors associated with sexually transmitted infection prevalence at first ANC visit in pregnant women in South Africa (2016 - 2018)

	All (n, %)	Any STI (n, %)	No STI (n, %)	OR 95% CI	aOR 95% CI
Total	**669**	250 (37)	419 (63)		
Age (median, IQR) years	**30 (25 - 34)**	29 (24 - 33)	30 (26 - 34)	**0.95(0.92 - 0.98)**	**0.96(0.92 - 0.98)**
GA at booking (median, IQR) weeks	**18 (13 - 24)**	20 (14 - 24)	18 (13 - 23)	**1.03 (1.00 - 1.05)**	**1.02 (1.00 - 1.05)**
Relationship with father of child					
Married/Cohabiting	**317 (48)**	98 (39)	219 (52)	Ref	
Not married/ Non-cohabiting	**352 (52)**	151 (61)	201 (48)	**1.69 (1.23 - 2.33)**	**1.58 (1.13 - 2.21)**
HIV status					
Positive	**534 (80)**	37 (15)	98 (23)	**1.75 (1.16 - 2.66)**	**1.91 (1.07 - 3.39)**
Negative	**135 (20)**	213 (85)	321 (77)	Ref	
Any STI symptoms					
Yes	**146 (22)**	60 (24)	86 (21)	1.22 (0.84 - 1.79)	
No	**523 (78)**	190 (76)	333 (79)	Ref	

IQR, Interquartile range; n, number of participants; GA , gestational age; OR, Odds ratio; aOR, adjusted odds ratio

1041 STILLBIRTH AND PREVALENT SYPHILIS IN THE US WOMEN'S INTERAGENCY HIV STUDY, 1994-2016

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Background: Syphilis rates have increased steadily in US women since 2013 and congenital syphilis cases are at a 20-year high. Syphilis infection during pregnancy can lead to stillbirth. The purpose of this study was to test the hypothesis that prevalent syphilis infection in women with and without HIV can identify those with elevated risk of stillbirth over time.
Methods: Women age 16-49 in the multisite US WIHS cohort between 1994 and 2016 with documented syphilis testing and pregnancy outcomes were included. Prevalent syphilis was defined as a positive RPR screen with confirmatory treponemal antibody testing at baseline. Birth outcomes were self-reported with stillbirth defined as an intrauterine fetal demise after 20 weeks of gestational age. History of stillbirth and stillbirth during follow up were examined separately. Logistic regression with backward selection was used to create adjusted models using HIV status, prevalent syphilis and pre-selected covariates. Information about drug use, alcohol intake and sex were collected during biannual visits using standardized questionnaires.
Results: The study included 3577 women: 2687 (75%) with HIV and 879 (25%) without HIV. (Fig. 1) Mean age at enrollment was 36 years and prevalent syphilis was more common in women with HIV vs women without HIV (8% vs 4%; p<0.05). In total, 4.6% reported prior stillbirth and 2.2% of women with pregnancy during follow up had stillbirth. During follow-up, 4.7% of women with prevalent syphilis had a stillbirth compared to 2.0% of syphilis seronegative women. Small numbers (n=13) did not permit modeling of stillbirth during follow up. Predictors of prior stillbirth in the unadjusted model (p<0.2) included syphilis at baseline, HIV-negative status, black race, non-heterosexual identity, income <$12000, HCV, older age, lifetime sexual partners, and younger age of sexual debut. In multivariable models, prior stillbirth was associated with syphilis at baseline (OR 1.8, 95% CI 1.0-3.0), HIV-negative status (OR 1.6, 95% CI 1.1-2.2), older age (OR 1.0, 95% CI 1.0-1.1), and younger age at sexual debut (OR 0.95, 95% CI 0.91-0.99).
Conclusion: Reported stillbirth rates were four times higher among US women living with and without HIV in this study compared to the general population. Women with prevalent syphilis had higher rates of prior stillbirth and stillbirth

during follow-up. Early prenatal care and universal syphilis screening is critical for US women living with HIV or at risk of HIV.

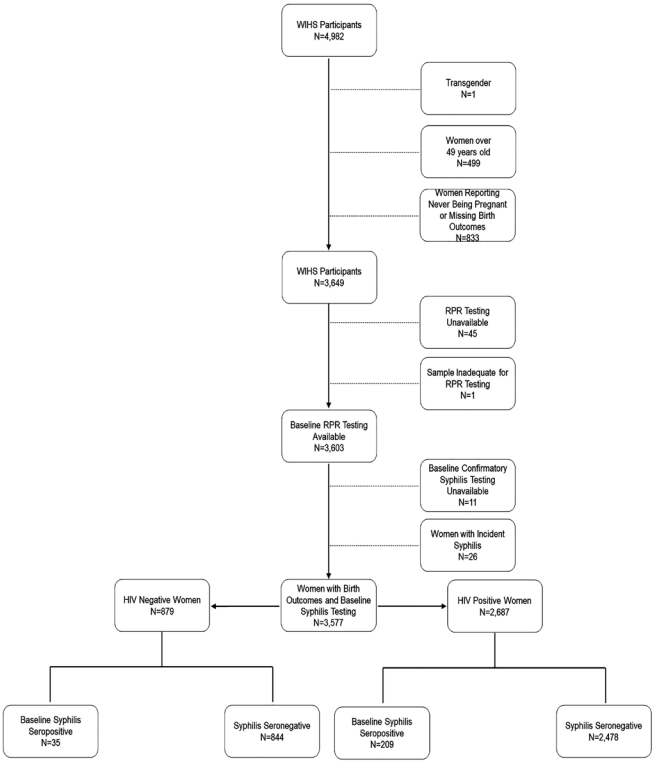


Figure 1. Exclusionary Cascade for Women <50 years old with Baseline Syphilis Test Results and Pregnancy Outcomes

1042 PREVALENCE OF MYCOPLASMA GENITALIUM AND PERINATAL OUTCOMES IN HIV+ PREGNANT WOMEN

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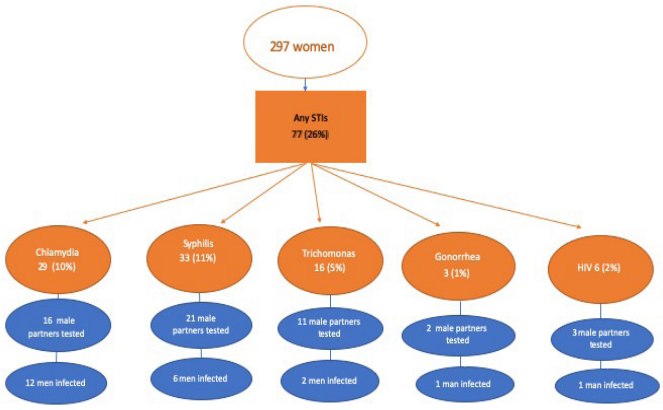
Background: The bacterium Mycoplasma genitalium (MG) is a sexually transmitted organism that may increase risk of adverse perinatal outcomes, including prematurity and pregnancy loss, but there are few data on the epidemiology of MG in HIV-infected pregnant women in sub-Saharan Africa.
Methods: We conducted two observational prospective studies of HIV+ pregnant women receiving antenatal care at two public sector facilities in Tswhane and Cape Town, South Africa. Women self-collected vulvovaginal swabs, tested using the Aptima® Mycoplasma genitalium assay (Hologic, USA). We report on prevalence (both sites) and incidence (Cape Town only) of MG, associated symptoms and perinatal outcomes in HIV+ women and using logistic regression.
Results: We enrolled 391 women: 299 from Tshwane (77%) and 92 from Cape Town (23%). Median age was 30 years (IQR=26-35) and gestational age was 18 weeks (IQR=14-23). Most women reported vaginal sex during pregnancy (89%). MG prevalence at first antenatal visit overall was 17% (n=66 of 391): 15% in Tshwane (n=44 of 299) and 24% in Cape Town (n=22 of 92, p=0.04). MG incidence was 5.7 infections per 100-woman-years (95% CI=0.96, 18.9) based on two newly acquired infections. Half of prevalent MG infections had another STI diagnosed at the same visit (50%, n=33) and were treated: Chlamydia trachomatis coinfection in 30% (n=20) and Trichomonas vaginalis in 26% (n=17). Most MG-infected women were asymptomatic (79%, n=52), but vaginal discharge was reported by 6% (n=4), vaginal bleeding in 6% (n=4), and pain with urination in 6% (n=4). Of 299 mono-MG-infected women (not diagnosed with other STIs) with pregnancy outcomes, 33 had adverse pregnancy outcomes including pre-term delivery, stillbirth, or low birth weight. In MG-infected women (n=57), 18% (n=10) of women had an adverse pregnancy outcome compared with 9.5% (n=23 of 242) of MG- women (age adjusted OR=2.03, 95% CI=0.90, 4.54).
Conclusion: We found a high prevalence and incidence of MG in HIV-infected pregnant women in this setting, and a trend towards worse perinatal outcomes in MG-infected women. MG warrants greater attention as part of the growing emphasis on STI diagnosis and treatment in HIV-infected individuals.

1043 DIAGNOSIS OF SEXUALLY TRANSMITTED INFECTIONS IN PREGNANT WOMEN AND MALE PARTNERS

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Background: Porto Alegre, Brazil has the highest rates of congenital syphilis and HIV in the country. Although studies have shown that congenital syphilis and HIV acquisition during pregnancy are associated with untreated sexual partners, male sexual partners infrequently attend clinic for diagnosis and treatment. Other treatable sexually transmitted infections (STIs) including gonorrhea (GC), trichomonas (TV), and chlamydia (GC) are associated with poor pregnancy and neonatal outcomes, but are only diagnosed by syndromic algorithms.
Methods: Starting 9/2018, we offered all pregnant women and their male sexual partners clinic-based STI testing for HIV and syphilis((via lateral flow assay rapid tests provided by the Brazilian Government) and for GC, CT and TV (via PCR-based testing provided by Gene Xpert, Sunnyvale Ca) in 6 public health clinics in Porto Alegre. Participating women and men also answer a brief survey via audio computer assisted survey instrument regarding demographics, partnerships and sexual behaviors. All infected individuals received appropriate treatment and referrals.
Results: Of 297pregnant women recruited, 26% were diagnosed with an STI including 2% with HIV, 11.5% with syphilis, 10% with CT, 1% with GC, 5.4% with TV (fig 1). All male partners were invited for evaluation, and 175 (60%) have attended clinic. In these male partners, 14.3% were diagnosed with an STI including 5.2% with syphilis, 8.1% with CT, 1.2% with GC, 1% with TV, and 0.5% with HIV. In our multivariate analysis, younger age (AOR 1.1, 95% CI 1-1.2), being non-white (AOR 2.3, 95% CI 1.3-4.2), having less education (AOR 2.1 95% CI 1.2-3.7), having a relationship <1 year (AOR 2.3 95% CI 1.2-4), were all independent predictors of women being infected with an STI. Having symptoms of an STI (ulcer, vaginal/urethral discharge) was not predictive of having a diagnosis of STI (OR 0.8, 95% CI 0.5-1.4). The concordance rate of STIs between couples where both were tested ranged from 18% for TV and 75% for CT.
Conclusion: STIs are common in pregnant women and are currently not being addressed using syndromic management. Given that most of these infections are easily treatable, they should be appropriately diagnosed and treated in both pregnant women and their sexual partners to decrease treatment failure and re-infection.

Figure 1: Schema of STI frequencies in pregnant women and their partners



1044 SEXUALLY TRANSMITTED INFECTIONS AMONG HIV SERODISCORDANT SEXUAL PARTNERS: HPTN 052

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Background: Sexually transmitted infections (STIs) remain a public health concern because of their interaction(s) with HIV. Infection with STIs among HIV-infected persons may reduce CD4+ level and increase HIV RNA in blood plasma and semen, thus increasing the potential for HIV transmission. In HIV-uninfected individuals, STIs increase genital inflammation that may enhance HIV acquisition during sex. Among both HIV-uninfected and HIV-infected individual, infection with any STI is a marker of unsafe sexual practices.

Methods: In the HPTN 052 study, STIs were evaluated in both HIV-infected index cases and their HIV-uninfected partners at enrollment and at yearly follow-up visits. Genital swabs were collected at the sites and shipped to HPTN Central Laboratory for etiology determination. In this analysis, our definition for STI was based on any infection with hepatitis B, Chlamydia trachomatis, Neisseria Gonorrhea, Syphilis, or Trichomonas vaginalis. We used log binomial regression models to identify factors associated with prevalent STIs. Generalized Estimating Equations models with Poisson link function were used to compare STI incidence between HIV-infected index cases and HIV-uninfected partners, stratified by gender.

Results: 10.4% of the participants had STIs at enrolment. The prevalence of STIs (13.6 vs 7.2) was higher in HIV-infected index cases compared to HIV-uninfected partners. Being female (prevalence ratio (PR) = 1.29; 95% CI: 1.01—1.66) or unmarried (PR = 1.61; 95% CI: 1.03—2.51) was associated with prevalent STIs. STI incidence during follow up is presented in the Table. Compared to HIV-uninfected male partners, HIV-infected female index cases had a higher risk of STI acquisition (Incidence Rate Ratio (IRR) = 2.50; 95% CI: 1.74—3.60).

Conclusion: STIs are common among HIV-serodiscordant couples. HIV-infected female index cases are more likely to acquire STIs from their HIV-uninfected partners or other partners. While we are implementing HIV prevention interventions for HIV-uninfected people, we should also intensify targeted STI prevention interventions, especially among HIV-infected women.

Table: Comparison of STI incidence between HIV-infected index cases and HIV-uninfected partners

	Gender	No. of Infections	Follow-up time (years)	Incidence Rate (/100 person years)	Unadjusted IRR (95% CI)	Adjusted IRR[†] (95% CI)
Partner	Male	89	3977.07	2.24	1.0	1.0
	Female	121	4189.72	2.89	1.26 (0.91–1.76)	0.82 (0.51–1.31)
Index	Male	58	4831.17	1.20	0.52 (0.35–0.77)	0.66 (0.40–1.07)
	Female	293	4700.98	6.23	2.70 (2.08–3.50)	2.50 (1.74–3.60)

STI: Hepatitis B or *Chlamydia trachomatis* or *Neisseria Gonorrhea* or *Trichomonas vaginalis*
IRR: Incidence rate ratio
[†] Adjusted for age, education, marital status and condom use

1045 HIV TRANSMISSION RISK FACTORS AMONG MEN LIVING WITH HIV WANTING A PREGNANCY IN UGANDA

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Background: Little is known about HIV risk behavior among men living with HIV (MLWH), who have sex with women, and want to have children. This group is of particular interest given increased HIV acquisition risks to women during periconception and pregnancy periods. We describe HIV transmission risk-factors among a cohort of MLWH planning for pregnancy in rural Uganda.

Methods: We enrolled 50 MLWH accessing HIV care and planning for pregnancy with an HIV-uninfected or unknown female partner (Nov 2018-Mar 2019). Men were offered comprehensive safer conception counseling, HIV viral load testing via GeneXpert, and STI testing for Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis via GeneXpert, and syphilis via immunochromatographic testing confirmed by rapid plasma reagin. Men also completed a questionnaire on socio-demographics, sexual and reproductive history, behavior, and relationship dynamics. We used descriptive statistics to analyze the data.

Results: Of the 50 study participants, the median age was 36.5 (IQR 32-43) years and most (N=49, 98%) were married or living as married with their pregnancy partner. Half (N=26, 52%) reported condomless sex at last sex, N=47 (94%) had HIV-uninfected partners, N=3 (6%) did not know their partners' HIV-serostatus, and N=46 (92%) disclosed their HIV-serostatus to their partner. Most men (N=48, 96%) accessed ART, and N=8 (16%) had detectable HIV-RNA (>40 copies/mL). Eleven (22%) had curable STIs, including chlamydia-6% and syphilis-16%.

Conclusion: Among MLWH planning for pregnancy in rural Uganda, most accessed ART, 92% disclosed their HIV-serostatus to their partner, and 84% were virally suppressed. We also observed a high prevalence of curable STIs, with significant repercussions for the health of men, pregnancy partners, and neonates.

Undetectable=Untransmittable (U=U) is an important concept to support men's reproductive goals. We found that comprehensive counseling and HIV-RNA testing are essential components of the success of U=U. Additionally, as Uganda and other settings consider laboratory-based STI screening, men and women planning for pregnancy should be a screening priority. Integration of comprehensive sexual and reproductive health into HIV care for men and women is critical to cultivating the health of individuals and families living with or affected by HIV.

1046 CHANGES IN SEXUAL RISK BEHAVIORS FOLLOWING AN STI DIAGNOSIS AMONG A COHORT OF MSM

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Background: Prevalence of sexually transmitted infections (STIs), rates of STI reinfections, HIV acquisition and changes in behaviors following STIs were examined in a cohort of men who have sex with men (MSM) in Los Angeles, CA.

Methods: Data from an NIH/NIDA funded longitudinal study of HIV-positive and high-risk HIV negative MSM participants enrolled from 2014 with at least one follow-up visit through May 2019 were analyzed (n=445; 1,556 study visits; 82% of parent cohort). Study visits every 6 months included computer assisted self-interviews for self-reports of behaviors and urine, pharyngeal and rectal swabs, and blood were tested for chlamydia, gonorrhea, syphilis and HIV. Changes in behaviors following an STI diagnosis were assessed using McNemar's test for paired data comparing the index visit to each of the follow-up visits. Participants not diagnosed with an STI during the study served as controls for a 'difference of difference' analysis of changes over time (difference in change in behaviors among those with no STI compared to difference in change in behaviors among those with an STI).

Results: Of the 445 participants, 50% (n=223) were diagnosed with an STI during the course of the study. At the first STI diagnosed visit, the average age was 31 with 41% identifying as Black/African American, 35% Latino/Hispanic, and 15% white. Following an STI diagnosis, significant declines were noted in substance use and sexual risk behaviors (see Table). Among the 91 HIV-negative participants with an STI, six seroconverted during the course of the study (incidence 6.6%). At 12-months post STI diagnosis, binge drinking declined from 50% to 38% (p value<.01), methamphetamine use declined form 50% to 40% (p value=0.03), and median number of sex partners declined from 5 (IQR: 2-12) to 3 (IQR: 1-10)(p value=0.02). No differences were noted overtime in the prevalence of PrEP use. The difference in difference analyses found that those in the STI group were consistently 'higher risk' when compared to those with no STIs.

Conclusion: STI reinfection in this cohort of MSM was not uncommon yet was accompanied by some decreases in risk behavior. Because HIV incidence was high and PrEP use low this suggests MSM with STIs occupy a high risk sexual network where even reductions in some risk behaviors do not protect them from ongoing high risk exposures to STIs and HIV.

Sexual risk behaviors following an STI diagnosis among young MSM participating in a cohort study in Los Angeles, CA (August 2014 – May 2019)

	Index visit with STI diagnosis(n=223)		Follow-up visit 1 post STI diagnosis (n=223)			Follow-up visit 2 post STI diagnosis (n=187)		
	n	%	n	%	P value~	n	%	P value~
Age at study visit, mean (SD)	31.3 (7.0)		32.0 (7.0)		--	32.8 (6.8)		--
Binge drinking, past 6 months	110	50.0	100	45.1	0.17	70	37.8	**<.01**
Methamphetamine use, past 6 months	109	49.6	98	44.1	**0.05**	74	40.0	**0.03**
IQR)	5 (2-12)		4 (1 - 8)		0.02	3 (1 - 10)		**0.02**
New Sex Partner, past 6 months	169	75.8	157	70.4	0.62	118	63.1	**0.01**
Concurrent Sexual Partnership, past 6 months	109	56.6	92	47.9	**0.05**	69	42.3	**<.01**
Received $/drugs/shelter for sex, past 3 months	48	22.6	36	17.3	0.07	27	15.9	**0.04**
PrEP use, past 6-months ^	37	33.6	36	39.6	0.37	29	40.9	0.18
Any STI diangosis (laboratory testing)								
Chlamydia	102	46.1	30	13.9	**<.01**	14	7.7	**<.01**
Gonorrhea	93	42.1	25	11.6	**<.01**	25	13.7	**<.01**
Infectious Syphilis	63	28.5	19	8.6	**<.01**	22	11.8	**<.01**

Abbreviations. STI=Sexually transmitted infection; SD=Standard deviation; IQR=interquartile range; PrEP=pre-exposure prophylaxis
^Among HIV-negative participants (n=91)
~ p value based on comparisons to baseline using McNemar's test for paired data

1047 VARIATION IN SYPHILIS AMONG BISEXUAL MEN AND ASSOCIATION WITH SYPHILIS IN WOMEN

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Background: The rate of syphilis among U.S. men who have sex with men (MSM) has been rising for over two decades, and rates of syphilis in women and of congenital syphilis are now also increasing. The extent to which these trends are related is uncertain. We evaluated what percentage of MSM early syphilis (ES) cases occurred in men who had both male and female partners (MSMW); how that percentage varied over time and among men of different race/ethnicity and between regions of the U.S.; and the relationship of measures of MSMW syphilis with syphilis rates in women. We hypothesized that the proportion of MSM ES cases occurring in MSMW would increase over time, would be higher in Black MSM and in the southern U.S., and that measures of syphilis morbidity in MSMW would be associated with higher syphilis (all stages) rates in women.

Methods: We solicited aggregate syphilis surveillance data from areas with the highest rates of ES in 2017, limiting the sample to states with >50 female ES cases and focusing on directly-funded cities if they contributed >50% of cases in their state. The initial sample included 22 jurisdictions, of which 16 (73%) provided data for 2013-2017. ANOVA and linear regression models were used to test hypotheses.

Results: Of 122,226 male ES cases from 2013-2017, data on gender of sex partners based on standard syphilis contact periods was available in 77.3%. The median percentages of ES cases in MSM only, men reporting sex with women only (MSW) and MSMW were 73.6 (range: 49.7-94.2), 14.9 (2.3-37.7) and 7.6 (1.2-26.4), respectively. The mean percentage of MSM ES cases occurring in MSMW was stable over time, but was higher in the South compared to all other regions, and was higher in Black men compared to White and Hispanic men ($p<0.01$, Table 1). The mean number of MSMW ES cases per 100,000 men across the five years likewise varied by region, from 5.6 in the South to 2.3 in the Midwest ($p<0.01$). The rate of syphilis in women was not associated with the percentage of MSM ES cases occurring in MSMW ($p=0.18$), but was associated with the number of MSMW cases per 100,000 men, with each 10% rise in this number yielding an estimated mean increase in syphilis among women of 0.71 per 100,000 (95% CI: 0.45-0.97).

Conclusion: Our findings are consistent with the hypothesis that syphilis rates in women are related to measures of syphilis in MSMW, and may in part explain some observed regional and racial/ethnic disparities in syphilis morbidity.

Table 1: Measures of Morbidity in MSMW with Early Syphilis by Region and Race/Ethnicity

	Mean Percent MSM with Early Syphilis who are MSMW, 2013-2017	p-value	Mean MSMW Early Syphilis Cases per 100,000 Men, 2017*	p-value
Region		<0.01		0.69
West	9.0%		4.6	
Midwest	8.0%		3.5	
Northeast	7.0%		3.8	
South	16.5%		7.0	
Race/Ethnicity		<0.01		<0.01
Black	14.7%		10.5	
White	8.8%		1.6	
Hispanic	10.9%		3.6	

Abbreviations: MSM (men who have sex with men), MSMW (men who have sex with men and women)
* Denominator includes total estimated population of men

1048 ASSOCIATION OF STI DIAGNOSIS WITH INCIDENT HIV IN A SOUTHERN STATEWIDE COHORT

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Background: Data on associations between diagnosis of sexually transmitted infections (STIs) and incident HIV beyond high-risk male subgroups is lacking. Identifying STIs associated with greatest risk of subsequent HIV could help better target HIV prevention interventions such as pre-exposure prophylaxis (PrEP). We hypothesized that some STIs as compared to others may confer a higher risk of subsequent HIV among a large statewide cohort.

Methods: Statewide surveillance data in Tennessee (TN) from 1/2013-12/2017 were extracted from the Patient Reporting Investigation Surveillance Manager (PRISM) and the electronic HIV/AIDS Reporting System (eHARS) and matched to identify reportable STI (chlamydia, gonorrhea, all stages of syphilis) and HIV diagnoses among individuals ≥13 years old. Individuals were followed from first STI diagnosis until HIV diagnosis or end of study. Cox regression with time-fixed exposure of STI at cohort entry was used to obtain adjusted hazard ratios (aHR) and associated 95% confidence intervals (CI) for incident HIV. Models accounted for age at time of STI test, sex, race, health department region, reported male-to-male sexual contact (MSM) and history of injection drug use.

Results: Over the study period, 148,632 HIV-negative individuals were diagnosed with a reportable STI in TN and followed for 503,298 person-years. Among them, 487 (0.33%) individuals were diagnosed with incident HIV following STI diagnosis, an incidence of 0.97 per 1000 person-years. Chlamydia was the most common STI at cohort entry (n=111,738, 75.3%), though a diagnosis of gonorrhea was most common at cohort entry among those with incident HIV (n=163, 34.5%). Incident HIV infection was 9 times likelier among persons with secondary syphilis as compared to chlamydia (aHR=9.2 95% CI: 6.0-14.1), controlling for demographic and behavioral risk factors. When stratified by self-identified MSM risk, secondary syphilis had greatest association of any STI with subsequent HIV infection among both MSM (aHR=3.2; 95% CI: 1.7-5.8) and non-MSM (aHR=32.8, 95% CI: 16.2-66.6) (Table).

Conclusion: Individuals ≥13 years old diagnosed with secondary syphilis were at greatest risk of subsequent HIV infection over the study period compared to those with other reportable STIs in TN, regardless of self-reported MSM risk behavior. These individuals should be especially prioritized for public health efforts and HIV prevention interventions, including PrEP, at the time of STI diagnosis.

Table. Relationship between sexually transmitted infection (STI) type and incident HIV diagnosis, stratified by self-identified sexual risk behavior of male-to-male sexual contact (MSM), among those with ≥1 reportable STI diagnosis in Tennessee, 1/1/2013-12/31/2017.

	Non-MSM (n=145,214; HIV events=287)			MSM (n=3,418; HIV events=200)		
STI Diagnosis	**HIV Incidence Rate (per 1000 p-y)**	**aHR**	**(95% CI)**	**HIV Incidence Rate (per 1000 p-y)**	**aHR**	**(95% CI)**
Chlamydia	0.29	Ref.	Ref.	11.97	Ref.	Ref.
Gonorrhea	2.58	**7.4**	5.5 - 9.9	20.10	1.7	0.1 - 2.8
Syphilis, Primary	4.18	**10.4**	1.4 - 75.7	27.21	2.4	1.0 - 5.7
Syphilis, Secondary	14.31	**32.8**	16.2 - 66.6	46.42	**3.2**	1.7 - 5.8
Syphilis, Early Latent	7.69	**15.2**	7.2 - 32.4	34.54	**2.5**	1.3 - 4.7
Syphilis, Late Latent	5.81	**14.60**	8.5 - 25.0	28.66	**2.4**	1.3 - 4.6
Syphilis, Unknown Duration	7.84	**20.3**	5.0 - 83.1	34.54	2.7	0.8 - 9.3
STI Coinfection (Any)	1.29	**4.1**	2.8 - 5.9	33.51	**2.5**	1.4 - 4.3

p-y: person-years
aHR: adjusted Hazard Ratio
CI: confidence interval
Ref.: reference category
MSM: men who have sex with men
Bold estimates have $p<0.05$

1049 THE BURDEN OF STIs IN AN HIV HYPERENDEMIC COMMUNITY WITH HIGH ART COVERAGE

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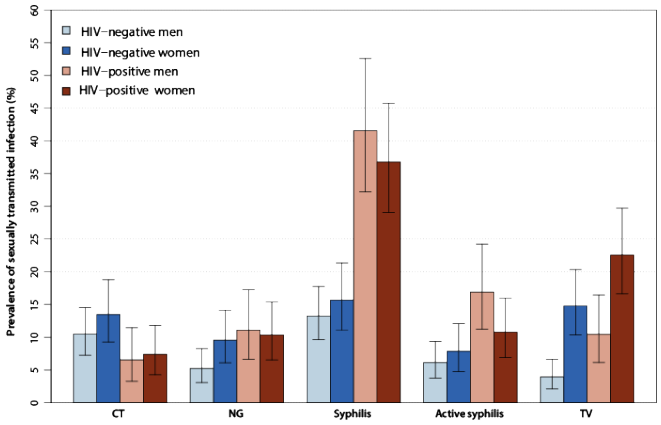
Background: Population-level data on sexually transmitted infections (STIs) are rare in sub-Saharan Africa. We measured the prevalence of HIV and five STIs following the roll-out of voluntary medical male circumcision and universal HIV

treatment programs in an HIV hyperendemic Lake Victoria fishing community in Uganda.

Methods: We measured prevalence of Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG), Trichomonas vaginalis (TV), syphilis, and herpes simplex virus type 2 (HSV-2) among all consenting adults aged 15-49 participating in the Rakai Community Cohort Study between May and July 2019. CT and NG testing was conducted using nucleic acid amplification testing (Abbott RealTime CT/NG assay). Point-of-care testing was done for TV (OSOM Trichomonas) and syphilis (non-treponemal SDBioline rapid syphilis tests), with subsequent laboratory confirmation of syphilis titers using a rapid plasma regain (RPR) test (Cypress Diagnostics). Participants were classified as having active syphilis infection if their RPR titers were ≥1:8. HSV-2 testing was performed with the Kalon HSV-2 IgG ELISA. Associations of STIs with ART use and male circumcision were estimated using Poisson regression.

Results: There were 898 participants, including 435 women (48%), of whom 9% (n=47) were pregnant. There were 398 (40%) who were HIV seropositive. Coverage of ART was 78% (n=301) among HIV seropositive persons and 57% of men (n=264) were circumcised. Overall, there was 8.5% prevalence of NG (n=76), 9.9% CT (n=88), and 12% TV (n=108) (Figure). Syphilis reactivity was 24% (n=216), with 9.4% (n=85) of the total population having titers indicative of active syphilis infection, including 6% of pregnant women (n=3). HSV-2 antibodies were detected in 70% of the population (n=626), including 94% of HIV-positive persons. While prevalence of at least one STI (NG, TV, CT, or active syphilis) was 1.57 fold higher among HIV-positive versus HIV negative persons (34 vs 21% ; 95%CI: 1.20-2.05), there was no differences in STI prevalence by ART status (Prevalence risk ratio [PRR]=0.95; 95%CI: 0.55-1.78) or male circumcision status among all men (PRR=0.93; 95%CI: 0.62-1.38).

Conclusion: Despite high coverage of HIV treatment and prevention interventions, the burden of STIs remains extremely high in Lake Victoria fishing communities. There is an urgent need to integrate STI diagnostic testing and treatment with HIV services in these high HIV burdened settings.



1050 A POINT-OF-CARE ASSAY FOR DIAGNOSIS OF NEUROSYPHILIS

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Background: Neurosyphilis (NS) can cause severe disability. Globally, the burden of NS remains high, and the ability to diagnose it in resource limited settings (RLS) is limited. We tested whether a point of care test originally developed to detect serum treponemal and nontreponemal antibodies could be used on cerebrospinal fluid (CSF) to diagnose NS.

Methods: Participant characteristics (table) and ROC curve (figure) are shown; cases and controls were well matched. We detected CSF treponemal antibodies in 31/36 cases and 5/36 controls, and CSF nontreponemal antibodies in 27/36 cases and 1/36 controls. This resulted in sensitivity of 86% and specificity of 86% for the treponemal test and sensitivity of 81% and specificity of 97% for the nontreponemal test. Treponemal test false negatives and true positives had a median sRPR of 128(IQ 128-384) vs 256(IQ 64-1024), median CSF-VDRL titer of 2(IQ 1-5) vs 4(IQ 2-8) and median CSF WBC 58(IQ 28-213) vs 77(IQ 49-160), respectively. Nontreponemal false negatives and true positives had median sRPR of 128(IQ 64-256) vs 256(IQ 128-1024), median CSF-VDRL 2(IQ 1-2) vs 4(IQ 2-8), and median CSF WBC 71(IQ 29-58) vs 76(IQ 49-131), respectively.

Results: Participant characteristics are shown (table); cases and controls were well matched. The AUC was .89(95%CI .81-.97) for the treponemal test and .91(95%CI .84-.99) for the nontreponemal test. We detected CSF treponemal antibodies in 31/36 cases and 5/36 controls, and CSF nontreponemal antibodies in 27/36 cases and 1/36 controls. This resulted in sensitivity of 86% and specificity of 86% for the treponemal test and sensitivity of 81% and specificity of 97% for the nontreponemal test. Treponemal test false negatives and true positives had a median sRPR of 128(IQ 128-384) vs 256(IQ 64-1024), median CSF-VDRL titer of 2(IQ 1-5) vs 4(IQ 2-8) and median CSF WBC 58(IQ 28-213) vs 77(IQ 49-160), respectively. Nontreponemal false negatives and true positives had a median sRPR of 128(IQ 64-256) vs 256(IQ 128-1024), median CSF-VDRL 2(IQ 1-2) vs 4(IQ 2-8), and median CSF WBC 71(IQ 29-58) vs 76(IQ 49-131), respectively

Conclusion: The diagnosis of NS in RLS is challenging due to the need for modern laboratory facilities, specialized equipment and trained technicians. The DPP® assay can be an option in the point-of-care diagnosis of NS. Further studies should examine its performance in RLS

Characteristic	NS Cases	Syphilis Controls
	Number (percent) or Median (IQR)	
Men	35 (97%)	36 (100%)
Age	39 (33-47)	39 (30-44)
PLWH	26 (72%)	27 (75%)
Syphilis stage*		
1	1	1
2	15	17
3	10	12
4	10	6
Serum RPR titer	1:256 (1:80-1:512)	1:128 (1:64-1:256)
CSF WBCs	58 (45-124)	2 (0-4)
CSF-VDRL titer	2 (2-8)	0

*1: Primary; 2: Secondary; 3: Early Latent; 4: Late Latent

1051 IDENTIFYING AN HIV AND NEURO/OCULAR SYPHILIS CLUSTER IN VERMONT

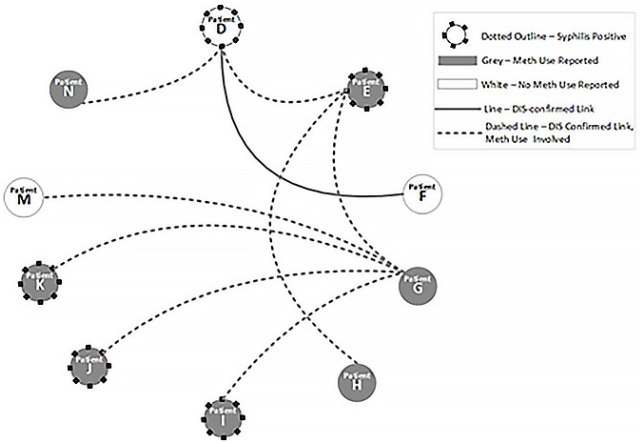
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Background: Since 2001, rates of syphilis in the U.S. have more than doubled, largely attributable to an increase among men who have sex with men (MSM). It is recognized that syphilis facilitates HIV acquisition, likely through a combination of biological and behavioral risk factors. National interest in neuro/ocular syphilis emerged following a cluster of cases in 2014-2015 in Seattle, Washington and San Francisco, California, with the majority of cases occurring among HIV-infected MSM. Our study characterizes a cluster of neuro/ocular syphilis cases among HIV-infected individuals in Vermont in 2017-2018.

Methods: All HIV and syphilis diagnostic test results are reported to the Vermont Department of Health (VDH). VDH Disease Intervention Specialists (DISs) conduct interviews with newly diagnosed cases of HIV and syphilis, outreach to all sexual contacts of these cases, and pursue sexual networking analyses. Descriptive statistics were used to summarize population characteristics. Fishers-exact and independent t-tests were used to compare cluster versus non-cluster groups.

Results: Between January 1, 2017 and December 31, 2018, 38 newly diagnosed cases of HIV were identified in Vermont. In this cohort, the mean age was 38.2 years and 82% were white, 79% were male, 79% were MSM, 29% had a positive syphilis serology with 11% classified as neuro/ocular syphilis, 21% reported methamphetamine use prior to sex in the past six months, 47% had HIV viral loads > 100,000 copies/mL, and 47% had CD4 cell counts <200/µL. Sexual networking analysis revealed a cluster of ten cases of HIV infection (four diagnosed in rural Vermont counties), of whom seven reported methamphetamine use, nine had viral loads >100,000 copies/mL, seven had CD4 cell counts <200/µL and four had neuro/ocular syphilis. Subjects in the cluster were more likely to have higher HIV viral loads at diagnosis versus those not in the cluster (90% with viral loads > 100,000 copies/mL vs. 33%, p=0.015) There were no other statistically significant differences in characteristics between the two groups.

Conclusion: This investigation of newly infected cases of HIV in the rural state of Vermont led to identification of a cluster of cases that appeared more likely to have advanced HIV disease (90% with viral loads > 100,000 copies/mL at diagnosis), and 30% had neuro/ocular syphilis.



1052 GYRASE A SERINE 91 GENOTYPING PREDICTS GONORRHEA CIPROFLOXACIN TREATMENT OUTCOME

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Background: Neisseria (N). gonorrhoeae infections are rapidly increasing and among the most common co-infections in human immunodeficiency virus-infected patients. With great public health concern, there have been cases of N. gonorrhoeae resistant to all available antibiotics. In order to slow the continued emergence of antimicrobial resistance, new treatment strategies are urgently needed. The use of resistance-guided therapy—treatment based on the antimicrobial susceptibility of the infection—is one such promising strategy. We developed an assay to predict the susceptibility of N. gonorrhoeae to ciprofloxacin based on the gyrase A (gyrA) serine 91 codon, a locus previously shown to be highly predictive of in vitro resistance. In this study, we tested the efficacy of that assay in predicting clinical outcomes.
Methods: We conducted a single arm multi-site clinical study of the efficacy of ciprofloxacin 500 mg by mouth for the treatment of wild-type gyrase A N. gonorrhoeae infections. We recruited and enrolled study participants from sexually transmitted disease clinics across the United States. We determined N. gonorrhoeae gyrA serine 91 wild type status using a previously Clinical Laboratory Improvement Act-verified laboratory-developed PCR assay with high-resolution melt analysis. We report outcomes in participants who were N. gonorrhoeae culture positive for gyrA serine 91 wild type infection at enrollment and had culture assessment 5-10 days after treatment. We also report treatment outcomes in cases with non-wild type gyrA serine 91 N. gonorrhoeae infections at enrollment.
Results: Among 106 patients with 117 urogenital, rectal or pharyngeal infections across 6 clinics, the frequency of microbiological cure was 100% (95% one-sided confidence interval 97.5-100%). The cure frequency did not vary by anatomic site of infection, sex or age of the study participant. Two cases with mutated gyrase A N. gonorrhoeae infection failed therapy (0% cure).
Conclusion: GyrA serine 91 N. gonorrhoeae genotyping was highly predictive of clinical outcomes in patients with gonorrhea treated with ciprofloxacin.

1053 IMPROVING DIAGNOSIS OF CT/NG AMONG PrEP USERS WITH MULTIPLE SITE SCREENING

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Background: PrEP users are under high risk of bacterial sexually transmitted infections. Sensitive and timely diagnostic strategies are crucial to allow rapid prescription of antimicrobial treatment. Several studies have shown that Chlamydia trachomatis (Ct) and Neisseria gonorrhea (Ng) screening at multiple anatomic sites may improve the diagnostic yield in high-risk populations.
Methods: In this retrospective cohort study, HIV-uninfected patients referred for PrEP were followed with periodic serologic testing of Syphilis (every 3 months) and culture/molecular testing of Ct/Ng (approximately every 6 months in asymptomatic patients; as needed for those with symptoms). We describe the baseline prevalence of Syphilis, Ct and Ng as well as the cumulative incidence of each infection at 6 and 12 months after PrEP initiation using Kaplan-Meier survival analysis. We also describe the frequency and percentage of Ct/Ng detection per anatomical site and calculate the percentage of missed diagnosis if molecular testing for Ct/Ng were applied only for symptomatic patients, or if screening is done in urine only.
Results: 386 PrEP users under follow-up in a single institution in Sao Paulo, Brazil, were included in the study. Most (94%) were men who have sex with men, with median age of 31 years old (interquartile range [IQR] 27-37). At baseline, active syphilis was detected in 23 participants (7%; 3 symptomatic and 20 latent or unknown stage), whereas Ct and Ng were detected in 9 patients each (8% and 9%) of whom only one Ng-positive patient had symptoms. After a median follow-up of 278 days (IQR 180-370), incident syphilis was detected in 24 PrEP users, with a cumulative incidence of 12% at 12 months; of those, 10 were symptomatic (3 in primary stage and 7 in secondary stage). Ct and Ng were detected in 13 patients and 10 patients, with a cumulative incidence of 12% and 10% at 12 months respectively. Had Ct/Ng molecular testing been used for symptomatic patients only, 15/16 (94%, 95% CI 70-100) cases would have been missed at baseline and 18/20 (90%; 95% CI 68-99) incident cases would have been missed. Had screening been performed in urine only, 12/16 (75%; 95%CI 48-93) cases would have been missed at baseline and 14/20 (70%; 95%CI 46-88) incident cases would have been missed.
Conclusion: Multiple anatomic site sampling is a powerful strategy to increment the diagnostic sensitivity of Ct/Ng molecular screening. This approach should be applied in high-risk PrEP users as to improve the capacity of accurate diagnosis and treatment.

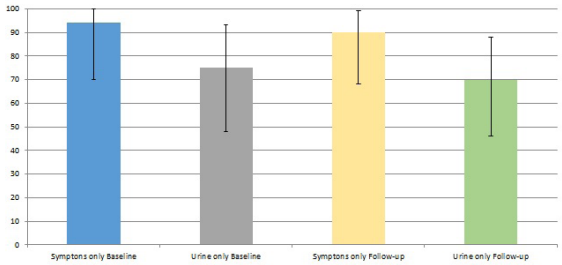


Figure 1: Percentage of missed CT/NG diagnosis at baseline and follow-up if molecular testing were applied to symptomatic patients only (blue and yellow bars) or tested in urine only (grey and green bars). Whiskers represent 95% confidence intervals

1054 THE PERFORMANCE OF POOLED 3-ANATOMIC-SITE CHLAMYDIA AND GONORRHEA TESTING

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Background: While molecular testing for Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG) is much more sensitive than traditional culture and immunostaining approaches, the cost can be more than 20 times higher per test. These costs are amplified further, as optimal testing requires specimens from 3 anatomic sites (rectal, pharyngeal and urogenital [urine or vaginal swab]), tested individually. While individual testing of samples from all three sites is currently recommended, pooled testing may offer a cost-saving alternative. We assessed the performance of routine versus pooled 3 anatomic site testing (1 test per person versus 3) for CT and NG.
Methods: Using the Xpert® CT/NG assay (Cepheid, Sunnyvale, CA) we tested urine, rectal and pharyngeal swabs for CT and NG. Remnant specimens (0.34 mL from each anatomic site specimen) were combined to perform a single 'pooled' test. We calculated positive and negative percent agreement between the pooled testing results with the single specimen Xpert CT/NG test results as the reference.
Results: We conducted 403 pooled tests. Of those, 366 (90.8%) gave valid results. Of the 37 pooled tests for which a valid result was not obtained, 3 were positive for CT, 3 were positive for NG and 1 was positive for both CT and NG on individual tests. The CT positive and negative percent agreement were 95.8% (95% CI: 85.7%, 99.5%) and 99.1% (97.3%, 99.8%), respectively. The NG positive and negative percent agreement were 96.9% (95% CI: 83.8%, 99.9%) and 99.7% (95% CI: 98.3%, 100%), respectively. Pooled testing identified 3 CT and 1 NG infections that were negative at all anatomic sites by individual testing.
Conclusion: Three-site pooled CT and NG testing performs similarly to single anatomic site testing among tests providing a valid result. Optimizing the

pooled testing protocol (e.g. using a single elution buffer for all 3 swabs) may further enhance this approach. In addition, future studies should evaluate pooled testing with multiple reference tests to allow for a more precise infection status determination. Future cost analyses should evaluate the cost effectiveness of pooled three-site testing to determine if such a strategy improves the feasibility and accessibility of molecular STI testing in both domestic and international settings.

1055 NO EVIDENCE OF CLINICAL IMPACT OF STIs ON SEMINAL HIV BURDEN DURING SUCCESSFUL ART

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Background: Sexually transmitted infections (STI) are known to increase the HIV shedding in semen of ART naïve patients. Their role in influencing the seminal compartment despite peripheral undetectable HIV-RNA is still unclear.
Methods: This ongoing study includes 25 HIV-1 patients (pts) with undetectable viremia (<20cps/ml) for at least 1year. At enrolment, 10 were STI-positive (cases:7syphilis, 1M.genitalium, 1U.urealyticum urethritis, 1syphilis/C. trachomatis/U.urealyticum co-infection), while 15 were STI-negative. HIV-DNA and residual viremia (detection limits of 32cps/10^6 CD4+ and 2 cps/ml, respectively) in both blood and seminal compartments by home-made protocols using ddPCR have been analyzed.
Results: Pts are mainly MSM (80%), with a median(IQR) age of 37(32-47) years, and median(IQR) CD4+ 772(578-1037) cells/µL. 20 pts were on NRTI-based regimen (3rd drug:11INSTI; 5NNRTI; 4PI), 5 pts were on a dual regimen (2DR):3DRV/c+3TC, 1DRV/r+RAL, 1ETR+RAL. No baseline differences were found between cases and controls. Peripheral HIV-DNA was detectable in 20 pts (80%) with a median(IQR) of 612(154-2571)cps/10^6CD4+ (table1). Differently, seminal HIV-DNA was detectable only in 3 pts (12%) 1 case and 2 controls, always with a quantification <32cps/10^6CD4+. Peripheral HIV-RNA was detectable in 16 pts (64%) with a median(IQR) of 2.7(<2.0-4.2) cps/ml, whereas 14(56%) pts had seminal detectable HIV-RNA levels (median[IQR] 3.9[2.1-7.9] cps/ml). In both compartments residual RNA levels never exceeded the 20 cps/ml with the exception of 1 2DR-control (congenital infection) who had 39 cps/ml in the seminal compartment. No differences were found when HIV-DNA and -RNA values in both compartments were compared between cases and controls (p>0.13). However, 6 out of 25pts (24%) showed a seminal HIV-RNA detectability despite the peripheral HIV-RNA undetectability. This discordance was more frequently observed in cases (40%) respect to controls (13%) (p=0.17). 7STI cases were analyzed also after antibiotic treatment and resolution. Among these, seminal HIV-RNA was maintained undetectable or showed a reduction in 6 pts (86%), while only one (16.7%) experienced an increase to 12.1cps/ml.
Conclusion: These preliminary data show that successful combined ART (3DR or 2DR) avoids the presence of HIV-DNA in the seminal cells in the majority of pts,

Table 1. Residual viremia and Total HIV-DNA in peripheral and seminal compartments.

	Residual viremia		Total HIV-DNA	
ID	Blood plasma copies/mL	Seminal Plasma copies/mL	PBMCs copies/10^6CD4+T	Seminal cells copies/10^6cells
1 STI triple	TND	3.45	4547	TND
2 STI triple	TND	TND	612	TND
3 STI triple	<2	TND	TND	TND
4 STI triple	4.40	4.38	1614	TND
5 STI triple	<2	2.35	135	TND
6 STI triple	TND	12.24	763	TND
7 STI triple	3.07	TND	745	<32
8 STI triple	<2	5.49	16753	TND
9 STI triple	TND	TND	305	TND
10 STI triple	TND	TND	TND	TND
1 Control triple	7.47	6.12	6275	TND
2 Control triple	<2	TND	3433	TND
3 Control triple	4.00	TND	1386	TND
4 Control triple	TND	8.47	2581	TND
5 Control triple	<2	TND	254	TND
6 Control triple	TND	TND	TND	TND
7 Control triple	TND	TND	2560	TND
8 Control triple	2.80	TND	1157	TND
9 Control triple	2.67	10.35	417	TND
10 Control triple	TND	<2	4399	<32
11 Control dual	2.7	<2	TND	TND
12 Control dual	2.7	<2	172	9
13 Control dual	10.4	39.2	456	TND
14 Control dual	5.7	<2	TND	TND
15 Control dual	<2	3.5	512	TND

TND: target not detected

1056 RISK OF PELVIC INFLAMMATORY DISEASE WITH CONTRACEPTIVE METHOD USE IN THE ECHO TRIAL

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Background: Concerns regarding intrauterine devices (IUDs) and the risk of pelvic inflammatory disease (PID) have been debated for decades. Few data are available from high sexually transmitted infections (STI) settings or have compared PID risk with IUDs with use of other contraceptives. Additionally, previous research is limited by inconsistent definitions, partial or passive follow-up, self-report, and non-randomized comparisons.
Methods: We analyzed data from the ECHO Trial, which assessed HIV risk in 7,829 women from 12 sites in sub-Saharan Africa randomized to intramuscular depot medroxyprogesterone acetate (DMPA-IM), levonorgestrel (LNG) implant, or copper IUD. Women were tested for gonorrhea and chlamydia (NG/CT) at screening. At enrollment, IUDs were inserted without waiting for NG/CT results, but were delayed for at least 7 days after treatment when mucopurulent discharge or cervicitis were seen. Asymptomatic women testing positive for NG/CT were treated once results were available. All participants returned at 1 month for scheduled follow-up visits, and IUD users had routine pelvic exams. Participants in any group who reported abdominal/pelvic pain at any time were examined and treated for presumptive PID based on CDC minimal criteria (abdominal/pelvic pain and either cervical motion, uterine, or adnexal tenderness). We assessed PID incidence over time and compared PID incidence by arm. We conducted sensitivity analyses using specific criteria for PID (minimum criteria plus mucopurulent discharge, friable cervix, or baseline NG/CT).
Results: This analysis included 7720 women; median age was 23 years, 24.8 % reported condomless sex in the last 3 months, and 20.9 % had NG/CT at baseline. We diagnosed 405 cases of presumptive PID. PID incidence per 100 woman-years was 1.5, 9.3, and 2.0 among women using DMPA-IM, copper IUD, and LNG implant, respectively. Among copper IUD users, PID rates were higher in the first 30 days after insertion, particularly among women with baseline NG/CT.
Conclusion: Our trial found higher rates of presumptive PID among copper IUD users than previously reported, and higher rates among IUD users compared with women using DMPA-IM or LNG implant. Further analyses will evaluate possible diagnostic bias among copper IUD users and the risk of PID after HIV seroconversion.

Table. PID incidence by study arm

		N events	Woman-years	Incidence per 100 woman-years [95% CI]	HR (95% CI)
DMPA-IM (n = 2598)		45	2990	1.5 (1.1, 2.0)	
Copper IUD (n = 2519)	Overall	293	3166	9.3 (8.2, 10.4)	
	≤30 days after insertion	32	206	15.6 (10.6, 22.0)	
	>30 days after insertion	261	2960	8.8 (7.8, 10.0)	
LNG Implant (n = 2603)		67	3355	2.0 (1.5, 2.5)	
Total (n=7720)		405	9510	4.3 (3.9, 4.7)	
Copper IUD vs. LNG Implant					4.7 (3.6, 6.1)
Copper IUD vs. DMPA-IM					6.2 (4.6, 8.6)
DMPA-IM vs. LNG Implant					0.7 (0.5, 1.1)

1057 VALIDATING INCIDENT PREGNANCIES AMONG WOMEN USING CONTRACEPTIVES AND ANTIRETROVIRALS

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Background: A prior cohort study from Kenya demonstrated reduced effectiveness of contraceptive implants when used in combination with efavirenz-containing antiretroviral therapy (ART). To further validate this finding, we conducted two-phase random sampling with an expanded cohort of women living with HIV (WLHIV) using data from the East Africa International Epidemiology Databases to Evaluate AIDS.
Methods: We conducted a random sampling study of WLHIV, from 15 to 45 years of age enrolled in HIV care in western Kenya between January 2011 and December 2015, to validate the exposure of a combination of contraceptive method and ART regimen and primary outcome of incident pregnancy. We generated a cohort of WLHIV utilizing electronic medical records, and then conducted detailed file reviews for a stratified random subset of the women. We used multivariate Poisson models to compare pregnancy rates among women using different contraceptive and ART combinations, accounting for the second phase sampling with generalized raking inverse probability weighted methods. Lastly, we conducted phone interviews with a further subset of women sampled for the file reviews to compare self-reports against medical records.
Results: 85,819 women contributed 172,378 person-years (p-y) to this analysis. We conducted file reviews for 4,987 women (contributing 16,991 p-y) and phone interviews for 1,275 women (contributing 5,775 p-y). Based on data from the file review, among women using implants in the overall cohort, the pregnancy incidence was 1.1 and 3.3 per 100 p-y for nevirapine- and efavirenz-containing ART users, respectively (incidence rate ratio [IRR] 3.1, 95% CI 2.1-4.5; Table). Among the subset of women using implants with whom we conducted phone interviews, the pregnancy incidence was 2.4 and 9.0 per 100 p-y for nevirapine- and efavirenz-containing ART users, respectively (IRR 3.8, 95% CI 2.0-7.2).
Conclusion: Using probabilistic subsampling, we confirm the prior finding that contraceptive implant effectiveness is reduced with concomitant efavirenz use. Dolutegravir-containing ART, which is not anticipated to reduce implant effectiveness, should be considered for WLHIV already using or interested in contraceptive implants. Self-reports largely corroborated medical records, though the higher rates may be due to recall bias. Our robust and novel validation methodology also highlights a way forward for other studies conducted with electronic medical records.

Table: Pregnancy incidence per 100 person-years, by combinations of contraceptive method and ART regimens

	Number of pregnancies	Person-years (p-y) of follow-up	Pregnancy rate per 100 p-y (95% CI)*	Pregnancy rate ratio (95% CI)*
Implant				
Nevirapine	154	5651	1.1 (0.8, 1.5)	Ref.
Efavirenz	196	3270	3.3 (2.6, 4.4)	3.1 (2.1, 4.5)
Protease-inhibitor	20	762	1.3 (0.7, 2.6)	1.2 (0.6, 2.6)
No ART	110	2364	1.6 (1.0, 2.7)	1.5 (0.9, 2.6)
Injectables				
Nevirapine	964	10901	3.1 (2.1, 4.5)	Ref.
Efavirenz	535	5047	4.2 (3.0, 5.9)	1.4 (0.9, 2.1)
Protease-inhibitor	143	1476	4.2 (2.6, 6.8)	1.4 (0.8, 2.4)
No ART	558	5457	5.0 (3.6, 7.1)	1.6 (1.1, 2.5)
No contraceptive method				
Nevirapine	2152	40418	2.2 (1.6, 3.2)	Ref.
Efavirenz	1439	22973	3.6 (2.1, 6.1)	1.6 (0.9, 3.1)
Protease-inhibitor	288	4828	2.0 (0.8, 4.7)	0.9 (0.3, 2.3)
No ART	1343	15209	2.0 (1.3, 3.1)	0.9 (0.5, 1.6)

* Modelled via generalized raking inverse probability weighting, and adjusted for program site and an interaction between contraceptive method and ART regimen.

1058 AN EVALUATION OF AN ENHANCED MODEL OF FP/HIV SERVICE INTEGRATION IN LUSAKA, ZAMBIA

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Background: Women living with HIV (WLHIV) in sub-Saharan Africa continue to experience high rates of unplanned pregnancies. Ready access to family planning (FP) within HIV treatment programs allows women to make informed fertility choices. We implemented an enhanced model of integrating FP and HIV services at 6 health facilities in Lusaka, Zambia aimed at increasing contraceptive uptake among WLHIV wanting to avoid pregnancy and to improve safer conception counseling for those desiring a pregnancy.
Methods: The model included: training HIV clinic staff in FP service delivery; offering a full range of FP methods within the HIV clinic; improving FP documentation within HIV monitoring systems; and introducing facilitated referral to community-based distributors to support FP use between HIV treatment visits. For the evaluation, systematic, independent samples of WLHIV aged ≥16 years were interviewed pre and post-intervention about their fertility desires and FP use, and clinical data was abstracted from their medical charts. Differences between pre and post-intervention participants were tested using Pearson Chi-square tests. Unadjusted and adjusted logistic regression models were used to examine differences in self-reported FP uptake between the two time periods.
Results: A total of 629 WLHIV were interviewed pre-intervention and 684 post-intervention. During the pre-intervention period, only 38% of women not desiring a pregnancy reported currently using an effective FP method compared to 49% post-intervention (p=.003, Table 1). Uptake by method at the two time points was: pills (10% vs. 8%, p>.05), injectables (15% vs. 25%, p<.0001), implants (5% vs. 8%, p>.05), and intrauterine devices (IUDs, 1% vs. 1%, p>.05). The percent of women reporting dual method use increased from 9% to 18% (P=.0003); while, unmet need for FP decreased from 59% to 46% (P=.0003). Among women wanting to get pregnant, receipt of safer pregnancy counseling increased from 27% to 39%. The total intervention cost was estimated at $83,293 (2018 USD) over the 12-month period including labor (40%), supplies (26%), training (14%) and administration (20%).
model of FP/HIV integration was associated with a significant increase in the number of WLHIV reporting use of an effective FP method and a met need for FP. These results support continued efforts to integrate FP and HIV services to improve women's access to these services.

Table 1. Comparison of Key Outcome Variables Before and After Integration of Family Planning within HIV Treatment Services at Six Health Facilities in Lusaka, Zambia

Variable	Pre-intervention n (%)	Post-intervention n (%)	Unadjusted p-value	Adjusted p-value*
Women Not Desiring a Pregnancy	N=379	N=402		
Use of highly effective method	133 (38)	195 (49)	.0020	.0025
Use of dual methods[1]	30 (9)	73 (18)	.0001	.0003
Unmet need for FP[2]	210 (59)	184 (46)	.0003	.0003
Women Desiring a Pregnancy	N=210	N=249		
Discussed safer pregnancy	56 (27)	97 (39)	.0093	N/A*

*Adjusted model includes facility, age group, and time since diagnosis. The adjusted model could not be fit for discussion of safer pregnancy due to insufficient data.
[1]Defined as condom use plus another effective method of contraception.
[2]Defined as not desiring a pregnancy in the next six months but not currently using any FP method to prevent becoming pregnant

1059 A COMBINED ESTROGEN/PROGESTIN VAGINAL RING IMPROVES VAGINAL MICROBIAL COMMUNITIES

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Background: ACTG study A5316 found that during contraceptive intravaginal ring (IVR) use over 3 weeks, efavirenz-based ART (EFV) significantly decreased both ethinyl estradiol (EE) and etonogestrel (ENG) plasma exposure, while atazanavir/ritonavir-based ART (ATV) decreased EE, yet increased ENG. We explored the role of the IVR on vaginal microbial communities and vaginal small chain fatty acids (SCFA) as well as the role of the vaginal microbes/SCFA on hormone concentrations.
Methods: Of the 74 participants (25 ART Naïve; 25 EFV, 24 ATV), 71 had 16S rRNA sequencing of the V4 region on vaginal swabs at weeks 0 (pre-IVR insertion), 1, 2, 3, and 4 (1 week post-IVR removal); and 73 had vaginal aspirate SCFAs measured by Metabolon® at weeks 0, 1 or 2, and 4. Sequences were filtered and taxa assigned using DADA2, species using SPINGO with SILVA database, and Lactobacillus using BLAST. Negative binomial and linear regression models identified differentially abundant microbiome and SCFA features, respectively. Spearman correlation assessed relationships between microbiome relative abundance and weekly EE/ENG concentrations.
Results: At baseline, microbial communities of participants could be robustly classified as L. crispatus¬-dominant (Community State Type (CST) I, n=8), L. gasseri-dominant (CST II, n=2), L. iners-dominant (CST III, n=20), or mixed anaerobic communities (CST IV, n=41). Start of IVR therapy was associated with an increased probability of transition into Lactobacillus-dominant community types (OR=3.39, CI=0.36-32.15), Fisher's exact test, p<0.001). ENG levels were negatively correlated with abundance of Prevotella timonensis.

After IVR removal, an increased probability of transition into CST IV (OR=7.75, CI=1.56-38.49), p<0.001) was observed, with a decrease in lactic acid levels (p<0.001). Negative binomial modeling of the most abundant taxa between week 3 (during IVR use) and 4 (1 week after IVR removal) showed significant increases in Gardnerella vaginalis, unclassified Prevotella sp., and P. timonensis, and decreases in L. crispatus.
Conclusion: The shift in vaginal microbial communities from Lactobacillus-dominant types (CST I-III) to CST IV following removal of the ENG/EE IVR is concerning. Some women had a favorable response to the IVR, which may suggest this IVR is a therapeutic option for women with bacterial vaginosis. Further investigation is needed to fully assess interactions and safety of vaginal hormonal contraception in women with HIV-1.

1060 CONTRACEPTIVE USE INDUCES DURABLE SHIFTS IN THE FEMALE GENITAL-TRACT MICROBIOTA

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Background: Vaginal bacterial microbiota modulate genital immunity and susceptibility to HIV and other sexually transmitted pathogens. However, it is unclear how contraceptive use affects the composition and dynamics of these communities.
Methods: Within the ECHO trial, designed to compare the relative HIV-1 incidence among women randomized to copper intrauterine device (Cu-IUD), levonorgesterol implant (LNG-implant), or DMPA-IM, this nested three-site (Cape Town, Johannesburg, Kisumu) sub-study aimed to evaluate the impact of these contraceptives on genital tract microbiota. 201 were randomly selected from among the 430 in the sub-study for analyses of samples collected at enrollment (pre-contraceptive initiation), 1-month, and 6-months post-contraceptive initiation. For all samples, the 16S rRNA gene was amplified and sequenced from fluid collected via lateral vaginal wall swabs.
Results: Baseline Shannon diversity was elevated in women randomized to LNG-implant compared to DMPA-IM, but not Cu-IUD. After 1 month of use, there were no differences in Shannon diversity between randomization arms. However, after 6 months of use, there were significant differences in Shannon diversity between all arms, with women randomized to DMPA-IM displaying the lowest bacterial diversity (mean 0.583), followed by LNG-implant (mean 1.06) and Cu-IUD (mean 1.64). Lactobacillus abundance was significantly reduced between baseline and 6-months post-contraceptive initiation for women randomized to Cu-IUD, which was concurrent with a significant increase in taxa associated with Bacterial Vaginosis. Conversely, women who were randomized to DMPA-IM exhibited significant reductions in the abundance of dysbiotic Prevotella taxa. Significant differences in beta-diversity between randomization arms suggested that community-wide alterations persisted at both 1-month (p=0.034), and 6-months post contraceptive initiation (p=0.004), with women assigned to Cu-IUD transitioning to more diverse bacterial communities.
Conclusion: These are the first data comparing vaginal bacteria among women randomized to effective contraceptives. That Cu-IUD elicits increases in overall bacterial diversity and abundance of dysbiotic taxa relative to DMPA-IM and LNG-Implant suggests that non-hormonal IUDs may have consequences on vaginal microbiota. These results are central to informing contraceptive options for sexual and reproductive health.

1061 GENITAL SECRETIONS FROM WOMEN WITH BACTERIAL VAGINOSIS ENHANCE HIV INFECTION EX VIVO

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Background: Women with bacterial vaginosis (BV) are more susceptible to HIV. We hypothesize that increased HIV susceptibility is mediated by direct or indirect effects of bacteria on mucosal immunity and the epithelial barrier. To test this hypothesis, we conducted a longitudinal study in women with clinical BV before and after treatment, quantified the ability of cervicovaginal fluid (CVF) to inhibit or enhance HIV infection ex vivo, and correlated the activity with vaginal microbiota, cytokines, chemokines and other soluble immune molecules.
Methods: Cervicovaginal lavage and vaginal swabs were collected from 20 HIV negative adult women in Bronx, New York with symptomatic BV (3 or 4 Amsel criteria). Repeat sampling was done 1 week and 1 month after completion of 7 days of twice daily oral metronidazole treatment. Vaginal pH, Nugent scores, CVF cytokines and chemokines, CVF inhibitory or enhancing activity against HIV infection in a TZMbl assay with BaL, and quantities of select vaginal microbiota in swabs (qPCR) were measured. Results were compared between visits by Friedman's test. Spearman correlation coefficients were calculated to assess associations between HIV inhibiting/enhancing activity and other measures.
Results: Proinflammatory cytokines were significantly higher and chemokines were significantly lower in women with BV compared to sampling done after BV treatment (IL-1a p<0.001; IL-1b p=0.04; CXCL9 p=0.01; CXCL10 p=0.03). CVF from women at the time of BV diagnosis enhanced HIV infection significantly by 26% (IQR -1%, 128%) and enhancement decreased significantly 1 month after treatment (p<0.05). HIV enhancement correlated positively with Nugent score (r=0.48), IL-1a (r=0.5), Gardnerella vaginalis (r=0.55), Atopobium vaginae (r=0.48), BVAB2 (r=0.4), Sneathia (r=0.62), and Megasphaera Type 2 (r=0.5) and negatively with L. crispatus (r=-0.4), MIP-1b (r=-0.43), CXCL9 (r=-0.4), and CXCL10 (r=-0.43) (all p<0.002). Preliminary mechanistic studies indicate that CVF increases the binding of HIV to target cells.
Conclusion: CVF from women with BV enhanced HIV in vitro and the enhancing activity was associated with specific BV-associated bacteria and IL-1a. Treatment with metronidazole led to a reduction in the enhancing activity. Additional mechanistic studies are in progress to better understand links between HIV enhancing activity and the vaginal microbiome.

1062 DMPA-IM DRIVES CERVICAL Th17 HIV TARGET-CELL ACCUMULATION IN WOMEN IN ECHO TRIAL

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Background: To definitively assess the relationship between selected contraceptive methods and HIV acquisition risk, the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial randomised women to the copper-T IUD, DMPA-IM and levonorgestrel (LNG) implant with HIV seroconversion as the primary endpoint. Within this trial, we nested mucosal CD4+ T cell studies to determine the impact of contraceptive initiation on Th17 HIV target cells in the genital tract as a potential mechanism for HIV risk.
Methods: Cervical cytobrushes and cervicovaginal secretions from women enrolled in the ECHO trial (n=80) were collected at baseline and within 3 months of initiating contraception. Cervical cytobrush-derived T cells were phenotyped ex vivo by multiparameter flow cytometry, staining for T cell (CD3, CD4, CD8), activation (CD38), mucosal homing (CCR5, a4b7), and Th17 subset markers (CCR6, CCR10). Soluble cytokines and chemokines were measured in secretions using 27-plex Luminex assay.
Results: DMPA-IM induced an increase in the frequency of activated (CD38+) cervical Th17-like cells (p=0.04), while the other contraceptive arms did not. Despite no contraceptive specific changes in the overall expression of HIV receptors CCR5 or a4b7, 90% of all activated Th17 cells expressed either receptor and were therefore potentially infectable by HIV. Co-expression analyses revealed that women using DMPA-IM had a higher frequency of highly susceptible CD38+CCR5+a4b7+ Th17 cells compared to baseline. Neither the copper IUD nor LNG-implant induced an increase in any Th17 population expressing CD38, CCR5 or a4b7 in any combination. Increases in the frequency of susceptible Th17 populations in women using DMPA-IM were not associated with higher concentrations of T cell chemotactic markers IL-8, Eotaxin, IP10, RANTES, MIP-1a

or MIP-1b, suggesting that chemotaxis was not the major mechanism for the DMPA-IM driven accumulation of target cells in the genital tract.
Conclusion: For the first time in a randomised clinical trial, we demonstrate that DMPA-IM, but not the copper IUD nor LNG-implant, induced an increase in the abundance of potentially infectable Th17 HIV target cells expressing CD38, CCR5 and a4b7 in the female genital tract. Despite their possible susceptibility to HIV infection, Th17 cells play an important role in epithelial barrier repair. It is therefore interesting to speculate whether increased Th17 cell frequency and activation status associated with DMPA-IM reflect epithelial barrier damage.

1063 INCREASED GENITAL INFLAMMATION IN WOMEN RANDOMIZED TO COPPER IUD IN THE ECHO TRIAL

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Background: The inflammatory milieu of the lower female genital tract contributes substantially to HIV acquisition risk. In the randomized ECHO trial, we investigated whether the intramuscular injectable depo-medroxyprogesterone acetate (DMPA-IM) influenced genital inflammation, relative to the levonorgestrel implant (LNG-Implant) and non-hormonal copper intrauterine device (Copper-IUD).
Methods: Cervicovaginal secretions (CVS) were collected via menstrual cups at three sites (Cape Town and Johannesburg [South Africa], and Kisumu [Kenya]) from women who participated in the ECHO trial comparing HIV incidence rates among women randomized (1:1:1) to different types of contraceptives. For this sub-analysis, concentrations of 27 cytokines were measured by Luminex in matched CVS from 190 women (DMPA-IM: n=67; LNG-Implant: n=63; Copper-IUD: n=60) with samples collected at baseline (pre-contraceptive initiation), 1 and 6 months post-contraceptive initiation.
Results: After adjusting for multiple comparisons, genital cytokine concentrations were significantly elevated at 6 months post-contraceptive initiation in women randomized to Copper-IUD compared to matched baseline. These included IL-1b (p=0.0002), IL-6 (p=0.0003), TNF-a (p=0.0002), MIP-1a (p=0.0002), MIP-1b (p=0.0003), IP-10 (p=0.005) and IL-8 (p=0.001). In contrast, there were no significant changes in cytokine levels in DMPA-IM and LNG-Implant users at 6 months post-contraceptive initiation. No changes in CVS cytokines were observed at 1 month post-contraceptive initiation in any arm.
Conclusion: Overall, these results show that use of the Copper-IUD non-hormonal contraceptive option in ECHO, appeared to be more inflammatory than the hormonal contraceptives DMPA-IM or LNG-Implant. Despite the ECHO trial showing no significant difference in HIV incidence between the three contraceptive arms, our finding of late rather than early genital inflammation in women using the Copper-IUD requires further investigation.

1064 ELEVATED GENITAL CYTOKINES IN HIV-INFECTED WOMEN USING COPPER AND LEVONORGESTREL IUDs

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Background: Intrauterine contraceptive devices (IUCD) may increase genital inflammatory cytokine concentrations in HIV+ women despite antiretroviral therapy (ART). We compared the effect of copper (cIUCD) versus levonorgestrel intrauterine system (LNG-IUS) on genital cytokines in both ART using (ART+) and non-ART using (ART-) women.
Methods: In a secondary analysis of an RCT, menstrual cup cervicovaginal secretions (CVS) were collected in ART- and ART+ women randomized 1:1 to cIUCD or LNG-IUS. 28 cytokines were measured in 104 age-matched participants with CVS collected at enrolment and then 3m and 6m post-IUCD insertion (ART- n=48; ART+ n=56). We compared cytokine clustering by IUCD and ART use by Principle Component Analysis (PCA) and Partial Least Squares Discriminant Analysis (PLSDA).
Results: CVS cytokines clustered separately at baseline, with 17/28 higher in ART- than ART+ women, including IL1b, IL1a, IL6, MIP1a, MIP1b, RANTES, IP10, and Eotaxin. In ART- only, genital tract VL (gVL) correlated positively with IL1b (R=0.72; 95%CI 0.55-0.84) and IL8 concentrations (R=0.66; 95%CI 0.47-0.80). None of the cytokines predicted gVL in ART+. Compared to baseline CVS, cIUCD insertion in ART- women resulted in significantly elevated concentrations of IL-6, MCP-1, MIP-1a, MIP-1b, RANTES, GCSF, IL-15 at 3-month follow-up, of which MCP1, MIP1a, and GCSF remained high at 6m. A more significant increase in CVS cytokines was observed after cIUCD insertion in ART+ WLHIV, with 19/29 cytokines elevated at 3-months, of which 15 remained high at 6m. In contrast, among ART- women, LNG-IUS resulted in suppression of IL12p70, IP10, VEGF, GM-CSF at 3-months (IL12p70 and VEGF remaining low at 6 months). In ART+ women, LNG-IUS had a more moderate effect than cIUCD, with 6/28 cytokines elevated at 3 months, of which half resolved by 6 months. Despite differences in cytokine changes in cIUCD compared to LNG-IUS users, overall profiles did not differ significantly by IUCD type by PCA. PLSDA suggested that MCP1 best differentiated IUCD groups, irrespective of ART status.
Conclusion: These data suggest that cIUCD insertion was associated with increased genital cytokine concentrations in HIV+ women irrespective of ART status. LNG-IUS was initially less inflammatory, particularly in ART- women. Although certain genital cytokines were positively associated with gVL in ART-, changes in inflammatory profiles associated with either IUCD did not increase gVLs in ART+.

1065 MOLECULAR PERTURBATIONS INDUCED BY DMPA, COPPER IUD, AND LNG IMPLANT IN ECHO TRIAL

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Background: Previous studies have suggested alterations in mucosal immunity in women using hormonal contraceptives, specifically intramuscular depot medroxyprogesterone acetate (DMPA-IM). The results of the ECHO trial found that women randomized to DMPA-IM, copper intrauterine device (IUD), and the levonorgestrel (LNG) implant experienced similar HIV incidence rates. Transcriptomics and proteomics of genital samples, collected from women in the ECHO trial, were used to characterize molecular perturbations induced in the vaginal compartment by initiation of contraception.
Methods: Endocervical cytobrush and vaginal soft cups were collected from a total of 202 women at enrollment and after one month of initiating DMPA, LNG or IUD for RNA-Seq and proteomic analysis. RNA exome capture beads were used to generate enriched libraries for Illumina based RNA-Seq. Paired analyses were carried out for each study-arm using DESeq2, with participant ID and visits as input factors. Gene set enrichment analysis (GSEA) was conducted for each study-arm to identify gene-sets or pathways specifically enriched in one or more study-arm.
Results: The number of differentially expressed genes detected between month 1 and enrollment visits were 505, 314, and 83 among women randomized to DMPA-IM, LNG and IUD, respectively. Women using DMPA-IM or LNG showed a higher perturbation in vaginal gene-expression relative to IUD users. GSEA demonstrated that prevalent antiviral signaling pathways (IFNA, IFNG, KEGG RIG-I like and T-cell signaling), had similar enrichment across the three study-arms. Gene-sets comprising genes related to inflammatory responses, NFkB target genes and serpins were differentially induced in the three study-arms. Mass spectrometry based proteomic analysis of mucosal fluid identified 1021 human proteins in the (150) participants profiled, identifying proteins involved in inflammation, antimicrobial activity, epithelial function, and humoral immunity.
Conclusion: These data demonstrate enhanced perturbation of inflammatory pathways among women using DMPA-IM and LNG that provide mechanistic insights into the biological impact of these contraceptives. While the magnitude and/or durability of these changes do not ultimately impact HIV susceptibility, they may have implications for other sexually transmitted infections.

1066 COPPER IUD AND LEVONORGESTREL IMPLANT INCREASE GENITAL INFLAMMATION IN THE ECHO TRIAL

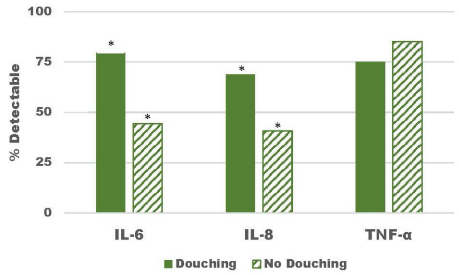
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Background: The Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial found no substantial difference in HIV acquisition risk between women randomised to injectable depot medroxyprogesterone acetate (DMPA-IM), copper intrauterine device (IUD) or the levonorgestrel (LNG) implant. However, ECHO did not address whether these contraceptives increase HIV risk relative to other contraceptive methods or to no contraception. We investigated the impact of DMPA-IM, copper IUD and LNG implant on cervicovaginal inflammatory profiles previously associated with HIV acquisition, among a sub-cohort of ECHO participants.
Methods: This study included 168 ECHO participants at the Setshaba Research Centre in Tshwane and MRU in eThekwini, South Africa. Eleven cytokines and antimicrobial peptides were measured in duplicate using Luminex in lateral vaginal wall swabs. Changes in cytokine concentrations were assessed using Wilcoxon signed rank test and generalized linear modelling. P values were adjusted for multiple comparisons using a false discovery rate procedure.
Results: Baseline cervicovaginal cytokine concentrations were elevated in women with Neisseria gonorrhoeae infection and dampened among herpes simplex virus (HSV)-2 seropositive women. Younger women had higher concentrations of IL-8 and IL-1β. The copper IUD and LNG implant were associated with rapid increases in inflammatory markers following contraceptive initiation. Pro-inflammatory IL-1β and IL-6 and chemotactic IL-8, IP-10, MIP-1α and MIP-1β were significantly elevated one month following copper IUD insertion. No changes were evident at one month post LNG implant insertion, however at three months, TNF-α, IP-10, MIP-3α and SLPI were significantly raised relative to baseline. Significant effect modification was observed by N. gonorrhoeae and HSV-2 infection.
Conclusion: The copper IUD and the LNG implant are associated with increased cervicovaginal inflammatory markers that have been linked to HIV infection risk. These effects are modified by STI status. Recent studies have demonstrated the important interplay between inflammation, the microbiome, contraception and HIV risk. Continued research to understand these effects are critical for safe contraceptive use and to inform novel contraceptive development.

1067 DOUCHING IS ASSOCIATED WITH RECTAL INFLAMMATION IN HIV-NEGATIVE SEXUAL MINORITY MEN

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Background: Rectal douching may increase vulnerability to HIV and other sexually transmitted infections (STIs) in sexual minority men (i.e., gay, bisexual, and other men who have sex with men). However, relatively little is known about the pathways whereby rectal douching could amplify biological vulnerability to HIV and other STIs.
Methods: Participants were recruited in four STI clinics in South Florida operated by the AIDS Healthcare Foundation. Rectal swabs for 92 participants who reported engaging in condomless receptive anal intercourse (CRAI) and no antibiotic use in the past three months were selected to measure inflammatory cytokines using LEGENDplex. Multivariate logistic regression analyses examined the independent associations of rectal douching with detectable levels of rectal interleukin-6 (IL6), interleukin-8 (IL-8), and tumor necrosis factor – alpha (TNF-α). Models were adjusted for age, pre-exposure prophylaxis (PrEP) use, and number of CRAI partners in the past three months.
Results: Participants were between 19 and 80 years old (mean age=34.6; SD=13.7), and 54% were ethnic minorities (37% Hispanic/Latino, 14% Black/African American, and 3% other ethnic minority). Approximately 28% of participants were taking PrEP, 90% reported testing negative for HIV in the past year, and nearly 70% reported rectal douching. Participants who douched reported more CRAI partners (Cohen's d = 0.51; p < 0.01) and more instances of CRAI with ejaculation (Cohen's d = 0.50; p = 0.03). As shown in the Figure, a significantly greater proportion of men who douched had detectable rectal IL-6 (80% versus 44%; p = 0.002) and IL-8 (69% versus 41%; p = 0.019). In adjusted analyses, douching was independently associated with more than 4-fold greater odds of detectable rectal IL-6 (adjusted odds ratio [AOR] = 4.78; 95% CI = 1.45 – 15.76) and more than 3-fold greater odds of detectable rectal IL-8 (AOR = 3.12; 95% CI = 1.06 – 9.19).
Conclusion: This study is among the first to observe that rectal douching is independently associated with rectal inflammation, which was assessed using non-invasive rectal swabs. Novel behavioral and biomedical approaches that mitigate heightened rectal inflammation in sexual minority men who douche could reduce biological vulnerability to HIV or other STIs.



1068 SEXUAL VIOLENCE EXPOSURE DYSREGULATES HIV-ASSOCIATED IMMUNE BIOMARKERS IN WOMEN

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Background: HIV/AIDS and sexual violence act synergistically to adversely and disproportionately impact women's health. Yet immuno-biological mechanisms linking sexual violence and increased HIV susceptibility are incompletely understood. We aimed to determine systemic and mucosal immune dysregulation in women who had experienced recent sexual violence.
Methods: We conducted a cross-sectional study of premenopausal, HIV-negative women from the Washington DC area, comparing 13 cases who had experienced forced vaginal penetration (FVP) within the past 12 weeks and 25 controls who had never experienced FVP. Clinical data as well as plasma and cervicovaginal lavage (CVL) samples were collected and ELISA assays performed to measure inflammatory, anti-inflammatory, anti-HIV, and wound healing biomarkers. We modeled differences between cases and controls using linear and logistic regression with inverse probability of treatment weighting based on age, race, insurance status, menstrual cycle phase, hormonal contraceptive use, and other contraceptive use. We used the Benjamini–Yekutieli method to control the false discovery rate (FDR) for 47 tests.
Results: In CVL, cases had reduced levels of chemokines MIP-3α (p=.003) and MCP-1 (p<.001) and anti-HIV/wound-healing marker Thrombospondin-1 (TSP-1) (p=.027). Conversely, they had increased inflammatory cytokine IL-1α (p=.001) and were more likely to have detectable levels of wound-healing platelet derived growth factor (PDGF) (OR=7.89; p=.019). In plasma, cases had decreased levels of chemokines MIP-3α (p<.001) and IL-8 (p=.004), anti-inflammatory cytokine TGF-β (p=.016), anti-HIV factor beta defensin 2 (HBD2) (p=.017), and wound-healing protease MMP-1 (p=.019). They had higher levels of protease Cathepsin B (p=.010) and TSP-1 (p=.003) and were more likely to have detectable chemokine IP-10 (OR=12.24; p=.064). The associations of case status with reduced MCP 1 in CVL and reduced MIP 3α in plasma remained statistically significant at α = .05 after FDR adjustment.
Conclusion: We found indications of distinct systemic and mucosal immune dysregulation in women who had experienced recent sexual violence. As some of these biomarkers have been associated with HIV infection and pathogenesis, dysregulation may increase HIV susceptibility in these women. This data informs future studies on HIV prevention in the setting of sexual violence and directs development of novel therapeutic interventions and trauma-informed care.

Changes in Selected Immune Biomarkers in HIV-Uninfected Women Exposed to Recent Sexual Violence (N = 13) vs. Unexposed Women (N = 25)

	CVL (*Log10 pg/mL*)			Plasma (*Log10 pg/mL*)		
Biomarker [a]	Weighted Mean Difference	P-value [b]	Adjusted P-value [c]	Weighted Mean Difference	P-value [b]	Adjusted P-value [c]
IL-1α	0.46	**0.001**	0.051	NA	NA	NA
TGF-β	NA	NA	NA	-0.91	**0.016**	0.365
MIP-3α	-1.04	**0.003**	0.123	-1.05	**< 0.001**	**0.028**
IL-8	0.03	0.862	1.000	-1.05	**0.004**	0.145
MCP-1	-1.26	**< 0.001**	**0.028**	0.06	0.450	1.000
HBD2	0.32	0.172	1.000	-0.80	**0.017**	0.365
TSP1	-0.69	**0.027**	0.460	0.98	**0.003**	0.123
Cathepsin B	-0.03	0.619	1.000	0.12	**0.010**	0.307
MMP1	NA	NA	NA	-0.32	**0.019**	0.365
	CVL (*% Detectable*)			Plasma (*% Detectable*)		
Biomarker	Weighted Odds Ratio	P-value [b]	Adjusted P-value [c]	Weighted Odds Ratio [a]	P-value [b]	Adjusted P-value [c]
IP-10	0.74	0.670	1.000	12.24	0.064	0.895
PDGF	7.89	**0.019**	0.365	NA	NA	NA

[a] No significant differences found for TNF-α, IL-6, IL-1β, SerpinA1, SLPI, Elafin, VEGF, MMP2/7-9, TIMP1/2, CRP, or FGF.
[b] Linear regression (continuous biomarkers); logistic regression (dichotomous biomarkers), inverse propensity score weighted.
[c] Benjamini & Yekutieli false discovery rate method (2001), 47 tests.

1069 ASSESSMENT OF IMMEDIATE INITIATION OF ANTIRETROVIAL THERAPY IN NEW YORK CITY

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Background: Rapid or immediate initiation of antiretroviral therapy (iART) after a positive HIV test has been shown to decrease time to viral suppression (VS), in turn reducing transmission of HIV. New York City (NYC) and New York State (NYS) have expanded access to iART for people living with HIV (PLWH) through targeted programs at clinics in NYC. We evaluated iART knowledge, attitudes, and practices among clinical and non-clinical staff in NYC clinics, as well as barriers and facilitators to iART implementation.
Methods: We recruited at least one clinical (i.e., medical provider) and one non-clinical (i.e., administrator or social service provider) staff member to complete an online survey from a purposive sample of 30 NYC clinics providing primary care to one or more PLWH. Clinics were selected to ensure a diverse representation of health outcomes (e.g., clinic VS), clinic resources (e.g., iART funding) and clinic location and type (e.g., borough, hospital-based clinic). Descriptive and bivariate analyses were performed on collected data.
Results: We received 46 survey responses, representing 25 NYC clinics, 98% of which reported prior knowledge of iART. Over 80% of respondents identified iART as decreasing time to VS and increasing patient retention. Overall, 80% and 67% of respondents agreed that ART should be initiated on the same-day or within three to four days of a positive HIV test, respectively. Conversely, 51% of respondents believed ART should not be initiated prior to confirmatory test results, with non-clinical staff being more likely to hold this belief (odds ratio [OR]: 4.64, 95% confidence interval [CI]: 1.24-17.37). Among all respondents,66% reported zero to four days as the typical length of time from a positive HIV test to ART initiation. Clinics serving a majority people of color were less likely to meet the same-day benchmark (OR: 0.15, 95% CI: 0.02-0.95). Commonly reported facility-level and patient-level barriers to iART included: insurance barriers (76%), medication prior authorizations (50%), financial barriers (46%), and concern about false positives (37%). ART medication starter packs (63%) and patient education materials (52%) were the most commonly reported facilitators to iART.
Conclusion: Despite high levels of knowledge around the benefits associated with iART, it is not yet the standard of care across NYC clinics. The proven benefits of iART warrant further efforts to overcome barriers to implementation, with a focus on achieving health equity.

Table 1. Knowledge, attitudes, and practice around immediate initiation of antiretroviral therapy (iART) by staff role and clinic-level patient demographics

		Staff Designation			Patient Demographics		
		Non-clinical Staff N=26 % (n)	Clinical Staff[a] N=20 % (n)	OR (95% CI)	Majority POC[b] N=28 % (n)	Majority Non-POC[a,b] N=14 % (n)	OR (95% CI)
Knowledge	**iART impact on time to viral suppression:**						
	Increases	14.3 (3)	0.0 (0)	---	4.2 (1)	14.3 (2)	---
	Decreases	85.7 (18)	100 (20)	---	95.8 (23)	85.7 (12)	3.83 (0.31-46.69)
	iART impact on patient retention:						
	Increases	90.5 (19)	94.7 (18)	0.53 (0.4-6.34)	92.0 (23)	91.7 (11)	1.05 (0.09-12.81)
	Decreases	4.8 (1)	0.0 (0)	---	4.0 (1)	0.0 (0)	---
	Does not impact	4.8 (1)	5.3 (1)	---	4.0 (1)	8.3 (1)	---
Attitudes	**Agree with initiating ART[c]:**						
	Same-day as reactive test	78.3 (18)	89.5 (17)	0.42 (0.07-2.48)	84.0 (21)	84.6 (11)	0.95 (0.15-6.06)
	Within 3-4 days of reactive test	62.5 (15)	79.0 (15)	0.44 (0.11-1.76)	68.0 (17)	71.4 (10)	0.85 (0.20-3.56)
	Before confirmatory test	68.2 (15)	31.6 (6)	**4.64 (1.24-17.37)**	52.0 (13)	41.7 (5)	1.52 (0.38-6.09)
Practice	**Typical time from reactive rapid test to ART initiation:**						
	0-4 days	19.1 (4)	21.1 (4)	0.88 (0.19-4.16)	8.7 (2)	38.5 (5)	**0.15 (0.02-0.95)**
	≥5 days	81.0 (17)	79.0 (15)	---	91.3 (21)	61.5 (8)	---

[a]Referent group
[b]POC = People of Color
[c]Respondents were asked to indicate their level of agreement with initiating ART at various time points using the following response options: strongly agree, agree, disagree, strongly disagree, not sure, and prefer not to answer. Data presented in the table represents dichotomization of collected responses (agreement vs. disagreement).

1070 A STRUCTURED ALGORITHM FOR SAME-DAY ART INITIATION: SLATE II TRIAL PRIMARY OUTCOMES

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Background: Many countries, including South Africa, encourage same-day initiation (SDI) of antiretroviral therapy (ART), but evidence on how to implement SDI and its impact on outcomes remains scarce. Building on the Simplified Algorithm for Treatment Eligibility trial (SLATE I), in which nearly half of participants were ineligible for same day initiation due mainly to TB symptoms, we evaluated the revised SLATE II algorithm, which allowed SDI for patients with mild TB symptoms and other less serious reasons for delay.
Methods: SLATE II was a 1:1 individually randomized trial at public outpatient clinics in Johannesburg that enrolled patients presenting for an HIV test or any HIV care but not yet on ART. Intervention arm patients were assessed with a symptom self-report, medical history, brief physical examination, and readiness questionnaire to distinguish patients eligible for immediate ART dispensing from those requiring further care, tests, or counseling before initiation. Standard arm patients received usual care. Using routine clinic records, we report initiation in 0 (same day), 7, and 28 days after study enrollment and retention in care 8 months after study enrolment.
Results: From 3/14/18-9/21/18, we enrolled 593 adult HIV+, non-pregnant patients (median[IQR] age 35 [29-43]; 63% (n=373) female; median CD4 count 293 [133-487]). In the intervention arm, 87% initiated on the same day, compared to 38% in the standard arm (Table). Initiation was higher in the intervention vs standard arm by 7 days (91% vs 68%; RD: 23%; 95% CI: 17-29%) and 28 days (94% vs 82%; RD: 12%; 95%CI: 7-17%) after enrolment. By 8 months after study enrolment, 70% (207/296) intervention and 55% (163/297) standard arm patients had initiated ART ≤ 28 days and were retained in care (RD 15%; 95% CI 7-23%). Nearly half (140/296, 47%) of intervention arm patients reported >=1 TB symptom; 39 (13%) were severe enough to require delay for further investigation, and 6 (2%) were diagnosed with TB. No serious post-initiation adverse events were reported. Nearly all patients (98.5%) stated they would like to start same-day if possible.
Conclusion: More than 85% of patients presenting for HIV testing or care, including those newly diagnosed, were eligible and ready for same-day initiation under SLATE II algorithm. The algorithm increased initiation in ≤ 7 days by 28% and retention in care at 8 months by 15%, offering a practical model for implementing guidelines that can be immediately utilized.

Table: Time to ART initiation by study arm

Outcome	Standard arm n=297	Intervention arm n=296	Risk difference (95% CI)	Relative risk (95% CI)
Time to ART initiation				
0 days (same-day)	114 (38%)	257 (87%)	49% (42-55%)	2.26 (1.95-2.63)
≤ 7 days*	202 (68%)	270 (91%)	23% (17-29%)	1.34 (1.23-1.46)
≤ 28 days	243 (82%)	277 (94%)	12% (7-17%)	1.14 (1.08-1.22)
No record of initiation ≤ 28 days	54 (18%)	19 (6%)	-12% (-17 to -7%)	0.35 (0.21-0.58)
Retention 8 months after study enrolment				
Initiated ART ≤ 28 days and retained in care 8 months after study enrolment*	163 (55%)	207 (70%)	15% (7-23%)	1.27 (1.13-1.45)
Initiated ART ≤ 28 days but not retained 8 months after study enrolment	80 (27%)	70 (24%)	-3% (-5 to -9%)	0.88 (0.67 -1.16)
No record of initiation ≤ 28 days	54 (18%)	19 (6%)	-12% (-17 to -7%)	0.35 (0.21-0.58)
Viral suppression 8 months after study enrolment				
Initiated ART ≤ 28 days and virally suppressed ≤ 8 months **	93 (31%)	124 (42%)	11% (3-18%)	1.34 (1.08-1.66)
Initiated ART ≤ 28 days and virally unsuppressed ≤ 8 months	10 (3%)	9 (3%)	0% (-3 to 3%)	0.90 (0.37-2.19)
Initiated ART ≤ 28 days, retained in care but no VL result observed	60 (20%)	74 (25%)	5% (-2 to 12%)	1.24 (0.92 – 1.67)
Initiated ART ≤ 28 days, not retained in care	80 (27%)	70 (24%)	-3% (-5 to -9%)	0.88 (0.67 -1.16)
No record of initiation ≤ 28 days	54 (18%)	19 (6%)	-12% (-17 to -7%)	0.35 (0.21-0.58)

* Protocol-defined primary outcome
**Protocol-defined secondary outcome

1071 ASSOCIATION BETWEEN TIME TO ART AND LOSS TO CARE AMONG NEWLY DIAGNOSED PLWH IN RWANDA

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Background: Nearly all countries have adopted WHO "Treat All" guidelines to initiate antiretroviral therapy (ART) for all people living with HIV (PLWH) as soon as possible after diagnosis. An emerging literature suggests it is important to characterize the relationship between time to ART initiation and subsequent clinical outcomes under Treat All. We compared loss to follow up (LTFU) and viral suppression (VS) among PLWH in Rwanda by time from diagnosis to ART initiation.

Methods: Cohort study in 10 Rwandan health centers of adults (≥15 years) who were newly diagnosed with HIV from 1 July 2016 to 15 September 2018. We used Kaplan-Meier survival curves and Cox proportional hazard regression to examine associations between time from diagnosis to ART initiation (same day, 1-7, 8-30, >30 days) and LTFU (>120 days since last clinic visit and did not knowingly die or transfer) in the 15 months after diagnosis. Among patients with measured viral loads after ART initiation, we used log binomial regression to calculate risk ratios for VS (<200 copies/ml on most recent viral load >3 months after ART initiation), by time to ART.

Results: Among 1971 patients, 1895 (96%) initiated ART. Of ART initiators, 293 (15%) initiated on the same day as diagnosis, 452 (24%) from 1-7 days, 768 (41%) from 8-30 days, and 382 (20%) >30 days after diagnosis. Compared to those initiating ART later, same day initiators were more likely to be female (70 vs 54%), had lower median age (30 vs 33 years) and had higher median baseline CD4 count (468 vs 411 cells/mm_3, p<0.001 for all). LTFU occurred among 25%, 15%, 17% and 17% of same day, 1-7, 8-30, and >30 day initiators, respectively. After adjusting for health center, age, sex, enrollment source, BMI, WHO stage, and CD4 count, compared to those initiating on the same day, hazard of LTFU was lower among patients initiating ART later (1-7 days: adjusted hazard ratio [aHR] 0.66, 95% CI 0.47-0.92; 8-30 days: aHR 0.68, 95% CI 0.51-0.92; and >30 days: aHR 0.47, 95% CI 0.32-0.68). Among 1084 patients with measured viral loads >3 months after ART initiation, 958 (88%) were suppressed; there were no differences in probability of VS by time to ART.

Conclusion: In this cohort of PLWH entering care after implementation of Treat All, patients initiating ART on the day of diagnosis were more likely to be lost to care than those initiating later. Ensuring adequate support for PLWH initiating ART rapidly is important to maintain engagement in care.

1072 SAME-DAY ART IN THAILAND: THE IMPACT OF ART INITIATION PERIODS ON TREATMENT OUTCOMES

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Background: Despite the World Health Organization's recommendation on same-day antiretroviral therapy (ART) for clients who are ready, there are still concerns around the effect of immediate ART on care outcomes. This study evaluates the influence of different ART initiation durations on retention, viral load suppression, and adverse events on clinically-eligible clients in same-day ART cohort in Thailand.

Methods: Data was obtained from HIV-positive clients from 10 facilities in 6 provinces (Chiang Rai, Chiang Mai, Chonburi, Ubonratchathani, Bangkok and Songkhla) between July 2017–July 2019. Baseline laboratory tests and chest X-rays were performed according to national guidelines. ART eligibility was determined by a physician. Clinically-eligible clients were included in the analysis, and categorized into the duration between care engagement and ART initiation: same-day, 2-7 days, 8-14 days, 15-21 days, and more than 21 days. Logistic regressions were performed to identify factors associated with loss to follow-up at months 3, 6, and 12 after ART initiation, as well as adverse events (AEs).

Results: Of 4,642 clients who agreed to start ART, 3,888 (83.8%) were clinically eligible and started ART; 30%, 64%, and 6% of these identified as general population, men who have sex with men (MSM), and transgender women (TGW), respectively. The following results presented are in order of same-day, 2-7 days, 7-14 days, 14-21 days, and more than 21 days categories. The numbers of clients were: 3,053 (78.5%), 484 (12.5%), 164 (4.2%), 67 (1.7%), and 120 (3.1%), respectively. At month 3, retention rates were: 98.8%, 94.5%, 96.2%, 95.1%, and 96.5%. (p=0.695) At month 6, retention rates were 92%, 95.5%, 96.6%, 90.9%, and 90.7%. (p=0.153) At month 12, retention rates were: 95.6%, 95.7%, 100%, 100%, and 95.2%. (p=0.921) Reports on clinical AEs were: 15.5%, 15.3%, 14%, 13.4%, and 10.8% (p=0.685); Reports on death were: 0.4%, 0.6%, 0.6%, 0%, and 0.8% (p=0.895). Viral load suppression rates were: 94%, 94%, 84.4%, 100%, and 88.2% (p=0.054). When compared to general population, TGW were more likely to be lost to follow-up (aOR:1.7;95%CI:1.03-2.8;p<0.05) and had AEs (aOR:1.52;95%CI:1.07-2.17;p<0.05).

Conclusion: Same-day ART did not lead to an increase in loss to follow-up, adverse events, or death among clinically eligible clients, and viral load suppression did not differ by timing of ART initiation. Service for TGW may need to integrate gender-affirming care to enhance ART retention.

1073 RAPID START LEADS TO SUSTAINED VIRAL SUPPRESSION IN YOUNG PEOPLE IN THE SOUTH

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Background: HIV incidence continues to increase in young men of color. Youth living with HIV, also, have lower rates of viral suppression and retention in care. Rapid Start is a linkage-to-care intervention to start people newly diagnosed with HIV immediately on ART and support equity in care. Our prior data has shown that rapid ART initiation improves linkage and viral suppression. Rapid Start data for US youth has not been published. To verify that youth were achieving similar outcomes, we developed a continuum of care for our young adult rapid start population and compared this continuum to our adult population.

Methods: Newly diagnosed patients were linked within 72 hours of diagnosis (often same-day) to CrescentCare, a Federally Qualified Health Center in New Orleans. The first dose was directly observed and patients were provided a 30-day dose pack. Labs were drawn and patients underwent expedited insurance enrollment. The proportion achieving viral suppression, time to viral suppression, sustained viral suppression 12 months post-diagnosis and engagement in care at 12 months were compared between youth (18 – 24) and adults.

Results: 124 patients were enrolled in our rapid start intervention between 12/1/2016 and 5/15/2018. Ninety-three were 25 or older with a median age of 33. Thirty-one were under 25 with a median age of 21. All patients chose to start ART, and none stopped due to adverse effects. 96.8% (30/31) of the youth population achieved viral suppression with a median of 29 days from diagnosis. 83.9% (26/31) remained virally suppressed at 12 months post-diagnosis and 96.8% (30/31) remained engaged in care.

97.9% (91/93) of the adult population achieved viral suppression with a median of 28 days from diagnosis. 92.5% (86/93) remained virally suppressed at 12 months post-diagnosis and 97.9% (91/93) remained engaged in care. There were no significant differences in these outcomes between the two groups.
Conclusion: The intervention outcomes demonstrate that starting adults and youth on ART immediately after diagnosis, before labs are obtained, is safe, well-tolerated, and effective. Viral suppression was quickly achieved and maintained. Rapid Start is a paradigm shift that upholds equity and effectively engages youth.

	24 and under N=31	25 and older N=93	p
Sex			
Male	25 (80.7%)	64 (68.8%)	P = 0.2042
Female	5 (16.1%)	23 (24.7%)	P = 0.3230
Trans female	1 (3.2%)	6 (6.5%)	P = 0.4934
Race			
African-American	21 (67.7%)	54 (58.1%)	P = 0.3456
White	9 (29.0%)	25 (26.9%)	P = 0.8212
Latin/other	1 (3.2%)	14 (15.1%)	P = 0.0800
HIV Risk factor			
MSM	25 (80.6%)	50 (53.8%)	P = 0.0085
Heterosexual	5 (16.1%)	40 (43.0%)	P = 0.0072
IDU	1 (3.2%)	3 (3.2%)	P= 1.00
Median age	21 (18 – 24)	33 (25 – 61)	
Achieved VS	30 (96.8%)	91 (97.9%)	P = 0.7286
Median days to VS	29	28	P = 0.85
Sustained VS after 12 months	26 (83.9%)	86 (92.5%)	P = 0.1619
Engaged in Care after 12 months	30 (96.8%)	91 (97.9%)	P = 0.7286

1074 TREAT-ALL HIV POLICIES AND PATIENT ATTRITION IN SOUTH AFRICA: A PROSPECTIVE STUDY

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Background: We aimed to determine whether the Universal Test & Treat (UTT) and same-day antiretroviral therapy (ART) policies, instituted in South Africa in September 2016 and 2017,resulted in improvements in patient attrition at 12-month after HIV diagnosis and viral suppression (<400 copies/ml) at six months after ART start.
Methods: We enrolled three cohorts of newly diagnosed HIV infected adults from two primary health clinics in Johannesburg from April to November 2015 (Pre-UTT, n=144), May-September 2017 (UTT, n=178) and October-December 2017 (same-day ART period, n=88). A baseline survey was administered after HIV diagnosis and clinical records were reviewed up to 12 months after HIV diagnosis. We compared patient attrition, defined as being >90 days late for a visit (lost to follow-up (LTFU)) at 12-months, between HIV policy periods using Cox regression. Six-months viral suppression was assessed using log-binomial regression.
Results: The median age among the 410 participants was 33.5 years (Intequartile range: 28.3-39.3), and 242 (56.9%) were female. Overall 172 (42.0%) were LTFU at 12 months, 47.2% pre-UTT vs. 37.1% under UTT, and 43.2% under the same-day ART policy. Among those LTFU at six months, 92.4% were also lost at 12 months, whereas 29.9% of those in-care at six-months were LFTU at 12 months (34.3% pre-UTT, 26.9% under UTT and 29.6% during the same-day ART policy). However, when adjusted for ART uptake in the first 30 days, the same-day ART cohort was 60% more likely to incur losses at 12 months (adjusted hazard ratios (aHR) 1.6, 95% confidence intervals (CI): 1.0-2.6) than the pre-UTT cohort (Figure 1). Initiating ART 15-30 days (aHR 0.4, 95% CI: 0.1-1.0) after diagnosis had a 60% lower LTFU rate than starting ART on the day of HIV diagnosis. Having a baseline CD4>500 vs. <200 cell/mm_3 (aHR 1.6, 95%CI: 1.0-2.6) carried a higher risk of becoming LTFU at 12 months. However, among the 30-days ART initiates, initiating ART on the day of HIV diagnosis increased the likekelihood of viral suppression at six months (adjusted risk ratio 0.9 for 1-14 days ART vs. same-day ART, 95% CI:0.8-1.0).
Conclusion: While ART access and uptake have increased, higher 12-months attrition during the Same-day ART policy period may limit the benefits of the expanded ART program. However, participants who initiated ART on the day of diagnosis have improved viral suppression rates six months after starting ART.

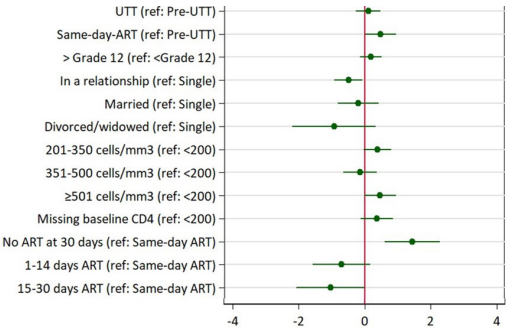


Figure 1. Predictors of LTFU in the first 12 months of HIV care in Johannesburg, South Africa

1075 IMPACT OF UTT ON VIRAL SUPPRESSION IN SOUTH AFRICA: A NATIONAL COHORT STUDY

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Background: Universal Test-and-Treat (UTT) aims to increase rates of viral suppression by extending treatment eligibility to all patients and reducing barriers to initiation of antiretroviral therapy (ART).
Methods: We developed a national HIV cohort through novel linkage of the complete historical laboratory records of South Africa's public sector HIV program, Apr 2004-Mar 2018. Using this cohort, we analyzed the longitudinal patient-level care cascade as observed through routine laboratory monitoring, and how it has changed over time within levels of presenting CD4 counts. Per national treatment guidelines, CD4 counts are collected when a patient first presents clinically with HIV. We analyzed progression from presentation (first CD4) to different stages of the HIV care cascade observed in the labs: an ART lab workup within 90 days of presentation (ALT/HG/CRT, taken prior to starting ART), HIV viral monitoring within 15 months of presentation (indicating a patient is on ART and retained in care), and viral suppression within 15 months of presentation. Patients were followed for 15 months to include routine viral loads at 6 and/or 12-months, with a 3-month buffer. Analyses were stratified by CD4 count at presentation and prevailing treatment guidelines at time of presentation.
Results: 11M patients had a first CD4 count 2004-2016, including 266,479 in the UTT era (Sept-Dec 2016). The share of patients progressing from presentation to ART workup increased over time, from 46% before Aug 2011 to 91% under UTT. These gains were due in part to expansions of ART eligibility, leading to the elimination of discontinuities at prior CD4 thresholds, and in part to improvements affecting patients at all CD4 counts (Fig 1a). Eligibility expansions – and improved access to viral monitoring – also increased the share of patients progressing from presentation to documented viral suppression within 15 months (Fig 1b). Comparing the period just prior to UTT with the UTT era (Fig 1c), the share of patients presenting for care who had an ART workup increased from 78% to 91%; the share virally monitored increased from 54% to 61%; and the share reaching documented viral suppression increased from 38% to 44%.
Conclusion: Despite high rates of progression from first CD4 to ART workup in the UTT era, many patients who present with HIV are not retained through viral monitoring and suppression. UTT has had a small impact on progression from clinical presentation to viral suppression.

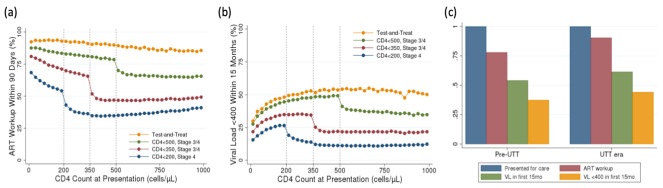


Fig 1. Figure shows percent of patients presenting for care who (a) had an ART workup within 90 days and (b) had a suppressed viral load within 15 months after presentation. These numbers are shown by CD4 count at presentation and results are stratified by the prevailing treatment guidelines on date of presentation: CD4<200 or Stage 4 (2004-Aug 2011), CD4<350 or Stage 3/4 (Aug 2011-Dec 2014), CD4<500 or Stage 3/4 (Jan 2015-Aug 2016), UTT (from Sept 2016). (c) Longitudinal HIV care cascades show the proportion of patients presenting for care who had an ART workup, were virally monitored, and had a suppressed viral load in the pre-UTT (Jan 2015-Aug 2016) and UTT (Sept-Dec 2016) eras.

1076 HIV-1 DYNAMICS FOLLOWING UNIVERSAL TESTING-AND-TREATMENT WITHIN HPTN 071 (POPART)

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Background: A universal HIV testing-and-treatment (UTT) approach has been shown to be effective as an intervention in high prevalence areas in sub-Saharan Africa (SSA) to reduce HIV incidence. Community-wide interventions may change the dynamics of the epidemic. Understanding these changes will inform future policy towards achieving zero new infections. Using an individual-based model (PopART-IBM), developed as part of the HPTN 071 (PopART) trial, we project the impact of four scenarios of UTT to 2030 on the distribution of incident cases stratified by categories of sexual risk-taking behaviour.

Methods: Model predictions were made with the PopART-IBM calibrated to data from a representative trial community in Zambia from the HPTN 071 (PopART) trial. The model has been previously validated against the primary endpoint of the trial. The model separates the population into three groups according to sexual risk-taking behaviour based on behavioural questionnaire data, including number of sex partners and use of condoms. The proportions of individuals in each risk group (low 50%, medium 35%, high 15%) were assumed to be static through time. Model projections to 2030 are based on four scenarios: 1) PopART then continuation of UTT in the PopART community; 2) PopART then no UTT; 3) no PopART but nationwide UTT from 2020; 4) no PopART and no UTT.

Results: Making antiretroviral therapy universally accessible to all who are HIV-positive in the PopART community would lead to a decline in prevalence in all risk groups but would concentrate new cases in those with the highest levels of risk-taking behaviour (65% of incident cases vs 54% if no UTT was implemented; figure 1). While population HIV incidence to 2030 decreases, the model predicts continued persistence of an HIV epidemic in the high-risk subpopulation in all scenarios unless nationwide UTT is adopted.

Conclusion: Our results predict that even with a UTT intervention, the proportion and absolute number of new HIV cases in those with the highest levels of sexual risk-taking behaviour would increase, despite overall HIV prevalence decreasing. Our results highlight that targeting of high-risk individuals may be necessary following successful UTT interventions in order to eliminate HIV as a public health issue in SSA.

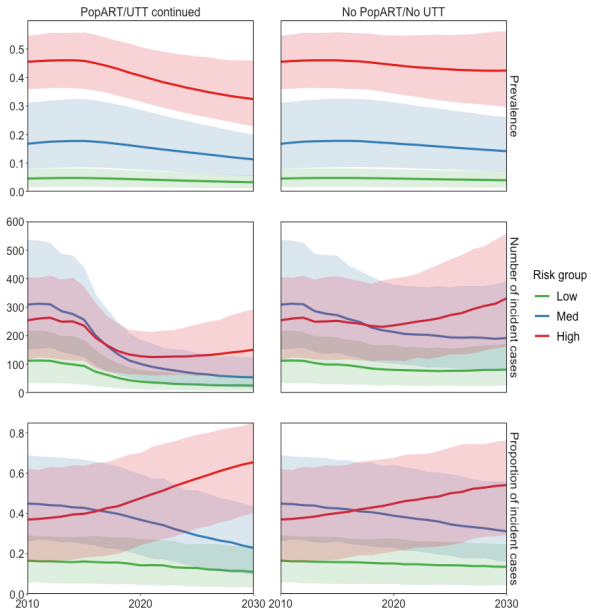


Figure 1: Projections of HIV prevalence and incidence in a Zambian community in the HPTN 071 (PopART) trial under two scenarios of UTT (scenarios 1 & 4).

1077 DRAMATIC DECLINE OF NEW HIV DIAGNOSES IN SUBJECTS NATIVE FROM FRANCE

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Background: In France, universal ART (TasP) was recommended at the end of 2013 and PrEP in January 2016. The 3rd UN target (90% patients on cART with virological suppression), was reached in 2013, and the 2nd target (90% of individuals diagnosed on sustained cART) was achieved in 2014. As the trends in new HIV diagnosis is a measure of HIV epidemic, we conducted a 6-year longitudinal study to evaluate the change in rates of new HIV diagnosis and describe their epidemiology in a large French multicenter cohort.

Methods: Data were obtained for subjects with a new HIV diagnosis date between 2013 and 2018 from the metropolitan centers of the French Dat'AIDS cohort. HIV diagnosis date was defined as the date of the first known positive HIV serology. Analyses were performed by place of birth (France and abroad) and by contamination route.

Results: During the study period, a total of 68,376 people living with HIV were followed in the Dat'AIDS cohort; 9,543 subjects were newly diagnosed with HIV, 4,253 born in France (90% male; 70.5% MSM), and 4,737 born abroad (39.1% heterosexual women; 23.0% heterosexual men, 21.9% MSM). The annual number of new HIV diagnosis decreased from 1,856 in 2013 to 1,149 in 2018 (-38.1%); it was more pronounced among subjects born in France, from 858 to 484 (-43.6%) than in those born abroad (-23.8%, from 821 to 626). Among subjects born in France, the decrease over the period was -46.7%, - 43.5% and -33.3% among MSM, heterosexual women and heterosexual men, respectively; the proportion of patients with CD4 cells count >350/mm_3 at diagnosis decreased by 45.6% from 2013 to 2018. In contrast, the proportion of patients with CD4 cell count <200/mm_3 at diagnosis declined by 26% among patients born in France and remained stable among patients born abroad (-5.8%).

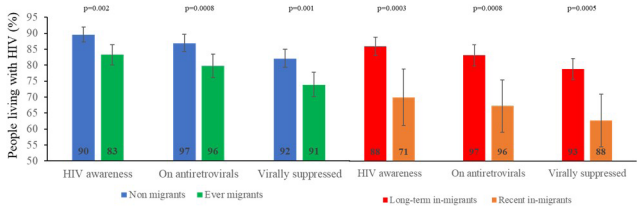
Conclusion: Our findings show changes in HIV epidemiology between 2013 and 2018 in subjects followed in metropolitan France, with a more pronounced decrease of new HIV diagnoses in subjects born in France, particularly among MSM and heterosexual women. Our results support the long-term effectiveness of TasP strategy among the various tools for HIV prevention.

1078 MOBILITY, NEW HIV INFECTIONS, AND PROGRESS TOWARD THE 90-90-90 TARGETS IN NAMIBIA

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Background: Namibia has high HIV prevalence and migration rates, yet little is known about how migration affects HIV transmission. We assessed the impact of mobility on HIV transmission and treatment outcomes using data from the 2017 Namibia Population-based HIV Impact Assessment (NAMPHIA).
Methods: NAMPHIA included a nationally representative sample of adults aged 15–64 years. Recent infection (<130 days) was measured using HIV-1 LAg avidity combined with viral load (>1000 copies/mL) and antiretroviral (ARV) testing data. Awareness of HIV status and ARV use were based on self-report and/or detectable ARVs in blood. Viremia was defined as no viral load suppression (VLS, <1000 copies/ml) regardless of serostatus; community viremia was a weighted average across the sampled enumeration area. Ever migrants (EM) included those who had lived outside their home region, or away from home >1 month in the past 3 years. Recent in-migrants (RM) were those who moved to the community <2 years prior, even if this was an intra-regional move, compared to long-term in-migrants. Hazardous alcohol use was defined using the AUDIT-C scale. Analyses were run on weighted data.
Results: Of eligible adults, 84% (9,671/11,510) of women and 73% (7,268/9,954) of men were interviewed and tested for HIV. Overall, 6.1% reported living outside Namibia, 52.5% had lived in another region, and 28.8% had lived away from home for >1 month, for a total of 62.5% of adults classified as EM; 15.3% of adults were RM. HIV prevalence was 12.6%, and did not differ by migration status; population VLS was 77.4%. RM was associated with recent HIV infection (adjusted odds ratio [aOR], 4.16; 95% confidence interval [CI]: 1.05–16.51) but only in communities with viremia >1%. Both EM and RM had lower proportions of VLS primarily due to less awareness of being HIV positive (Figure). If aware, there were no significant differences in proportion on ART for EM or RM. There was weak evidence that RM on ARVs had less VLS than long-term in-migrants (93% vs. 88%, p=0.059). On multivariable analysis, adjusted odds of VLS were low for RM (aOR, 0.57; 95% CI: 0.35–0.92) and for those with hazardous alcohol use (aOR, 0.29; 95% CI: 0.45–0.92).
Conclusion: Namibia has achieved a high level of population VLS. Understanding how to reach at-risk migrants with prevention and treatment can help further optimize the national HIV response.

Figure. Awareness of HIV diagnosis, antiretroviral status, and viral suppression by migration status in Namibia (2017)



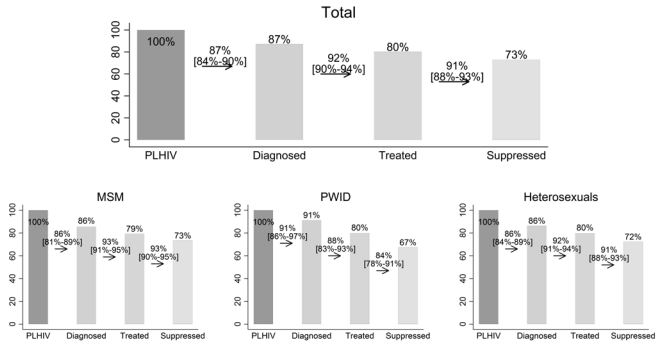
Inset numbers are conditional percentages, and bar height indicates the proportion of all people living with HIV (PLHIV). Antiretroviral status was determined by self-report and/or those who tested positive for nevirapine, lopinavir, and efavirenz. P-values indicate significance of difference between overall proportions, using chi-squared analysis on weighted data. There were no significant differences between conditional percentages.

1079 PROGRESS TOWARDS THE 90-90-90 HIV TARGETS IN 11 EU COUNTRIES

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Background: Despite the availability of highly effective antiretroviral treatment (ART), delayed diagnosis and ART initiation, and poor retention in care remain barriers to reducing HIV incidence. We aimed to estimate progress towards the UNAIDS 90-90-90 targets by constructing the continuum of HIV care (CoC) in 2016 in 11 European Union (EU) countries, overall and by key population and sex.
Methods: Using surveillance and cohort data from Austria, Croatia, Denmark, Germany, Greece, France, Italy, the Netherlands, Spain, Sweden and the United Kingdom, a CoC was constructed with four stages: i) number of people living with HIV (PLHIV); ii) proportion of PLHIV ever diagnosed; iii) proportion of diagnosed who initiated ART; iv) proportion of treated who achieved viral suppression (≤200 copies/mL) at their last visit (July 2015- December 2016). The 11 countries represent 73% of EU population and 85% of PLHIV in the region.
Results: The estimated number of PLHIV in the participating countries at the end of 2016 was 702,848, corresponding to 0.19% adult prevalence. Overall, we estimated that 87% of PLHIV were diagnosed; 92% of those diagnosed had initiated ART; and 91% of those on ART were virally suppressed. Therefore, among all PLHIV 73% were virally suppressed. The corresponding figures for men having sex with men (MSM) were: 86%, 93%, 93% (and among all PLHIV 74%); for people who inject drugs (PWID): 91%, 88%, 84% (67%); for heterosexuals: 86%, 92%, 91% (72%); for men: 87%, 92%, 91% (73%) and for women: 89%, 92%, 89% (73%). Substantial variation across countries was observed.
Conclusion: The EU is near to reaching the 90-90-90 UNAIDS targets, and achieved the UNAIDS final target of 73% of all PLHIV with viral suppression. This finding represents a significant progress compared to 2013, where 60% of all PLHIV were virally suppressed. However, differences between countries and key populations persisted in 2016. To improve outcomes along the CoCs, annual numbers of newly-acquired HIV infections and time intervals spent between stages need to be reduced. Furthermore, strengthening of testing programs and stronger treatment and adherence support, along with HIV prevention measures, are needed to achieve HIV epidemic control and, ultimately, AIDS elimination by 2030.

Figure: Continuum of HIV care for 2016, overall and by key population.
The numbers between the bars correspond to proportion of the previous stage, while the numbers on the bars correspond to proportions of all PLHIV indicated in first column.



1080 IMPROVING HIV CARE IN WEST AFRICA: EFFECTS OF A COMMUNITY TREATMENT OBSERVATORY

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Background: In West and Central Africa, 64% of people living with HIV (PLHIV) are aware of their status, 51% are accessing antiretroviral therapy (ART), and 39% are virally suppressed. Progress is stymied by low demand for services, drug stock-outs, weak health systems and poor quality of care. In 2017, the International Treatment Preparedness Coalition (ITPC) established a Regional Community Treatment Observatory in West Africa to increase accountability for the 90-90-90 targets.
Methods: ITPC trained and supported national networks of PLHIV to collect and analyze facility-level HIV treatment data from 125 health centers in 11 West African countries. From January 2018-June 2019, the treatment observatory conducted 1781 monthly monitoring visits to the health centers, complemented by 1501 interviews, and 143 focus group discussions. Feedback was provided to communities, government and health center staff on a quarterly basis to help improve performance.

Results: At the monitored health centers, the number of HIV tests performed increased from 161,647 in the first six-month period, to 246,604 in the second, and fell to 223,612 in the third. HIV-positive yield rose from 3.0%, to 5.4%, to 5.5%, respectively. The frequency of ART stock-outs decreased over the course of the project. Stock-outs were recorded during 23.6% (95% CI 19.9%-27.2%) of health center visits in the first period, declining to 16.4% (95% CI 13.6%-19.3%) in the second, and 15.2% (95% CI 12.3%-18.1%) in the third. The number of viral load tests performed more than doubled, increasing from 16,532 in the first period, to 31,472 in the second, to 33,376 in the third. The rate of viral suppression also increased dramatically, from 48.3% in the first period, to 67.9% in the second, and 77.4% in the third. According to patients, the quality of services improved. The average quality of care rating rose from 3.8/5.0 in the first period, to 4.0/5.0 in the second, to 4.2/5.0 in the third.
Conclusion: The treatment observatory improved data transparency, creating a culture of collective problem-solving among patients, healthcare workers and policy-makers. The project triangulated anecdotal evidence of facility-level improvements with macro data trends that show regional-level progress. This provides proof of concept for the positive effects of community-led monitoring when done at scale. The approach should be expanded to help achieve global HIV treatment targets.

1081 ROUTINE LABORATORY DATA FOR ESTIMATING POPULATION VIRAL SUPPRESSION IN SOUTH AFRICA

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Background:
There are few population-wide data on viral suppression (VS) that can be used to monitoring programmatic targets in sub-Saharan Africa. We describe how routinely collected viral load (VL) data from ART programmes can be extrapolated to population VS and validate this using a combination of empiric and model-based estimates.
Methods: We used routine VL testing data for the Western Cape province for the January 2008 to September 2018, obtained from the South African National Health Laboratory Service. We carried out record linkage using a combination of deterministic and probabilistic linkage with hierarchical clustering to obtain linked results for individuals. Test- and individual-level VS rates were based on test VL values <1000 cps/ml, and individual VL <1000 cps/mL in a calendar year, respectively. We calculated population VS among people living with HIV (PLWH) in the province by combining census derived mid-year population estimates, HIV prevalence estimates and individual level VS estimates from routine VL data. Sensitivity analyses examined subgroups by age, year and gender.
Results: Approximately 1.9 million tests from 530 clinical sites were included, with VL testing volumes increasing by 500% between 2008 and 2018. Among individuals in care, VS increased from 84% in 2008 to 90% in 2018. Population VS among all PLWH in the province increased from 12.2% in 2008 to 51.0% in 2017. The estimates derived from this method are comparable to those from other published studies including surveys specifically designed to estimate HIV prevalence and population viral suppression (HSRC National HIV Prevalence, Incidence, Behaviour and Communication Survey - SABSSM V), where 54.7% of PLWH had VS in 2017. This method also demonstrates close alignment with National Department of Health estimates (<2% difference across all years). Sensitivity analyses showed that the results are robust to variations in linkage method, but sensitive to the extreme combinations of assumed ART coverage and population HIV prevalence.
Conclusion: While validation of this method in other settings is required, this approach provides a simple, robust method for estimating population VS using routine data from ART services that can be employed by national programmes in high-burden settings.

TABLE: Proportion of all HIV-positive adults aged 15-59 years on ART with VL <1000 cp/mL; proportion of individuals with VL<200 cp/mL among those with VL<1000 cp/mL, and percentage of those with <200 cp/mL among participants on ART and self-reported ART ≥12 months, Population-based HIV Impact Assessment (PHIA) Surveys — six sub-Saharan African Countries, 2015-2018

Country	Percentage of HIV-positive adults on ART with VL<1000 among all HIV-positive adults% (95% CI)	Percentage of HIV-positive adults on ART with VL<200 cp/mL among those with VL<1000 % (95% CI)	Percentage of HIV-positive individuals on ART, self-reported ≥12 months on ART, and VL <200 cp/mL among all individuals with VL<1000 cp/mL % (95% CI)
Uganda	83.9 (81.6-86.2)	92.8 (90.8-94.7)	94.4 (92.3-96.4)
Lesotho	87.7 (86.1-89.3)	95.6 (94.8-96.4)	96.7 (95.9-97.7)
Tanzania	87.0 (84.2-89.8)	95.6 (94.5-97.2)	97.4 (95.8-98.9)
Malawi	91.2 (89.1-93.2)	95.7 (94.3-97.1)	97.0 (95.6-98.4)
Zambia	89.2 (87.3-91.1)	96.1 (95.0-97.3)	97.4 (96.3-98.5)
Cameroon	79.4 (74.1-84.7)	95.5 (93.3-97.6)	97.8 (95.7-99.9)
Total	86.9 (86.4-87.4)	95.1 (94.7-95.4)	96.6 (96.2-96.9)

1082 POPULATION-BASED HIV IMPACT ASSESSMENTS AND VIRAL LOAD RESULTS: IMPLICATIONS FOR U=U

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Background: Undetectable equals Untransmittable ("U=U") is a message that conveys no risk of sexual transmission when people living with HIV (PLHIV) have a viral load (VL) <200 HIV RNA copies per milliliter of blood (cp/mL). VL assays that use dried blood spots (DBS) have a minimum detection threshold of 700-839 cp/mL, in contrast to VL assays that use plasma which can detect <200 cp/mL. Because some countries rely on DBS-based VL testing that is unable to detect the U=U threshold of <200 cp/mL, some providers are reluctant to adopt U=U messaging, especially in areas where plasma VL assays are not universally available. To address this potential barrier, we assessed the proportion of those with VL <200 cp/mL among PLHIV participants with VL <1000 cp/mL and were taking antiretroviral therapy (ART).
Methods: We conducted a pooled multi-country secondary data analysis using complex survey design and weights of the 2015-2018 cross-sectional Population-based HIV Impact Assessments (PHIA) in six sub-Saharan African countries. Inclusion criteria were: adults aged 15-59 years who tested HIV-positive in the PHIA surveys; on ART, defined as detectable antiretrovirals and/or self-report of current ART use; and available plasma VL results. Of the HIV-positive adults on ART who had a VL <1000 cp/mL (World Health Organization's definition of viral load suppression (VLS)), we calculated the proportion who met the U=U cutoff of <200 cp/mL. .
Results: Overall, of the 8,031 HIV-positive adults on ART, 86.9% (95% confidence interval (CI) 86.4-87.4) had a VL <1000 cp/mL. Of the 7,003 participants on ART with a VL <1000 cp/mL, 95.1% (95% CI 94.7-95.4) had a VL <200 cp/mL. Of the 4,970 participants with a VL <1000 cp/mL who were on ART and self-reported current ART for ≥12 months, the proportion with VL <200 cp/mL was 96.6% (95% CI 96.2-96.9).
Conclusion: These nationally representative population-based data demonstrate that a very high proportion of all HIV-positive adults on ART with VL <1000 cp/mL also had VL <200 cp/mL, suggesting that U=U messaging may be suitable even in settings limited to DBS-based VL measures. With continued ART adherence and high-quality laboratory sample collection and systems to verify VLS, PHIA data supports that the scale-up of U=U messaging may be appropriate regardless of which VL testing platform is available.

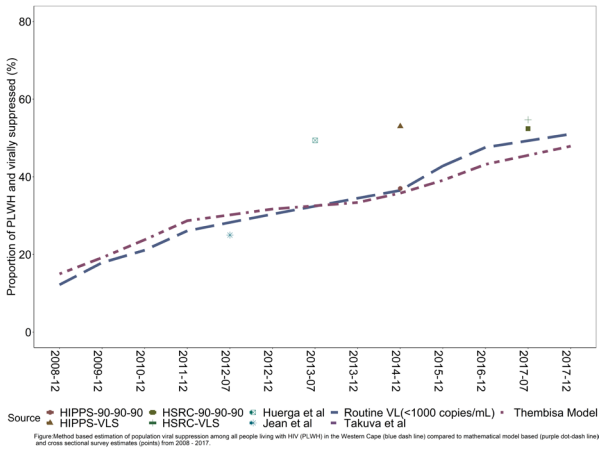


Figure:Method based estimation of population viral suppression among all people living with HIV (PLWH) in the Western Cape (blue dash line) compared to mathematical model based (purple dot-dash line) and cross sectional survey estimates (points) from 2008 - 2017.

1083 VIRAL SUPPRESSION TRAJECTORIES AMONG HIGH-NEED PATIENTS IN LOW-BARRIER HIV CARE

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Background: Ending the HIV epidemic will require intensive efforts to sustain viral suppression among persons with HIV who have complex medical and social barriers to care. We previously showed that a clinic offering walk-in, incentivized care (the Max Clinic) improves viral suppression. Here we examine viremia trajectories among Max Clinic patients.

Methods: We included patients with ≥180 days of observation time after enrollment during Dec 2014-Jan 2019, starting on the enrollment date and ending at the time of death, relocation, or July 31, 2019. We categorized patients into groups defined a priori based on knowledge of common viremia trajectories: 1) early consistent suppression [first viral load (VL)<200 copies/mL ≤6 months (mo) after enrollment; all subsequent VL<200]; 2) late consistent suppression (first VL<200 >6 mo after enrollment, all subsequent VL<200), 3) transient/intermittent suppression (≥1 VL<200, subsequent VL>200); and 4) no suppression (no VL<200). We compared the characteristics of patients in each group using $\chi 2$ tests for categorical variables and Kruskal-Wallis One-way ANOVA for continuous variables.

Results: Among 167 patients with a median observation time of 27 mo [interquartile range (IQR): 16-39 mo], 69% were homeless or unstably housed at enrollment, 54% used methamphetamine, 51% injected drugs, and 32% had a diagnosed psychotic, bipolar or personality disorder. Most patients (59%) had transient/intermittent suppression, followed by early consistent suppression (26%), no suppression (10%) and late consistent suppression (5%). The groups differed by the median observation time, which was shorter in the no suppression (15 mo) and early consistent suppression (20 mo) groups than in the transient/intermittent suppression (34 mo) and late consistent suppression (37 mo) groups (p<0.001). The groups did not differ significantly by gender, race, ethnicity, housing status, substance use or depression/anxiety disorder diagnoses. Patients with psychotic, bipolar disorder or personality disorder were less likely to be in the late or no suppression groups (p<0.04). The median time from the first suppressed VL to a subsequent unsuppressed VL was 4 mo (IQR 2-10 mo).

Conclusion: The vast majority of patients in the low-barrier clinic reach viral suppression even in the context of unstable housing, substance use, or severe mental illness, but most are intermittently unsuppressed. Even with low-barrier care and high-intensity support, most patients continue to have periods of viremia.

1084 ROUTINE PHARMACY REFILLS PREDICT WOMEN'S PLASMA ARV DETECTION AND VIRAL SUPPRESSION

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Background: Detection of antiretrovirals (ARV) is an objective adherence measure that predicts HIV treatment outcomes, however, routine ARV testing is currently not feasible in high-burden settings. We examined how pharmacy refill data predicts ARV detection in plasma and viral suppression (VS) in a routine care cohort in Cape Town, South Africa.

Methods: HIV+ women who initiated TDF+XTC+EFV during pregnancy and achieved VS (≤50 cps/mL) were followed for up to 24 months. Plasma viral load and presence of ARV (>20 ARVs tested for using mass-spectrometry) were measured at multiple study visits. Patient-level routine pharmacy data were used to classify each visit as: having no ARVs in hand (i) today, (ii) for >30 days, or (iii) >90 days prior. Generalised estimating equations were used to calculate associations between ARV in hand, VS, and detectable ARV in plasma. Secondary analyses were restricted to a) women who stayed in one of three large clinics to minimize heterogeneity in routine data, and b) the first visit to calculate diagnostic characteristics.

Results: Across 237 women and 417 visits (median 10 months on ART, IQR=7-14) 46% were not VS. Any ARV was detected in plasma at 60% of visits, of which EFV was detectable in 98%, TFV in 65% and FTC in 73% of visits. Patients were classified as having no ARV in hand at 56% of visits, with 81% and 63% of these having no ARV in hand for >30 and >90 days, respectively. Absence of any ARV in plasma was strongly associated with viraemia (OR 70.6, 95% CI 35.7-139.6). No ARVs in hand today (OR 7.7, 95% CI 4.7-12.6), for >30 days (OR 15.0, 95% CI 6.5-25.3) and >90 days (OR 19.7, 95% CI 10.8-35.6) were also associated with viremia; similar associations were observed between drugs in hand and plasma ARV detection (Table). Associations with VS, but not plasma ARVs, strengthened when restricted to women who were in care at one of three large clinics. At the first visit, increasing time with no ARV in hand resulted in decreased sensitivity (VL 76% to 33%; plasma ARV 83% to 35%) and increased specificity (VL 67% to 92%; plasma ARV 68% to 92%).

Conclusion: Although ARV detection in plasma was the best predictor of virologic outcomes, having ARV in hand was a strong predictor of VS and presence of ARV. Routine pharmacy data provides a feasible, inexpensive alternative objective measure of ART adherence for public sector programme evaluation in high-burden settings.

Table. Crude odds ratios (OR) and diagnostic characteristics of pharmacy and self-reported adherence indicators to predict i) viral load >50 cps/mL and ii) absence of ARVs in plasma. Presented with 95% confidence intervals (CI).

	All points	Sensitivity analysis [a]	Diagnostic characteristics [b]	
Number of observations	417	131	237	
Number of women	237	76	237	
i. Viral load > 50 copies/mL	**Crude OR (95% CI)**	**Crude OR (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
No ARVs in plasma (assay)	70.6 (35.7-139.6)	82.4 (20.4-332.3)	48 (26-70)	94 (90-97)
No drug in hand today (pharmacy)	7.7 (4.7-12.6)	13.88 (6.2-30.9)	76 (53-92)	67 (60-73)
No drug in hand for >30 days (pharmacy)	15.0 (8.9-25.3)	24.2 (8.6-68.0)	62 (38-82)	82 (77-87)
No drug in hand for >90 days (pharmacy)	19.67 (10.8-35.6)	41.82 (11.64-150.28)	33 (14-57)	92 (87-95)
Any missed doses in the past 30 days (self-report)	1.9 (1.3-2.3)	1.3 (0.6-2.9)	29 (11-52)	86 (80-90)
ii. No ARVs detected in plasma	**Crude OR (95% CI)**	**Crude OR (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
No drug in hand today (pharmacy)	9.7 (6.1-15.3)	9.3 (3.8-22.7)	83 (61-95)	68 (62-75)
No drug in hand for >30 days (pharmacy)	14.0 (8.5-23.3)	14.4 (5.6-36.9)	70 (47-87)	84 (78-88)
No drug in hand for >90 days (pharmacy)	15.5 (9.0-26.8)	14.3 (5.3-38.3)	35 (16-57)	92 (88-95)
Any missed doses in the past 30 days (self-report)	1.6 (1.1-2.5)	1.2 (0.5-2.6)	13 (3-34)	84 (78-87)

[a] Restricted to women who attended one of three large primary care clinics and did not receive care at multiple sites
[b] Restricted to the first measurement point for each women

1085 HIGHER INCOME INEQUALITY IS ASSOCIATED WITH LOWER CUMULATIVE ANTIRETROVIRAL ADHERENCE

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Background: Tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) is associated with viral suppression and predicts future viremia. However, its association with the social determinants of health (SDoH) in people living with HIV (PLWH) has not been evaluated.

Methods: DBS for TFV-DP were prospectively collected from a clinical cohort of PLWH receiving tenofovir disoproxil fumarate (TDF)-based therapy (up to 3 visits over 48-weeks between 2014 and 2017). Zip code was collected at enrollment and matched with the relevant SDoH data from 2016 obtained from AIDSVu (aidsvu.org). SDoH data included household income, percent living in poverty, education level and income inequality (the latter was quantified using the Gini coefficient, where 0 and 1 represent absolute income equality and inequality,

respectively). Log-transformed TFV-DP concentrations were analyzed using a mixed-effects model. Baseline statistics are presented as median (interquartile range). Model results are percent change [95% confidence interval] in TFV-DP for every significant change in the SDoH. All results are reported with no adjustment for multiple comparisons.

Results: A total of 950 person-visits from 430 participants were analyzed, encompassing zip codes within the following Colorado counties: Denver, Arapahoe, Jefferson, Adams and Douglas. Baseline household income, Gini and TFV-DP concentration were $56,227 ($46,763, $70,369), 0.418 (0.391, 0.487) and 1721 (1181, 2441) fmol/punch, respectively. After adjusting for age, sex, race, estimated glomerular filtration rate, body mass index, hematocrit, CD4+ T-cell count, antiretroviral drug class and 3-month self-reported adherence, Gini was inversely associated with TFV-DP in DBS. For every 0.1 increase in Gini, TFV-DP concentration decreased by 9.2% [0.5, 17.1%; P=0.039]. Gini remained significant after adjusting for HIV viral suppression with the same 0.1 increase estimating a decrease of 8.7% [0.3 17.9%; P=0.042] in TFV-DP concentrations. No statistically significant associations were identified between TFV-DP concentration and the other SDoH (Table).

Conclusion: Greater income inequality was associated with lower TFV-DP concentrations in PLWH on TDF, suggesting that adherence may be influenced by population level characteristics that exist in the presence of income inequality and impact individual level health outcomes. Future studies on the utility of this adherence biomarker to improve clinical care and adherence in marginalized PLWH are needed.

Table. Percent change in TFV-DP concentration in DBS (fmol/punch) for every change in the social determinant of health.

Social Determinant	Adjusted*		
	Percent change in TFV-DP concentration in DBS (fmol/punch)	95% CI	p-value
0.1 increase in Gini coefficient	-9.2%	(-17.1, -0.5%)	0.039
10% increase in persons living in poverty	1.9%	(-6.0, 10.5%)	0.65
10% increase in persons with high school diploma or equivalent	-3.5%	(-8.8, 2.1%)	0.22
$10,000 increase in median household income	-0.2%	(-3.3, 3.0%)	0.90

*Adjusted for age, sex, race, estimated glomerular filtration rate, body mass index, hematocrit, CD4+ T cell count, antiretroviral drug class, and 3-month self-reported adherence.

1086 OPTIMIZATION OF HIV CLINIC INTAKE PROCESS TO REDUCE TIME TO VIRAL SUPPRESSION

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Background: This study describes a novel clinic intake process to more rapidly initiate antiretrovirals (ARVs) and compares mean time to initiate ARVs as well as time to viral suppression from before and after the advent of this new intake process.

Methods: In April 2018, the UC San Diego Owen Clinic developed a new intake process that included an initial visit with a multidisciplinary team to improve access while providing the opportunity for rapid initiation or optimization of ARVs at first visit using clinical pharmacy services. Prior to this new process, patients only met with licensed vocational nurses (LVNs) at their initial intake visit. We conducted a retrospective study comparing time to initiate ARVs as well as time to viral suppression before and after this new intake process was implemented. We also evaluated clinic retention rates within both 1 month and 6 months of initial visit. Predictors of lack of retention in care were also evaluated.

Results: We included 379 patients in the analysis. Table 1 shows demographic data, psychosocial data, and baseline virologic data. In the new intake cohort, there were significant reductions in mean time to initiate ARVs (54.2 days vs. 7.8 days, p=0.0002) and mean time to viral suppression (217.9 days vs. 75.9 days, p<0.0001). There was no significant difference in the proportion of patients retained either short or long term. Although not statistically significant, after logistic regression there was a trend that black patients were more likely to fall out of care long term (p=0.0535).

Conclusion: We observed significant reductions in time to initiate ARVs and time to viral suppression in the new, pharmacist driven intake cohort. Similar intake processes that facilitate rapid modification and initiation of ARVs should be routine in order move toward more rapid viral suppression among PLWH.

Table 1. Characteristics of the Patients at Baseline

Variable	Multidisciplinary (new) Intake Cohort (n=186)	LVN (old) Intake Cohort (n=193)	P-Value
Mean age – yr. (range)	44 (25-76)	45 (23-77)	**0.0023**
Female sex – n (%)	19 (10.2)	19 (9.8)	0.90
Race – n (%)			
White	114 (61.3)	101 (52.3)	0.078
Black	21 (11.3)	30 (15.5)	**0.03**
Asian	10 (5.4)	6(3.1)	0.27
Unknown	38 (20.4)	43 (22.2)	0.66
Other	3 (1.6)	13 (6.7)	**0.013**
Ethnicity – n (%)			
Non-hispanic	128 (68.8)	133 (68.9)	0.98
Hispanic	56 (30.1)	52 (26.9)	0.50
Unknown	2 (1.1)	8 (4.1)	0.06
Psychosocial factors – n (%)			
Active neuropsychiatric disease	67 (36.0)	81 (42.0)	0.24
Ongoing substance abuse	77 (41.4)	69 (35.8)	0.26
Ongoing EtOH use	95 (51.1)	60 (31.1)	**0.00008**
Intake status			
Mean CD4 count – n (range)	548 (0-1656)	522 (5-1409)	0.43
Mean VL if viremic – copies/mL	154586	150225	0.95
Viral load <40 at intake – n (%)	99 (53.2)	106 (55.9)	0.74
On ARVs at time of intake – n (%)	130 (69.9)	126 (65.3)	0.34
Mean time since diagnosis – months	117.3	167.4	**<0.0001**
Recent HIV diagnosis (<6 months) – n (%)	43 (23.1)	20 (10.4)	**0.0008**

1087 USE CASE FOR NEAR POINT OF CARE HIV VIRAL LOAD: TARGETED TESTING AT LARGE FACILITIES

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Background: Point-of-care (POC) technologies in resource-limited settings can circumvent challenges of centralized laboratory testing, leading to an increased proportion of results used for clinical management. However, higher device costs and uncertain use cases for POC in routine care have inhibited scale-up. To address this gap, we investigated the feasibility and cost of targeted near-POC viral load (VL) testing in two large HIV clinics in Lilongwe, Malawi.

Methods: VL testing using GeneXpert was targeted for patients suspected of treatment failure or returning to care following a previously elevated VL (>1,000 copies/ml). Descriptive analysis of retrospective clinical and cost data are presented.

Results: During the 12-month study period, 2813 near-POC VL tests were conducted. 1511 (54%) tests were for onsite patients for whom results and reason for test were documented: 53% (794/1511) of tests were to confirm a previously high VL, and 31% (462/1511) were due to clinical indications. Overall, 61% (926/1511) of patients had a high VL, of whom 78% (719/926) had a recorded clinical action: 77% (557/719) switched to second line ART and 15% (194/719) were referred for intensive adherence counseling. Nearly 79% (567/719) of patients received a clinical action on the same day as testing. The 'all-in' cost was $33·71 for a valid near-POC VL test, compared to an international benchmark for a centralized VL test of $28·62.

Conclusion: Targeted, near-POC VL testing was feasible and consistently enabled prompt clinical action. According to national data, fewer than 3% of patients are on a second-line regimen, suggesting that routine VL results are likely underutilized; near-POC VL may be an attractive modality to ensure patients are on optimized regimens. The difference between the 'all in' cost of near-POC VL and centralized testing of $5·09 could be further reduced in an optimized national program combining targeted near-POC testing and centralized testing.

Cost Category	Study Amt (USD)	Scale-up Amt (USD)
Materials	$15.80	15.80
Staff	$2.31	2.31
Quality Control	$0.00	0.04
Equipment	$4.66	1.42
Other	$6.53	2.09
Overhead	$4.40	3.25
Total per Test	**$33.71**	**$24.92**
Total Per Result	**$35.46**	**$26.22**

1088LB 3- VS 6-MONTHLY DISPENSING OF ART IN COMMUNITY ART GROUPS: A CLUSTER-RANDOMIZED TRIAL

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Background: Multimonth dispensing (MMD) of antiretroviral treatment (ART) is a differentiated service delivery model aiming to reduce patient-related barriers to care and improve health system efficiency in low-income settings. There is increased interest in MMD models, however, randomized evidence of its clinical effectiveness is lacking. We performed a cluster-randomized trial comparing three and six-monthly MMD in community-based ART refill groups (CARGs) versus standard-of-care facility-based ART delivery in Zimbabwe.

Methods: A three-arm, unblinded, pragmatic cluster-randomized, non-inferiority trial. Thirty healthcare facilities (clusters) and linked CARGs were allocated to either: ART collected three-monthly at facility (3MF, control); ART provided three-monthly in CARGs (3MC); or ART provided six-monthly in CARGs (6MC). Stable adults receiving ART ≥six months with baseline viral load (VL) <1000 copies/ml were enrolled. Retention in ART care (primary outcome) and viral suppression (VS) 12 months after enrolment were compared by arm, using regression models specified for clustering. ClinicalTrials.gov, NCT03238846.

Results: 4800 participants were enrolled; 1919, 1335 and 1546 in 3MF, 3MC and 6MC, respectively. Retention was high and similar in all arms, 93.0%, 94.8% and 95.5% in 3MF, 3MC and 6MC, respectively (table). The pre-specified non-inferiority limit (-3.25%, risk difference [RD]) was met for comparisons between all arms; 3MC vs. 3MF, adjusted RD=1.1% (95% CI: -0.5% to 2.8%); 6MC vs. 3MF: aRD=1.2% (CI: -1.0% to 3.6%); and 6MC vs. 3MC: aRD=0.1% (CI: -2.4% to 2.6%). VL completion at 12 months was 49%, 45% and 8% in 3MF, 3MC and 6MC, respectively.VS in 3MC (99.7%) was high and not different to 3MF (99.1%), relative risk=1.0 (CI: 1.0-1.0). VS was marginally reduced in 6MC (92.9%) vs. 3MF, relative risk=0.9 (CI: 0.9-1.0).

Conclusion: Retention in CARGs receiving three and six-monthly MMD was noninferior to standard-of-care facility-based ART delivery in Zimbabwe for stable patients, and is a strategy that can be scaled-up. VS in six-monthly CARGs requires further evaluation.

	Retention (primary outcome)						Viral suppression (secondary outcome)						
	Enrolled	Retained		Adjusted Risk Difference (RD)			Viral load done	Viral load completion	Suppressed		Relative Risk (RR)		
Arm	N	n	%	RD	95% CI	P	N	%	n	%	RR	95% CI	P
3MF (control)	1919	1784	93.0%	Reference	-	–	865	49.0%	857	99.1%	Reference	-	-
3MC	1335	1265	94.8%	1.1%	-0.5 to 2.8	0.174	566	44.8%	564	99.7%	1.0	1.0–1.0	0.49
6MC	1546	1477	95.5%	1.2%	-1.0 to 3.6	0.277	113	7.7%	105	92.9%	0.9	0.9–1.0	0.070
6MC vs. 3MC				0.1%	-2.4 to 2.6	0.932					0.9	0.9–1.0	0.083

1089LB F/TAF VS F/TDF FOR PrEP: HOW MUCH IS "BETTER" WORTH?

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Background: F/TAF is approved as a safer, non-inferior PrEP option compared with F/TDF. With generic F/TDF expected in 2020, we examine how much more payers should be willing to pay for the improved safety profile of branded F/TAF.

Methods: We assembled safety data for F/TAF and F/TDF in an age-stratified population of 123,610 US MSM without HIV and from studies of people with HIV. Data were used to forecast fractures, ESRD cases, quality-adjusted life years (QALYs), costs, and incremental cost-effectiveness ratios (ICERs) over 5y. To determine the maximum price differential for F/TAF (currently $16,600/year, Federal Supply Schedule) over generic F/TDF, we portrayed F/TAF as favorably as possible, ignoring any ASCVD effects and overstating its safety. For example, we assumed for those on F/TDF that: 1) severe loss of bone mineral density resulted in osteoporosis-related fractures and that all fractures occurred at the hip, leading to a one year 30% quality of life (QoL) decrement and a cost of $70,400; 2) background ESRD rates were more than double their reported value and ESRD was immediate and irreversible, resulting in a 47% QoL decrement and costs of $92,100-$95,500 each year; and 3) the generic F/TDF alternative would achieve a modest (50%) price reduction to $8,300/year. We also examined the budget impact of F/TDF vs. F/TAF, comparing PrEP coverage and transmissions.

Results: Compared to F/TDF, F/TAF averted 2,101 fractures and 30 ESRD cases, the ICER exceeded $7 million/QALY gained (Table). At a willingness to pay of $100,000/QALY, the maximum justifiable price for F/TAF was $8,680/year. Even among patients at highest risk of fracture and ESRD (>55y), the ICER for F/TAF exceeded $3 million/QALY and the maximum justifiable price was $9,020/year. Results were robust to alternative time horizons and PrEP-using population sizes; regardless of age and F/TDF costs, the maximum justifiable markup over generic F/TDF was <$750/yr. Using the entire US HIV prevention budget ($900.8M) and base case assumptions of F/TAF and F/TDF costs, 54,270 people could receive F/TAF and 105,210 could receive F/TDF annually; this difference in PrEP coverage would result in an additional 8,610 new HIV infections with F/TAF.

Conclusion: Given its minimal impact on adverse events, F/TAF justifies a markup no greater than $750 over generic F/TDF in the US. At a higher price, it may well do more harm than good.

Table. Five-year clinical and cost outcomes of F/TAF compared to generic F/TDF as PrEP for MSM in the US*

		F/TAF Outcomes		F/TDF Outcomes				
Age group (years)	# on PrEP	QALYs	Costs ($)	Excess cases of ESRD	Excess fractures	QALYs	Costs ($)	ICER ($Δ/ΔQALYs)
13-24	16,069	80,344	1,333,700,000	0	128	80,305	675,930,000	16,958,000
25-34	49,442	247,210	4,103,700,000	3	393	247,090	2,080,700,000	16,363,000
35-44	28,429	142,150	2,359,600,000	5	764	141,910	1,235,900,000	4,664,700
45-54	19,777	98,884	1,641,500,000	8	568	98,695	864,430,000	4,104,800
55+	9,888	49,442	820,740,000	14	250	49,333	434,850,000	3,544,000
Total**	123,610	618,030	10,259,000,000	30	2,101	617,330	5,291,800,000	7,081,100

F/TAF: tenofovir alafenamide/emtricitabine; F/TDF: tenofovir disoproxil fumarate/emtricitabine; PrEP: pre-exposure prophylaxis; MSM: men who have sex with men; QALY: Quality-adjusted life year; ESRD: end-stage renal disease; ICER: incremental cost-effectiveness ratio
*All costs reported in 2018 US dollars; **Values may not add to total due to rounding to five significant digits.

1090 COST-EFFECTIVENESS OF POINT OF CARE VIRAL LOAD ADOPTION STRATEGIES IN SOUTH AFRICA

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Background: Viral load (VL) testing is the recommended method for monitoring HIV patients on ART. South Africa, through the National Health Laboratory Service (NHLS), currently operates a highly centralized VL network that conducted > 5 million VL tests in 2018 at 16 laboratories. Despite this wide network, the system faces challenges surrounding sample integrity, result delivery and clinical action delays. Recent evidence suggests that point of care (POC) instruments could improve patient retention/viral suppression. We assessed the cost-effectiveness of POC adoption strategies to improve patient outcomes.

Methods: We developed a geospatial cost model utilizing existing data from NHLS, including geospatial data on facilities in South Africa who send blood samples to centralized laboratories for VL testing, their annual VL volume, suppression rates (<1000 copies/ml), sample rejection rates, turn-around time (TAT), and the cost per test. We assessed the impact of the adoption of two validated VL POC technologies (Cepheid GeneXpert and Abbott m-PIMA) under 4 scenarios: 1) status-quo (all centralized); 2) POC coverage at facilities with a combination of low suppression rates, and high rejection rates and TAT; 3) targeted POC just at facilities with low suppression rates; and 4) a complete switch from centralized to POC testing. For each scenario and POC technology we determined the total cost, effectiveness (total expected number of people with suppressed VL) and incremental cost-effectiveness ratio (ICER) based on expected improvement in suppression rates from POC adoption. The effectiveness of POC VL in improving viral suppression was varied in a sensitivity analysis.

Results: The centralized network costs $121m annually with a VL suppression rate of 85.2%. Scenario 3 (targeted testing) using the GeneXpert is considered highly cost-effective at $40 per additional person suppressed, compared to the centralized network. Should resources allow, the all-POC scenario using a mix of GeneXpert and m-PIMA may still be cost-effective with an ICER of $1,095 compared to Scenario 3, requiring an additional $52m annually. All other scenarios were dominated in the incremental analysis. When POC VL resulted in lower levels of viral suppression than expected, ICERs proportionally increased.

Conclusion: Assuming POC confers patient benefits, the most cost-effective strategy for POC adoption in South Africa is likely to be a targeted approach, with POC placed at facilities with high rates of viral failure.

Table 1: Cost, number of ART patients virally suppressed, and cost-effectiveness of point of care adoption strategies

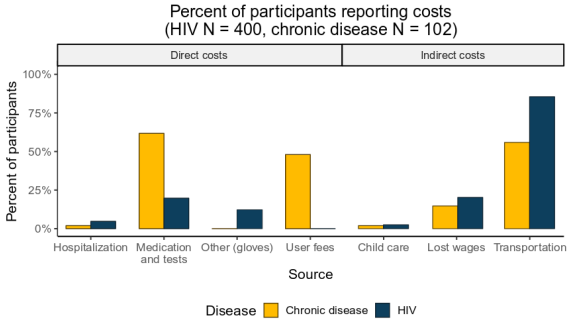
Scenario	Description	Technology	% Volumes tested by platform			Total cost (2019 USD)	Total number suppressed (%)	ICER
			m-PIMA	GeneXpert	Centralized			
1	All centralized/Status-quo	Centralized	0%	0%	100%	$121,304,818	4,396,698 (85.2%)	-
3	Targeted National*	GeneXpert only	0%	29%	71%	$123,191,104	4,443,810 (86.1%)	$40
3	Targeted National*	m-PIMA only	23%	0%	77%	$128,394,151	4,439,339 (86.1%)	dominated
2	Combination targeted**	GeneXpert only	0%	15%	85%	$132,843,388	4,418,763 (85.7%)	dominated
2	Combination targeted**	mix	13%	2%	85%	$136,562,405	4,418,763 (85.7%)	dominated
2	Combination targeted**	m-PIMA only	15%	0%	85%	$138,625,605	4,418,763 (85.7%)	dominated
4	All POC	mix	36%	64%	0%	$173,803,415	4,490,013 (87%)	$1,095
4	All POC	GeneXpert only	0%	100%	0%	$178,837,978	4,490,013 (87%)	dominated
4	All POC	m-PIMA only	100%	0%	0%	$236,421,405	4,490,013 (87%)	dominated

*Targeted to facilities with lowest viral suppression rates
**Targeted to facilities that have a combination of low viral suppression, long turnaround time and high sample rejection rates

1091 OUT-OF-POCKET SPENDING ON HEALTH FOR PEOPLE LIVING WITH HIV IN CÔTE D'IVOIRE

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Background: In Côte d'Ivoire (CI), out-of-pocket (OOP) spending on health services is a barrier to care and risk for impoverishment. Although people living with HIV receive free antiretroviral therapy (ART), OOP spending on other direct and indirect health costs may impede them from engaging with HIV treatment services.
Methods: A convenience sample of 400 HIV+ adults at 10 health facilities in rural and urban CI completed a tablet-based survey on health status, ART adherence, missed appointments, and OOP health spending. Participants (ppts) had been on ART for >1 year (yr) and missed >1 HIV appointment (appt) in the past yr. We performed descriptive statistics and simple linear regression analyses with bootstrapped 95% confidence intervals using the bias-corrected and accelerated method to test associations between OOP spending and number of missed HIV and chronic non-communicable diseases (NCD) appts.
Results Ppts were 77% female, 87% formally employed, and a median of 39 yrs old (IQR 33-49). Median time on ART was 4.7 yrs (IQR 2.8-7.4). 365 ppts (91%) reported OOP spending on HIV care, with a median of $16/yr (IQR 5-48). 34% of ppts reported direct costs –medications, tests, hospitalization, gloves– with a median of $2/yr (IQR 1-41). No ppts reported paying user fees on HIV services. 87% of ppts reported indirect costs –often on transportation, but also lost wages and childcare– with a median of $17/yr (IQR 7-41). 102 ppts (26%) reported having HIV and >1 NCD, most commonly hypertension or lung disease. Of these, 80 (78%) reported OOP spending on NCD care, with a median of $50/yr (IQR 6-107). In contrast to ppts with HIV only, 76 ppts (95%) with both HIV & NCDs reported direct costs and 48% reported paying user fees on NCD services. Ppts had missed a median of 2 HIV appts in the past yr (IQR 2-3). When asked for reasons for missing HIV appts, cost was the 6th most-common cause, cited by 7% of ppts. Higher OOP costs were not associated with number of HIV appts missed. 66% reported they or a household member used savings to pay for health care, while 30% borrowed money and 6% sold assets. 21% of ppts reported spending >10% of household income on HIV and/or NCD care. This result was similar whether OOP spending was on HIV, NCD or both.
Conclusion: Despite free ART, most ppts reported OOP spending. OOP costs were higher for ppts with co-morbid NCD, contributing to financial distress.



1092 ENDING THE HIV EPIDEMIC IN BALTIMORE: A MODELING STUDY

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Background: Last year, the US government announced a plan to reduce HIV incidence by 90% by 2030 through the "90-90-90" target. However, it is not clear how these targets will perform in local epidemics, such as the one in Baltimore City, driven by heterogeneities in HIV transmission and access to care.
Methods: We extended the Johns Hopkins HIV economic-epidemic model (JHEEM), a validated compartmental model of HIV transmission, to represent population by sex (male/female), race/ethnicity (black, non-black), age strata (13-24, 25-34, 35-44,45-54, 55+ years old), and CDC risk groups (MSM, injection drug users, heterosexuals), and to include pre-exposure prophylaxis (PrEP). We calibrated the model using 10,000 simulations against CDC-reported new HIV diagnoses and persons living with HIV from 2010-2017 in the Baltimore metropolitan statistical area.
We ran each simulation multiple times from 2020-2030 under a range of potential interventions, targeting HIV testing frequency, proportion of HIV-diagnosed individuals virally suppressed, and proportion of at-risk individuals prescribed and adherent to PrEP. Interventions were targeted at different combinations of high-risk subgroups. For each intervention and target group, we estimated the reduction in total Baltimore incidence that could be achieved between 2020 and 2030. We calculated 95% uncertainty ranges (UR) by weighting simulations according to how well they fit the observed data from 2010-2017.
Results: Continuing testing, suppression, and PrEP at current levels projected a reduction in incidence of 13% [95%UR: 2-35%] from 2020-2030. Interventions targeted to Baltimore's highest-risk subgroups, black MSM and injection drug users, could achieve reductions of 57% [39-67%] (Table) with yearly testing, 90% suppression among people with diagnosed HIV, and 50% adherence to PrEP, and reductions up to 60% [42-71%] with 75% adherence to PrEP. Achieving close to 90% reduction in incidence from 2020 to 2030 among our tested interventions required expanding these interventions across the entire population.
Conclusion: Ending the HIV epidemic in Baltimore will be challenging, and will require several, broadly targeted interventions to achieve high levels of HIV suppression among diagnosed individuals with HIV as well as high uptake of PrEP and frequent screening across multiple subgroups.

Table: Model-Projected Reduction in Incidence [95% Uncertainty Range] from 2020 to 2030 Under Interventions Targeting Demographic Groups in the Baltimore Metropolitan Statistical Area

	*Testing Frequency**	As Is§	Yearly				
	Suppressed Proportion†	As Is	70%	70%		90%		
	PrEP Uptake‡	As Is	25%	25%	50%	25%	50%	75%
Targeted Groups	Black MSM 13-34yo	13% [2,35%]	13% [2,34%]	15% [5,36%]	17% [8,37%]	20% [10,40%]	22% [12,41%]	23% [14,42%]
	Black MSM or IDU 13-34yo	13% [2,35%]	13% [3,35%]	15% [5,36%]	18% [8,38%]	21% [11,41%]	23% [13,42%]	24% [15,43%]
	All Black MSM	13% [2,35%]	13% [2,34%]	20% [11,39%]	28% [4,45%]	50% [29,62%]	53% [33,64%]	56% [37,68%]
	All Black MSM or IDU	13% [2,35%]	14% [4,35%]	22% [12,40%]	30% [6,46%]	54% [34,65%]	57% [39,67%]	60% [42,71%]
	All MSM or IDU	13% [2,35%]	14% [4,35%]	23% [14,41%]	32% [9,48%]	56% [37,66%]	60% [43,70%]	63% [47,73%]
	Whole Population	13% [2,35%]	14% [4,36%]	33% [25,50%]	51% [20,67%]	71% [53,81%]	79% [65,86%]	86% [77,91%]

*Testing Frequency = the average frequency of HIV testing in targeted demographic groups. †Suppressed proportion = the proportion of those with diagnosed HIV who are suppressed in targeted demographic groups. ‡PrEP uptake = the proportion of those without HIV in targeted demographic groups who are prescribed and adherent to PrEP at any given time. §As is = continued at 2019 levels.

1093 WHAT WILL IT TAKE TO "END THE HIV EPIDEMIC"? AN ECONOMIC MODELING STUDY IN 6 CITIES

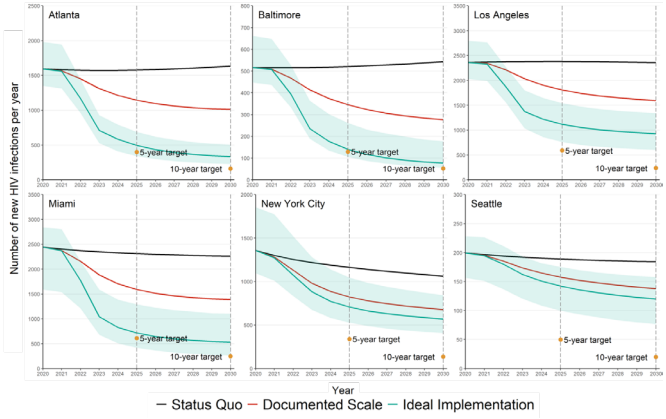
Bohdan Nosyk[1], Xiao Zang[1], Emanuel Krebs[1], Czarina N. Behrends[2], Carlos del Rio[3], Julia C. Dombrowski[4], Daniel J. Feaster[5], Matthew R. Golden[4], Brandon D. Marshall[6], Shruti H. Mehta[7], Lisa R. Metsch[8], Bruce R. Schackman[2], Steven Shoptaw[9], Steffanie A. Strathdee[10], for the Localized Economic Modeling Study Group
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Background: The HIV epidemic in the US is a collection of diverse local microepidemics. Targeted strategies have been proposed to reduce HIV incidence by 90% within 10 years. We aimed to identify optimal combination implementation strategies of evidence-based interventions to reach these targets in six cities, comprising 24.1% of people living with HIV/AIDS in the US.
Methods: Using a dynamic HIV transmission model calibrated with the best-available evidence on epidemiological and structural conditions for Atlanta, Baltimore, Los Angeles (LA), Miami, New York City (NYC) and Seattle, we assessed 16 evidence-based interventions (HIV prevention, testing, antiretroviral therapy (ART) engagement and re-engagement) to identify strategies providing the greatest health benefit while remaining cost-effective. Outcomes included averted HIV infections, quality-adjusted life-years (QALYs), total costs and incremental cost-effectiveness ratios (ICERs) (healthcare perspective; 3% annual discount rate; 2018$US). Interventions were implemented at previously-documented and ideal (90% coverage/adoption) scale-up, and sustained from 2020 to 2030, with outcomes evaluated until 2040.
Results: We assessed 23,040 combinations, with optimal strategies containing between eleven (NYC, Seattle) and thirteen (Atlanta, LA, Miami) interventions.

Implemented at previously-documented scale-up, these would reduce incidence by 30.8% (95% credible interval: 19.2%-43.8%) (Seattle) to 50.1% (41.5%-58.0%) (NYC) by 2030, at ICERs ranging from cost-saving in Miami to $136,718/QALY in Atlanta. These rose to 39.8% (26.7%-54.1%) in Seattle to 85.1% (72.3%-88.5%) in Baltimore at ideal implementation. Combined costs of implementing strategies at previously-documented scale-up totaled $671M/year at peak levels (2.3 times the initially-proposed 2020 funding allocation); however, costs were offset by long-term reductions in new infections and delayed disease progression, with Miami projecting cost-savings over the 20-year study period.

Conclusion: Evidence-based interventions can deliver considerable value, however, complementary strategies to overcome social and structural barriers to HIV care will be required to reach national 'Ending the HIV epidemic' targets by 2030.

Figure 1. Projected reductions in HIV incidence



1094 ASSESSING THE IMPACT AND COST-EFFECTIVENESS OF HIV AND NCD INTEGRATED CARE IN KENYA

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Background: With increasing ART coverage, non-communicable diseases (NCDs) are a growing cause of death and disability in many high HIV burden countries. Integrated community-based screening and treatment for HIV and NCDs is a promising approach for addressing the dual burden of these diseases. We model the national scale-up of this approach in Kenya to estimate its population-level impact and cost-effectiveness.

Methods: Coupling a microsimulation of cardiovascular diseases (CVDs) with a population-based model of HIV dynamics (the Spectrum model), we created a hybrid model of HIV/CVDs. We applied this model to estimate the impact of a community-wide integrated program for screening and treatment of HIV, hypertension and diabetes in Kenya. The intervention was projected to run from 2019 to 2023, with a model time horizon of 2033. We assumed that 20% of the population would be targeted on an annual basis, 73% of HIV-positive people would start ART if screened, and 50% of eligible post-screening NCD treatment time would be covered.

Results: At a national level in 2018, an estimated 7.62 million individuals were living with untreated hypertension, 692,000 with untreated diabetes, and 592,000 individuals in need of ART. ART coverage increased from 68% at baseline to 88% in 2033, and HIV incidence decreased by 64%. Providing NCD screening and treatment would avert 116,000 CVD events and 43,600 CVD deaths by 2033. The integrated HIV/NCD intervention could avert 7.76 million disability-adjusted life years (DALYs) over 15 years at an estimated total cost of $6.68 billion ($445.27 million per year), or $860 per DALY averted (Table 1). At a cost-effectiveness threshold of $2,010 per DALY averted, the probability of cost-effectiveness was 0.92.

Conclusion: Integrated screening and treatment of HIV and NCDs would be a cost-effective approach to avert substantial death and disability in Kenya. Substantial investments would be required to address the identified disease burdens.

Table 1: Epidemiological and economic impact of integrated services for HIV/NCD in Kenya. Values represent median difference between baseline and intervention scenarios across 2000 simulations. Models are initialized with a similar population in 2018 and are followed to year 2033. The baseline scenario assumes fixed ART coverage at 2018's levels over time and minimal NCD treatment. The intervention scenario models an annual campaign for screening and treatment of HIV, hypertension (HPT) and diabetes (DM) running from 2019-2023. Future costs are discounted at 3%.

Epidemiological outcomes (2019-2033)	HIV	Myocardial Infarction	Angina	Cardiac Arrest	Stroke
Events averted	346,730	24900	12500	3200	76000
Deaths averted	288760	4800	1500	3000	34200
Additional costs (2018 US dollars)	**ART**	**DM treatment**	**HPT treatment**	**Screening for HIV**	**Screening for DM & HPT**
	$1.18 billion	$1.28 billion	$3.95 billion	$0.6 billion	$0.03 billion
Saved costs (2018 US dollars)	**Acute CVD care**	**Non-acute CVD care**			
	($0.22) billion	($0.15) billion			
Incremental costs (2018 US dollars)	$6.68 billion				
Incremental DALYs averted	7.76 million				
Incremental costs per DALY (2018 US dollars)	$860				

1095 ACHIEVING 95-95-95 MAY NOT BE ENOUGH TO END THE AIDS EPIDEMIC IN SOUTH AFRICA

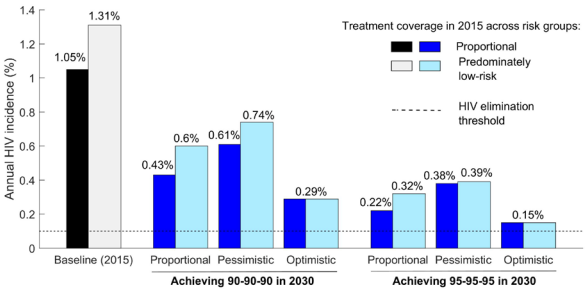
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Background: The ambitious 95-95-95 strategy was announced by UNAIDS in 2014, aiming to end the AIDS epidemic by 2030 by achieving 95% diagnosed among all people living with HIV (PLHIV), 95% on antiretroviral therapy (ART) among diagnosed, and 95% virally suppressed (VS) among treated. An intermediate goal of 90-90-90 was set for 2020. These targets have been adopted by many countries implying that treatment should be prioritized in resource allocation. We estimate the expected reduction in HIV incidence if the UNAIDS targets are met in South Africa by 2030 reaching different PLHIV groups by sexual risk behavior.

Methods: A risk equation model was used to simulate annual HIV incidence by tracking the transmission from PLHIV assuming 30% of them engaged in high-risk behavior (more frequent sex with multiple partners). Two baseline scenarios with different risk group coverage were parameterized with the HIV prevalence and 85-58-76 treatment cascade (i.e. 37% viral suppression of PLHIV), estimated in 2015 in South Africa, and calibrated to the 2015 HIV incidence among adult population (15-49 years). They were compared to scenarios in which UNAIDS targets are achieved and newly diagnosed, treated and virally suppressed PLHIV were: i) proportionally distributed between risk groups (proportional); ii) predominately recruited from the high-risk group (optimistic) and iii) predominately recruited from the low-risk group (pessimistic) with stable HIV prevalence up to 2030.

Results: Annual HIV incidence was estimated 1.05% - 1.31% in 2015 depending on how treatment coverage was distributed between risk groups (see figure). Reaching the 90-90-90 target by 2030, resulting in 73% overall VS, may reduce annual HIV incidence to 0.29% if the cascade is predominately improved through recruitment from the high-risk group or to 0.74% if the cascade is improved with low-risk PLHIV. Reaching the 95-95-95 target, resulting in 86% overall VS, may result in 0.15% and 0.39% annual HIV incidence if the cascade is improved with high-risk and low-risk PLHIV, respectively. The HIV incidence projections in all scenarios remain above the elimination threshold of 0.1% (1 infection/1000 person-years).

Conclusion: Reaching UNAIDS treatment cascade targets does not equate the end of the HIV epidemic in South Africa. Expected HIV incidence strongly depend on the risk heterogeneity and the ART and VS coverage achieved among high-risk PLHIV. Scale-up of other HIV prevention tools is needed to bridge the gap to AIDS elimination.



1096 HOW SHOULD WE PRIORITIZE AND MONITOR INTERVENTIONS TO END HIV EPIDEMIC IN AMERICA?

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Background: The goal of the US Ending the HIV Epidemic (EHE) plan is to reduce HIV incidence by 90% over the next decade. This initiative will direct a major scale-up of many prevention and care activities in high-burden areas. An important aspect for local jurisdictions will be the ability to monitor changes in their local HIV epidemic to ensure progress. Models can help inform what changes in potential indicators to expect as prevention interventions are implemented.
Methods: We developed a stochastic network-based HIV transmission model for men who have sex with men (MSM), calibrated to current surveillance-based estimates of HIV prevalence, PrEP use, and HIV care continuum levels in the Atlanta area (Baseline). Two counterfactual scenarios increased HIV screening rates to annual and quarterly. Additional scenarios included increases of 10x for ART retention relative to empirical rates, with and without increases in screening. Changes in HIV incidence and indicators readily available to local HIV surveillance programs – new HIV diagnoses and the proportion of those that were acute infections – were assessed for 10 years following implementation.
Results: Compared to current HIV screening rates, increasing HIV screening to annual or quarterly for all MSM would lead to approximately 97% and 99% of all extant HIV infections (among this risk group) being diagnosed. By year 5 of the intervention new diagnoses (dashed lines) would correspond directly with the unobserved true HIV incidence (solid lines) in all scenarios (Figure). The more rapid the build-up of HIV testing, the more quickly new diagnoses approximate HIV incidence, with an increase to quarterly testing leading to new diagnoses matching true incidence by year 3. The proportion of all new HIV diagnoses identified while acute increased with testing frequency from approximately 2% at baseline, to approximately 8% and 26% of all diagnoses with annual and quarterly rescreening. However, reductions in incidence through other mechanisms such as improved retention on ART do not increase the proportion identified while acutely infected.
Conclusion: These results suggest one strategy for jurisdictions seeking to simultaneously reduce HIV incidence and improve their ability to track their epidemic would be to dramatically increase HIV screening in the earliest stages of elimination efforts. This should lead to an initial dramatic increase in new diagnoses, after which new HIV diagnoses would accurately measure incident HIV infections

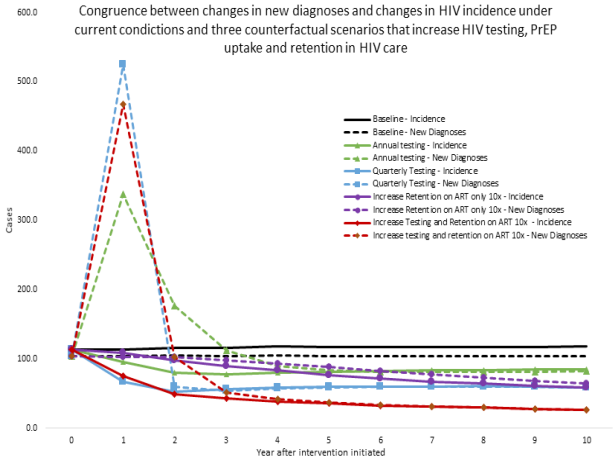


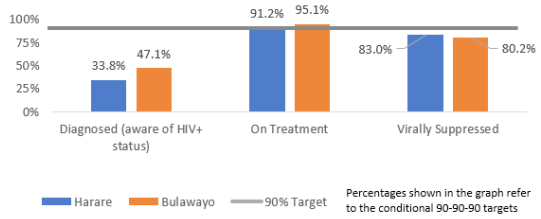
Figure
Number of new infections (solid lines) and new diagnoses (dashed lines) over 10 years of intervention under a baseline scenario calibrated to the observed epidemic among MSM in Atlanta, and compared to scenarios that increase testing to annual and quarterly, or increase testing and retention on antiretroviral therapy 10-fold relative to baseline.

1097 HIV CARE CASCADE: MEN WHO HAVE SEX WITH MEN & TRANSGENDER WOMEN/GENDERQUEER, ZIMBABWE

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Background: Men who have sex with men (MSM) and transgender women/genderqueer individuals (TGW/GQ) are at greater risk for HIV than the general population and face stigma and other barriers to receiving HIV services. However, little HIV data is available among these groups in Zimbabwe. We examined progress toward the 90-90-90 treatment targets (90% of HIV-positive persons know their status; of these, 90% are on antiretroviral treatment [ART]; and of these, 90% have viral load suppression [VLS]) among a sample of MSM and TGW/GQ in Harare and Bulawayo, Zimbabwe.
Methods: We used respondent-driven sampling to identify MSM and TGW/GQ individuals aged 18+ to participate in a biobehavioral survey in 2019. Consenting participants completed a questionnaire that obtained sociodemographic and HIV-related data and underwent HIV and viral load testing. VLS was defined as HIV RNA <1000 copies/mL. Univariate analyses were used to calculate sample estimates, as data did not reach convergence.
Results: In Harare, 416 MSM and 279 TGW/GQ received HIV testing (97% of participants). Median age was 24 years. HIV prevalence was 21.4% (MSM, 17.1%; TGW/GQ, 28.0%); of those testing positive, 61.7% (MSM, 69.0%; TGW/GQ, 55.1%) had VLS. Among those testing HIV-positive, 34.9% (MSM, 33.8%; TGW/GQ, 35.9%) reported knowing their status; of these, 90.4% (MSM, 91.7%; TGW/GQ, 89.3%) reported using ART; and of these, 83.0% (MSM, 81.8%; TGW/GQ, 84.0%) had VLS. In Bulawayo, 760 MSM and 56 TGW/GQ received HIV testing (>99% of participants). Median age was 26 years. HIV prevalence was 23.4% (MSM, 23.3%; TGW/GQ, 25.0%); of those testing positive, 61.3% (MSM, 61.6%; TGW/GQ, 57.1%) had VLS. Among those testing HIV-positive, 52.9% (MSM, 53.7%; TGW/GQ, 42.9%) reported knowing their status; of these, 95.1% (MSM, 94.7%; TGW/GQ, 100.0%) reported using ART; and of these, 80.2% (MSM, 78.9%; TGW/GQ, 100.0%) had VLS.
Conclusion: HIV prevalence was higher in sampled MSM and TGW/GQ than that in the general male population aged 15-64 years in both Harare (11.1%) and Bulawayo (16.1%). Self-reported awareness of HIV status was lower among MSM and TGW/GQ than among the general adult male population (68.3%) in Zimbabwe. HIV-positive participants who knew their status had high ART coverage and high VLS, indicating strong linkage to care and retention on treatment in this subgroup. Improvements in testing are needed among MSM and TGW/GQ, and programs could consider innovative approaches to optimize case finding among these populations.

FIGURE. HIV TREATMENT CASCADE FOR MEN WHO HAVE SEX WITH MEN AND TRANSGENDER/GENDERQUEER WOMEN IN ZIMBABWE



1098 IMPACT OF HIV CONTINUUM OF CARE INTERVENTIONS AND PREEXPOSURE PROPHYLAXIS IN KENYA

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Background: In Western Kenya up to one quarter of the adult population was HIV-infected in 2012. Médecins Sans Frontières (MSF) has implemented an HIV care program to reach the 90-90-90 UNAIDS targets and has surpassed those. In this generalized epidemic, our objective was to compare effectiveness of Pre-exposure Prophylaxis (PreP) with improving the continuum of care coverage to 95-95-95.
Methods: We developed a time-discrete, dynamic microsimulation model to project HIV incidence and infections averted resulting from different strategies in the adult population. We used two age group risk strata, younger adults (YAs), as the age strata where HIV incidence is the highest: women 15-30y and men 20-40y, and older adults (OAs): women >31y and men >41y. We modeled 3 strategies compared to a 90-90-90 continuum of care base case: 1) Scaling up the continuum of care to 95-95-95 (85.7% suppression), 2) PreP targeting the YA with 10% coverage, and 3) Scale up to 95-95-95 and PreP. The time horizon was 2018 to 2030. Transmission parameters, including number of sexual contacts within and outside the same age group, were calibrated to fit overall prevalence (24.1%) and incidence (1.9/100 PY) in 2012. Monthly probabilities for continuum of care matched the 2012 levels (61.8% tested, 68.2% on ART among tested, and 73.0% viral suppression among on ART) and 90-90-90 in 2020; PreP efficacy was set at 75%. We did sensitivity analyses on key parameters, including PrEP impact starting at higher continuum levels, as obtained in 2018 (93.0% tested, 95.0% on ART among tested, and 97.0% suppression among on ART).
Results: In the base case, by 2030 HIV incidence was 0.31/100 Person-Years (PY) in YAs, 0.35/100 PY in OAs, and 0.32/100 PY overall. Improving continuum levels to 95-95-95 averted 4.0% of infections in YAs, 9.0% in OAs, and 5.2% overall. PreP averted fewer infections: 3.7% in YAs, 1.5% in OAs, and 3.2% overall. Combining 95-95-95 and PreP averted 7.9% of infections in YAs, 9.1% in OAs and 8.1% overall. Sensitivity analysis shows that PreP coverage had to be 20% to avert as many infections as 95-95-95. With 88.0% overall suppression, as MSF has achieved, adding PreP is even less effective.
Conclusion: In a generalized epidemic with continuum of care levels at 90-90-90, improving continuum to 95-95-95 is substantially more effective than providing PreP. Continued focus on improving the continuum will have the greatest impact on decreasing new HIV infections.

Table: HIV incidence (/100 PY) and infections averted as a function of improved continuum of care and/or addition of PreP in rural Kenya

Population	No Intervention	95-95-95	PreP 10%	95-95-95+ PreP10%
Younger Adults				
Infections averted (%)	-	4.0	3.7	7.9
Incidence	0.31	0.23	0.26	0.16
Older Adults				
Infections averted (%)	-	9.0	1.5	9.1
Incidence	0.35	0.20	0.28	0.20
Overall				
Infections averted (%)	-	5.2	3.2	8.1
Incidence	0.32	0.22	0.27	0.18

1099 DIFFERENCES IN HIV CARE OUTCOMES: US HISPANICS/LATINOS WITH DIAGNOSED HIV INFECTION

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Background: HIV testing, linkage to and retention in HIV medical care and achievement of viral suppression are critical to prevent disease progression. Assessing HIV care outcomes among Hispanics/Latinos is important for guiding targeted prevention efforts and monitoring progress towards national goals.
Methods: Data from the National HIV Surveillance System from 42 jurisdictions that reported complete CD4 and viral load laboratory results to CDC through December 31, 2018 were used to determine the numbers of Hispanics/Latinos aged ≥13 years newly diagnosed and diagnosed at Stage 3 (AIDS) and percentages linked to care within one month, retained in care and virally suppressed by sex, age and transmission category. These data provide more granularity than in HIV surveillance reports.
Results: Among 8,517 Hispanics/Latinos with HIV infection diagnosed in 2017, 1,825 (21.4%) had infection classified as stage 3 (AIDS). Among males, the highest percentage of infections diagnosed as stage 3 (AIDS) was at 25-34 years (34.3%) and among females, 45-54 years (28.2%). By transmission category, the highest percentage of infections diagnosed at stage 3 (AIDS) attributed to injection drug use was at 45-54 years for both males (29.1%) and females (40.9%) and for infection attributed to heterosexual contact, among males, 35-44 years (33.0%) and females, 45-54 years (26.8%). In 2017, 6,750 (79.3%) were linked to care within 1 month after diagnosis. For males, females and all transmission categories, 13-24 years had the lowest linkage to care except for males with infection attributed to male-to-male sexual contact and injection drug use [25-34 years (67.1%)] and heterosexual contact [35-44 years (75.5%)]. Among 181,145 Hispanics/Latinos living with diagnosed HIV infection at year-end 2016, 130,195 (71.9%) received any care, 106,101 (58.6%) were retained in care and 111,107 (61.3%) were virally suppressed. The lowest retention in care for females was 25-34 years (56.5%) and for males was 35-44 years (55.7%). The lowest viral suppression was among males 25-34 years with infection attributed to injection drug use (43.8%) and 35-44 years with infection attributed to heterosexual contact (43.8%), followed by females 25-34 years with infection attributed to injection drug use (47.9%).
Conclusion: Tailored strategies for Hispanics/Latinos that increase care and achieve viral suppression in different groups such as those <35 years and persons who inject drugs are needed as highlighted in the national HIV prevention goals.

1100 IMPROVEMENTS ACROSS NAIROBI COUNTY'S HIV CARE CONTINUUM : CASE OF A FAST-TRACK CITY

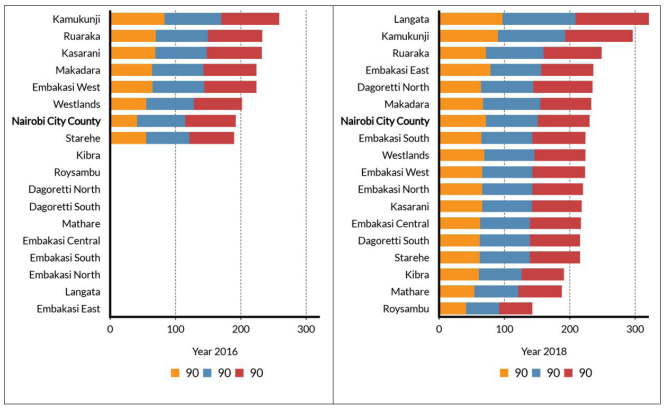
Sindhu Ravishankar[1], Erlyn Macarayan[2], Caroline Ngunu[3], Molly Pezzulo Collier[1], Harriet Kongin[4], Jose M. Zuniga[1], Ingrid Katz[5]
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Background: The Fast-Track Cities initiative is supporting municipalities to measure and monitor progress against the global 90-90-90 targets. Using 2016-2018 trend data from Nairobi County's Fast-Track City dashboard, we assessed progress against 90-90-90 targets at county and sub-county levels.
Methods: HIV care continuum data from 2016 (baseline) to 2018 (current) for Nairobi County and its 17 sub-counties were obtained from the Fast-Track City dashboard. Improvements in data from baseline to current were measured using two parameters: 1. Progress made against the 90-90-90 targets; and 2. completeness of HIV care continuum data. 90-90-90 targets (which use a floating denominator) were converted to care continuum indicators (using a consistent denominator of estimated PLHIV) resulting in the following targets: 90% of PLHIV diagnosed; 81% of PLHIV on ART; and 72.9% of PLHIV virally suppressed.
Results: The HIV care continuum for Nairobi County improved from 77% PLHIV diagnosed, 74% PLHIV on ART, and 41% of PLHIV virally suppressed in 2016 to 79% PLHIV diagnosed, 79% of PLHIV on ART, and 72% of PLHIV virally suppressed in 2018. Trend data between 2016 and 2018 were reported for eight of the 17 sub-counties. Of these eight sub-counties, seven demonstrated improvement across one or more indicators. As of 2016, no sub-county had surpassed the 90-90-90 targets but one sub-county had surpassed the second and third target. In 2018, two sub-counties reported surpassing all three targets, with five sub-counties surpassing one or more of the 90 targets. Ranges of improvement for the sub-counties from 2016-2018 were 4-11 percentage points on the first 90 target; 4-13 percentage points on the second 90 target; and 1-14 percentage points on the third 90 target. Between 2016-2018, the completeness of data also improved

with all 17 sub-counties reporting HIV care continuum data in 2018 compared to eight sub-counties reporting such data in 2016.

Conclusion: Nairobi County and many of its sub-counties have seen improvements across the HIV care continuum since their 2016 baseline. Given the quickly approaching 2020 deadline to attain the 90-90-90 targets, targeted focus to improve the HIV care continua in the poorest performing sub-counties is crucial. By reporting data on all sub-counties, Nairobi County is taking the steps needed to assess gaps and subsequently address geographic priorities.

Figure 1. Progress in attaining 90-90-90 targets for Nairobi sub-counties, 2016 vs 2018



1101 HIV CARE CONTINUUM AMONG NEWLY DIAGNOSED INDIVIDUALS IN MEXICO

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Background: The HIV care continuum (CC) is useful for monitoring HIV care. However, the impact of HIV diagnosis in circumstances of hospitalization in the CC is unknown. The aim of this study was to compare engagement in-care (EIC), proportion of patients on ART and viral load suppression (VLS) in patients who were hospitalized within diagnosis from those treated as outpatients.

Methods: We used retrospective, longitudinal data collected at a tertiary hospital in Mexico City. We included all adults newly diagnosed with HIV (within 3 months) between 2005 and 2015. All patients diagnosed in circumstances of hospitalization due to an AIDS-defining illness (ADI) or requiring hospitalization within 3 months of diagnosis were classified as severe group (SG). All o¬ther patients were classified as non-severe group (NSG). HIV CC was evaluated at one, three and five years from enrollment, estimating proportions of those contributing to follow-up at each period. EIC was defined as those who had 2 or more medical visits, ART prescriptions, CD4 or viral load (VL) tests at least 3 months apart in the previous year. VLS was defined as most recent VL of <50 copies/mL.

Results: Among 911 people living with HIV (PLWH) enrolled, 199 (22%) were classified as SG. Median age was 33.5 (IQR 28-42) years, and 91% were male. PLWH in the SG were more likely to be older (36 vs 33 years, p<0.001) and to have acquired HIV through heterosexual contact (35% vs 23%, p<0.001), had lower median baseline CD4 count (41 vs 203, p<0.001) and higher proportion of ADI (85% vs 28%, p<0.001) than individuals in the NSG. Figure 1 describes CC across time. Mortality and loss to follow-up (LTFU) were higher in the SG only within the first year (26% vs 2%, p<0.001; 15% vs 5%, p<0.001, respectively). In contrast, no significant differences in mortality, LTFU, proportion of patients on ART and VLS were found at three and five years of enrollment between groups.

Conclusion: Similar long-term outcomes in both groups along the HIV CC strongly suggest that first year disparities are mainly due to a higher early mortality and LTFU among hospitalized patients within 3 months of HIV diagnosis. Our findings emphasize the urgent need of strategies that increase early diagnosis in populations not traditionally considered at risk.

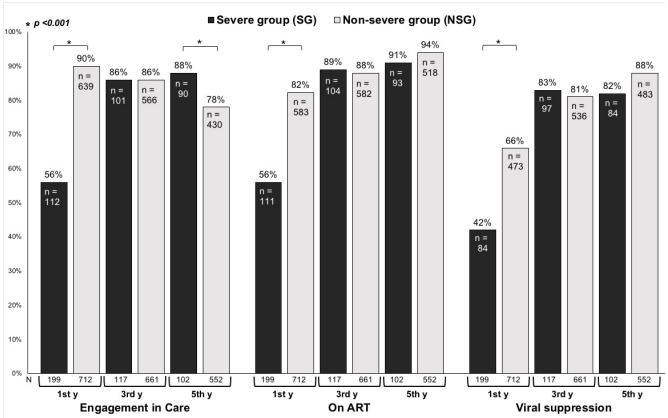


Figure 1: HIV Continuum of care at 1, 3 and 5 years from enrollment. N: number of patients contributing to data at each period. Missing patients from first to third year observation were deceased (SG=52, NSG=13) or lost to follow-up (SG=30, NSG=38). Missing patients from third to fifth year observation were deceased (SG=4, NSG=10), lost to follow-up (SG=7, NSG=45) or had <5 years of observation (SG=4, NSG=54).

1102 CHALLENGES TO HIV CARE ENGAGEMENT AMONG MOBILE POPULATIONS IN RURAL KENYA AND UGANDA

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Background: Population mobility may negatively impact care engagement for people living with HIV by disrupting continuity and this may portend poor treatment outcomes for patients while increasing the risk of onward disease transmission. We sought to identify the challenges mobility imposes on vital aspects of care engagement (enrollment in HIV care, being on ART, and treatment interruptions)

Methods: We conducted an analysis of survey data collected in 2016 among a random sample of 1,119 mobile adults within 12 communities across three regions (South West Uganda, East Uganda and West Kenya) out of the 32 communities participating in the SEARCH HIV test-and-treat cluster randomized trial (SEARCH NCT:01864603). The 12 communities were matched by trial intervention with individuals sampled on baseline residential stability and HIV status. We evaluated self-reported challenges to HIV care engagement across multiple metrics of mobility with specific attention to sex differences. We used multivariate logistic regression adjusting for age, educational level, marital status, household wealth and region to identify factors associated with poor engagement in HIV care.

Results: A total of 1,119 adults participated in the survey, 53.2% (595) were female, 82.2% (926) had primary or secondary level of education and 74.2% (830) were involved in informal low HIV risk occupations such as farming. Of the 1119, 106 reported missing clinic appointments, the median duration of missed appointment was 0.5 (IQR 0.25-2) months. The most common reasons for missing appointments, HIV medication interruptions and changing HIV clinics was mobility and inability to afford transport to clinics. Those who reported migration within the previous year had lower odds of receiving regular care and treatment OR 0.42(95%CI 0.19, 0.95) p=0.04 with males having lower odds (OR 0.31(95%CI 0.10, 1.01) p=0.05) as compared to females (OR 0.57(95%CI 0.18, 1.86) p=0.35). Factors associated with poor care engagement (failure to receive regular care and treatment) were younger age and poverty (being in the lowest wealth index quartile vs. higher quartiles) OR 0.28(95%CI 0.14, 0.54) p=<0.001.

Conclusion: Population mobility may hamper the gains made in controlling the HIV epidemic if care engagement for mobile persons remains unaddressed. Attention to different forms of mobility and differences by sex are warranted.

1103 PUBLIC HEALTH REFERRALS IMPROVE RE-ENGAGEMENT FOR ART INTERRUPTED PATIENTS

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Background: In 2016, the BC HIV Drug Treatment Program (DTP) partnered with regional public health offices to expand its prescriber alert system for ART interruptions to include person-specific outreach support for those who

remain off treatment for >4 months. We examined outcomes before and after launch of this Re-Engagement and Engagement in Treatment for Antiretroviral Interrupted and Naïve populations (RETAIN) Initiative.
Methods: We analyzed DTP participants with ART interruptions triggering a physician-directed alert (ART refill >2 months late) in pre-RETAIN (Jul-2013 to Apr-2016) and post-RETAIN periods (May-2016 to Oct-2017) with follow-up until Oct-2018. Persons who moved out of BC, died, or were on ART through other sources were excluded. We compared the proportions who re-started ART, or achieved viral suppression (pVL<200 copies/mL) in pre- and post-RETAIN periods and the time to ART re-initiation using generalized estimating equation. Cox modelling has been used to examine associations between time to ART restarts with time period (pre-RETAIN vs. post-RETAIN) as our primary explanatory variable.
Results: A total of 1805 individuals contributed 3219 ART interruptions of ≥2 months triggering physician-directed alerts: 2050 in pre-RETAIN and 1169 in post-RETAIN periods. Participants were predominantly male (74%) had a median duration on ART of 5 years and a median age of 47 years. We found no differences between the two periods in terms of proportion who re-started ART within 4 months of a physician alert (73% vs 73%), or achieved viral suppression within six months (60% vs 60%). Among persons who remained interrupted >4 months after a physician-directed ART interruption alert was sent, the median time from interruption to ART re-initiation declined from 8.7 (5.8-14.9) months to 7.4 (5.5-10.9) months (p=<0.001) from the pre- to post-RETAIN period. Interruptions in the post-RETAIN era were more likely to re-start ART (adjusted hazard ratio 1.50; 95% CI 1.34 - 1.69). ART re-initiation was associated with pVL suppression prior to interruption and ART duration prior to interruption (Table 1.) Similar findings were also found when examining only the first interruption in our study period.
Conclusion: Public health referrals for persons who did not re-engage in care after alerts to their physicians were sent shortens the length of ART interruptions. Similar programs should be considered in other jurisdictions.

Table 1. Multivariable Cox Proportional Hazards model - time to ART re-engagement following a physician-directed therapy interruption alert

	Interruption alerts sent to physicians		ART re-engagement before end of follow-up
Variable	**Total Alerts sent**	**n (%) of total Alerts sent**	**Hazard Ratio (95% CI)**
Period	3219		
Pre RETAIN (July 01, 2013 to April 30, 2016)		2050 (63.7)	REF
Post RETAIN (May 01, 2016 to October 31, 2017)		1169 (36.3)	1.51 (1.34-1.69)
Sex	3219		
Female		813 (25.3)	REF
Male		2371 (73.7)	0.89 (0.78-1.01)
Other		35 (1.1)	1.02 (0.56-1.87)
HIV Risk Factor	3219		
MSM		739 (23.0)	REF
IDU		1104 (34.3)	1.09 (0.93-1.29)
MSM and IDU		306 (9.5)	1.19 (0.96-1.46)
Heterosexual		279 (8.7)	0.91 (0.73-1.14)
Other		16 (0.5)	1.51 (0.87-2.60)
Unknown		775 (24.1)	0.96 (0.81-1.15)
pVL (last before alert send date)	3219		
Unsuppressed (≥200 c/mL)		970 (30.1)	REF
Suppressed (<200 c/mL)		2248 (69.8)	1.37 (1.22-1.55)
Unknown		1 (0.0)	
Adherence in the one year before last ART stop date	3219		
≤ 95%		2360 (73.3)	REF
> 95%		632 (19.6)	0.67 (0.58-0.77)
Unknown		227 (7.1)	0.63 (0.51-0.78)
Months from last pVL test date to the alert sent date (median (Q1-Q3)	3218	3 (2-5)	0.91 (0.89-0.92)
ART duration (years) before the current interruption (median Q1-Q3)	3219	5 (2-9)	1.05 (1.04-1.07)

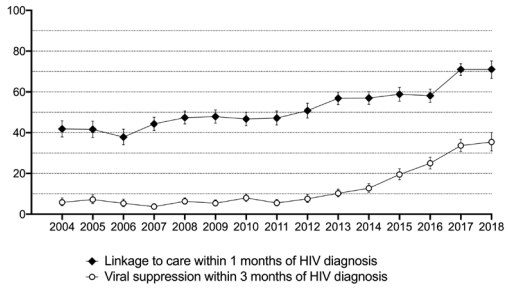
Abbreviations: ART – antiretroviral therapy, pVL - HIV plasma viral load, MSM - men who have sex with men, IDU - injection drug user

1104 MONITORING PROGRESS OF CARE IN PERSONS NEWLY DIAGNOSED WITH HIV IN SPAIN, 2004-2018

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Background: For newly diagnosed persons with HIV (NDP), early initiation of ART is essential in reducing morbidity and mortality and decreasing the risk of transmitting HIV. Two indicators have been proposed to monitor HIV care among NDP: the percentage of those linked to HIV medical care within 1 mo. of diagnosis (process) and the percentage of those achieving viral suppression (VS) within 3 mo. of diagnosis (outcome). We analyzed trends in both indicators in the Cohort of the Spanish AIDS Research Network (CoRIS).
Methods: The data source was the CoRIS database of ART-naïve adult persons living with HIV (PLWH) recruited from 2004 to 2018. VS was defined as ever having an HIV-RNA <200 copies/mL. We used logistic regression to assess differences by sex, country of origin, age, HIV transmission category, and CD4 count at diagnosis.
Results: A total of 13,260 PLWH were enrolled in the study period; 84% males, 59% native-born Spaniards, median age 34 years, median CD4+ cell count 384 cells/uL, 58% MSM. The percentage of NDP linked to care within 1 mo. of diagnosis increased from 42% in 2004 to 71% in 2018 (Figure). The percentage of NDP achieving VS within 3 mo. of diagnosis, increased from 6% in 2004 to 35% in 2018 (Figure). The odds of achieving VS within 3 mo. of HIV diagnosis was higher among females (adjusted OR, 95%CI: 1.42, 1.20-1.69), among non-Spanish Europeans and Latin Americans compared to native-born Spaniards (1.39, 1.20-1.62 and 1.26, 1.09-1.45, respectively), and among those older than 50 years (1.28, 1.06-1.54). Opposite, the odds of achieving VS within 3 mo. of diagnosis was lower among IDU compared to MSM (0.48, 0.36-0.65) and those with CD4 counts between 200-500 cells/uL (0.59, 0.52-0.67) and CD4 counts >500 cells/uL (0.36, 0.30-0.42) compared to those with CD4 < 200 cells/uL.
Conclusion: Progress has been made in HIV care among NDP in Spain during the 15-year analysis period, but there is still much room for improvement. The advance in the outcome indicator most likely reflects changes in treatment guidelines to offer ART to any PLWH regardless of CD4 count. These two indicators can guide our efforts to improve HIV care among NDP.

Figure. Percentages of newly diagnosed persons linked to care within 1 month and achieving viral suppression within 3 months of HIV diagnosis in CoRIS, 2004–2018.



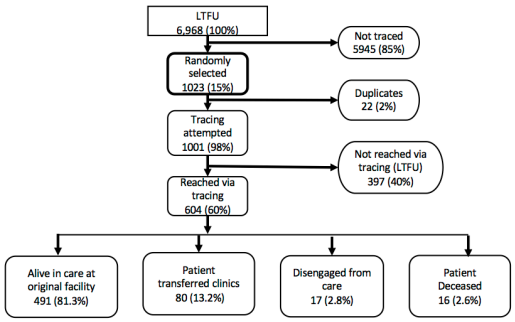
1105 A FIELD-BASED SAMPLING STRATEGY TO REVISE HIV TREATMENT PROGRAM RETENTION ESTIMATES

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Background: Loss to follow-up (LTFU) in Zambia's national treatment program threatens progress toward achieving HIV epidemic control. With CDC/PEPFAR funding, the Centre for Infectious Disease Research in Zambia (CIDRZ) supports the national program in Lusaka Province where a drop in 12-month retention was noted from 76% in FY17 to 65% in FY18. The recent CIDRZ BetterInfo study used a multi-stage sampling approach to generate revised, regionally representative estimates for mortality and LTFU in the national program. We adapted the study methodology to create a field ready "BetterInfo lite" sampling approach to ascertain true program status for patients apparently "LTFU" and drivers of retention decline.
Methods: Using routine data, we selected 10 high-volume facilities in Lusaka for "BetterInfo Lite" based on the largest net drop in program retention between Q3 and Q4 FY18. We randomly selected 15% of newly "LTFU" clients between Q3 and Q4 in each facility to be traced by phone or in person and to complete a brief vital status and retention questionnaire. Leveraging existing CIDRZ platforms, trained peer educators contacted patients or their contacts

to determine patient mortality and true program status (i.e. alive in care, transferred, disengaged from care, dead, or LTFU).
Results: 1,023 of 6,968 LTFU patients (15%) were randomly selected for tracing. Tracing was attempted in 1,001 (98%), with 604 of these (80%) reached by phone or in person. 397 (40%) could not be reached. Of the 604 contacted, 491 (81%) were found alive and in care at their original clinic or a neighboring satellite health post, 80 (13%) were "silent" transfers, 17 (3%) disengaged from care and 16 (3%) were deceased (figure 1).
Conclusion: It is feasible to adapt a rigorous sampling-based strategy used in a research context for routine program use to revise HIV treatment program retention estimates. We observed a high proportion of patients alive in care at the facility where they were flagged as "LTFU", suggesting data quality issues, likely due to increasingly decentralized ART distribution and data collection. We also observed numerous "silent" transfers after ART initiation and identified 16 missed deaths, resulting in a mortality underestimation and LTFU overestimation. Scale up of electronic data systems to decentralized ART dispensation points, use of unique identifier tools such as biometrics, and enhanced early patient support and follow-up are needed to improve, and better monitor, program retention.

Figure 1: Better Info Lite flow chart



1106 LOSS-TO-FOLLOW-UP RISK FACTORS AFTER ANTIRETROVIRAL THERAPY INITIATION IN UGANDA

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Background: In sub-Saharan Africa published data seem to indicate that loss to follow-up (LTFU) is higher in men and young individuals. We described the proportion of LTFU by age and gender, and explored gender differences in different age groups. We also identified risk factors for LTFU in patients on antiretroviral therapy (ART) in urban Uganda.
Methods: This was a retrospective analysis of routine data of patients aged ≥15 years who initiated ART in 6 clinics in Kampala (2005–June 2018). Patients defined LTFU if they did not return for >90 days at any time, and did not transfer. Confirmed deaths and transfers were not included. We compared LTFU by gender, age groups (young adults [YA], 15–25 years; adults [AD], 26–50 years; and older adults [OA], >50 years), point of entry into HIV care, and year of ART initiation. We used Cox proportional hazards models to determine factors associated (P<0.05) with LTFU. We imputed missing (33%) CD4 count using multiple imputation chained equation with 30 imputations.
Results: Of the 56,304 patients: 41,847 (74.3%) were women, median age 30 years (IQR, 25–36 years), 17.2% had WHO stage 3/4 disease, median CD4 count at ART start 271 cells/μL (IQR, 147–426 cells/μL), and 80.3% started efavirenz-based ART. Overall, 20,203 (35.9%) were LTFU; LTFU was higher in women (36.6%) than men (34.5%; P<0.001). LTFU declined across age groups: 45.8% in YA, 33.1% in AD, and 31.4% in OA. In YA, LTFU was higher among women (46.5%) than men (37.9%), but lower in women AD (32.6% vs 34.3%) and OA (29.9% vs 33.0%; all P<0.001). LTFU was higher among recent ART initiators. One quarter (25,5%) women entered care through prevention of mother-to-child transmission (PMTCT) programs; LTFU among pregnant women was 55.2% among YA, 45.1% among AD, and 35.7% among OA (P<0.001). On multivariate analysis, we found that men, women who entered care through PMTCT services, recent ART initiators were at higher risk of being LTFU. OA and AD were less likely to be LFTU than YA. Other factors are shown in Table 1.
Conclusion: LTFU varied across age groups and point of entry in care. Barriers to retention faced by young women initiating ART through PMTCT programs and recent initiators need further investigation. Similarly tracing studies may inform if high LTFU rates are partially driven by unreported deaths and silent transfers.

Table 1. Factors significantly associated with loss to follow-up among HIV-positive patients who Initiated antiretroviral therapy (ART) in urban Uganda between 2005 and 2018)

Characteristics at ART start	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Gender				
Female	1.00		1.00	
Male	1.00 (0.97–1.04)	0.84	1.12 (1.1–1.17)	<0.001
Age group, years				
Young adults (15–25)	1.00	<0.001	1.00	
Adults (26–50)	0.61 (0.59–0.63)		0.71 (0.68–0.73)	<0.001
Older adults (>50)	0.56 (0.54–0.63)		0.70 (0.64–0.77)	<0.001
Entry point				
Medical in and outpatients	1.00		1.00	
PMTCT	2.49 (2.38–2.61)	<0.001	1.68 (1.61–1.75)	<0.001
Baseline WHO stage				
1/2	1.00		1.00	
3/4	0.89 (0.85–0.93)	<0.001	1.22 (1.17–1.29)	<0.001
Baseline CD4 count (cells/μL)				
<200	1.00		1.00	
200–350	1.06 (1.02–1.11)	0.005	0.88 (0.84–0.93)	<0.001
≥350	1.41(1.35–1.47)	<0.001	0.85 (0.81–0.90)	<0.001
Year of ART start				
2005–2009	1.00		1.00	
2010–2014	3.33 (3.12–3.60)	<0.001	3.61 (3.31–3.92)	<0.001
2015–2018	6.30 (5.84–6.74)	<0.001	6.58 (6.00–7.21)	<0.001
ART initial regimen				
Efavirenz-based	1.00		1.00	
Nevirapine-based	0.55 (0.53–0.57)	<0.001	0.77 (0.73–0.81)	<0.001

Abbreviations: HR, hazards ratio; CI, confidence interval; PMCTC, prevention of mother-to-child transmission; WHO, World Health Organization.

1107 HIV STIGMA PREDICTS RETENTION IN CARE AMONG US PATIENTS IN CARE

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Background: HIV-related stigma is a known barrier to engagement in care yet no large-scale, nationally representative studies have prospectively evaluated the effect of stigma on retention for those in HIV care in the United States (US).
Methods: The Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort integrates medical record and survey data from patients in primary care at 7 academic HIV clinics across the US. We added a yearly, validated 4-item assessment of internalized HIV stigma (response scale 1=strongly disagree to 5=strongly agree, α=0.91) into patient surveys administered every 4-6 months at primary care visits. We used multivariable logistic regression models to evaluate associations between mean stigma and two common prospective retention in care outcomes: keeping the next primary care appointment after stigma assessment and keeping all scheduled primary care appointments in the year following the stigma assessment. We controlled for age, gender, race/ethnicity, sexual orientation, time since CNICS enrollment, and CNICS site. We checked for interactions between stigma and these covariates. We addressed missing covariate data under the missing at random assumption via direct maximum likelihood estimation using Mplus.
Results: From 4/16 – 10/17, 5,825 patients completed the stigma assessment. Median age was 49 (IQR 39-56), 80% were male, 39% were black, 15% were Hispanic, and 32% identified as heterosexual. Median (IQR) time since CNICS enrollment was 6 (3-11) years. Mean stigma was 1.9 (SD 1.08). Each unit increase in mean stigma was associated with decreased odds of keeping the next primary care appointment (aOR=0.93, 95% CI 0.87-0.99, p 0.015), as well as decreased odds of keeping all primary care appointments (median of 3 appointments, IQR 2-5) in the subsequent year (aOR=0.91, 95% CI 0.86-0.96, p < 0.001). In both models, younger age, black race, and non-cis gender identification were associated with suboptimal appointment attendance. There were no statistically significant interactions between stigma and covariates.
Conclusion: In one of the first multi-site, clinic-based studies of stigma in the US, internalized HIV stigma had a modest statistically significant independent effect on the likelihood of subsequent appointment attendance. This is the first study to demonstrate prospectively the effect of stigma on retention in

care, thereby providing support for the need to address HIV stigma in efforts to optimize retention in HIV care and virologic control.

1108 HOSPITALIZATIONS & MORTALITY DIFFER BY GENDER AMONG LONG-TERM ART PATIENTS IN UGANDA

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Background: We conducted an analysis to determine if differences in health-seeking behaviour may explain gender disparities in mortality among long-term survivors receiving antiretroviral therapy (ART) in rural Uganda.
Methods: From June 2012 to September 2013, we enrolled patients receiving a first-line ART regimen for at least four years without previous viral load (VL) testing in Jinja, Uganda. We measured HIV VL at study entry. We switched participants to second-line therapy, if VL was ≥1000 copies/mL on two measurements, and followed all participants for three years. We collected clinical and behavioral data at enrollment and every six months. We used Cox proportional hazards modeling to examine factors associated with hospitalization and mortality until September 2016.
Results: We enrolled 616 participants or whom 75.3% were female. The median age was 44 years (interquartile range [IQR]39-50 years), the median duration of ART was 6 years (IQR 5-7 years) and the median CD4 count at enrollment was 523 cells/μL (IQR 362- 707). Of these, 113 (18.3%) had VLs≥1000 copies/mL at enrollment. Participants were followed for a median of 2.8 years (IQR 2.6-3.2) years during which hospitalizations occurred in 101 participants (7% of men vs. 20% of women; p<0.001). A total of 22 (3.6%) deaths occurred; 9% of men vs. 2% of women (p <0.001). Participants who were hospitalized had a lower risk of mortality in the univariate analysis (HR=0.22; 95% CI 0.03-1.63), but it was not statistically significant (p=0.138) and was not included in the final model. In the multivariate model, mortality was associated with age (adjusted hazard ratio (AHR) = 1.07 per year increase; 95% CI 1.01-1. 13), male gender (AHR = 2.57; 95% CI 1.06-6.23) and time-updated CD4 counts (AHR = 0.67 per 100 cell increment; 95% CI 0.52-0.88). Virologic failure at enrollment was not associated with mortality (AHR = 1.18; 95% CI 0.40 - 3.47).
Conclusion: Female patients receiving ART for more than 6 years in rural Uganda were three times more likely to be hospitalized than men, but male mortality was nearly four times higher in the subsequent three years of follow-up. Facilitating care for acute medical problems may help to improve survival among male ART patients.

Table: Cox proportional hazards modeling of factors associated with time to mortality

List of clinical factors		Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
PVL at enrollment	< 1000 copies/mL	1.00	0.227	1.00	0.762
	≥1000 copies/mL	1.79 (0.69,4.63)		1.18 (0.40,3.47)	
Age at enrollment (per year increase)		1.06 (1.01,1.12)	0.014	1.07 (1.01, 1.13)	0.013
Gender	Female	1.00	<0.001	1.00	0.037
	Male	4.64 (1.98,10.87)		2.57 (1.06,6.23)	
Education	No education/do not know	1.00			
	Some/completed primary school	1.11 (0.30,4.11)	0.874		
	Some/completed high school	1.66 (0.46,6.05)	0.439		
Marital Status	Divorced/separated/ widowed/ single	1.00	0.506		
	Legally married	0.69 (0.23,2.05)			
Adherence (time-updated)	No missed doses	1.00	0.495		
	Any missed doses	1.71 (0.37,7.99)			
BMI (time-updated) per unit increase		0.85 (0.74,0.98)	0.027		
CD4 count (time-updated, per 100 cell increment)		0.66 (0.52,0.83)	0.002	0.67 (0.52,0.88)	0.004
Time on ARV (per year)		0.83 (0.59,1.17)	0.301		
Ever Hospitalized (yes vs. no)		0.22(0.03-1.63)	0.138		

1109 ALCOHOL USE AND THE HIV CARE CONTINUUM IN ZAMBIA: NATIONALLY REPRESENTATIVE SURVEY

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Background: Although increasing in sub-Saharan Africa (SSA), unhealthy alcohol use is not routinely screened for or treated within HIV prevention and treatment programs, in part due to lack of data on its intersection with the HIV epidemic. We evaluated the prevalence of unhealthy alcohol use among people living with HIV (PLWH) and its association with the HIV care continuum in Zambia.
Methods: We analyzed de-identified data from the 2016 Zambia Population-Based HIV Impact Assessment (ZamPHIA), a nationally-representative household survey. ZamPHIA included an assessment of alcohol use with the consumption questions from a modified Alcohol Use Disorders Identification Test (AUDIT-C), and rapid point-of-care HIV testing. PLWH also took an HIV care history survey and provided blood for detection of antiretroviral therapy (ART) and HIV RNA quantification. Unhealthy alcohol use was defined as an AUDIT-C score of 3-12 for women and 4-12 for men, abstinence was 0, and other scores were considered moderate use.Using multivariable regression, we identified the correlates of unhealthy alcohol use in the overall sample including sociodemographic factors and HIV status. Among PLWH, we evaluated the association of unhealthy and moderate alcohol use (versus abstinence) with HIV diagnosis, current ART use, and viral suppression (VS; RNA <1,000 copies/ml) using multinomial regression. PLWH were assumed to be diagnosed and on ART if ARVs were detectable.
Results: Among 18,796 participants included in the analytic sample, 11.9% were HIV-positive, and 15.3% (95% CI 14.6-16.1) reported unhealthy alcohol use. Male sex (relative risk ratio [RRR], 5.09), urban residence (RRR, 1.78), and HIV-positivity (RRR, 1.51) were independently associated with unhealthy alcohol use. Among PLWH, 71.4% were diagnosed, 87.1% were on ART, and 89.2% had VS. Unhealthy alcohol use (compared to abstinence) was associated with significantly lower odds of being diagnosed (adjusted odds ratio [AOR], 0.66; 95% CI, 0.49-0.87). We observed non-significant trends towards reduced odds of current ART use (AOR, 0.73; 95% CI, 0.48-1.10) and VS (AOR, 0.91; 95% CI, 0.57-1.44) among unhealthy users (versus abstainers).
Conclusion: Urban men living with HIV reported increased prevalence of unhealthy alcohol use in Zambia. Unhealthy drinking was associated with reduced awareness of HIV infection. Efforts to achieve control of the HIV epidemic in SSA should include alcohol reduction activities.

1110 RCT OF EARLY REFERRAL OF HIV+ ADULTS STARTING ART TO COMMUNITY-BASED ADHERENCE CLUBS

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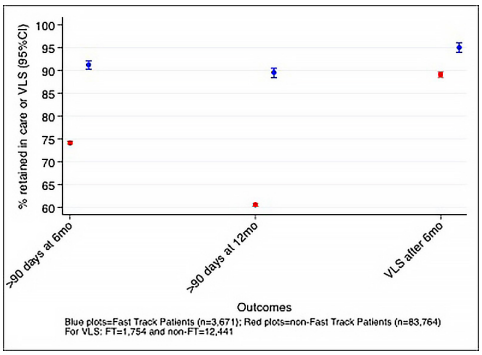
Background: Differentiated models of service delivery (DSD) are widely recommended to provide ART services for HIV+ patients established on ART, but there are few data on how soon stable patients may be referred to DSD after ART initiation.
Methods: We randomised adults 4 months after starting TDF+FTC+EFV in a large primary care service in Cape Town, South Africa, to either (a) immediate referral to the local DSD ['adherence clubs' (AC)] or (b) continued clinic-based care (NCT03199027). At randomisation all participants were eligible for ACs based on local criteria: VL<400 copies/mL with no reported adherence problems, TB or other comorbidities, or HIV/ART complications. In this setting ACs are based at community venues separate from the clinic with counsellor-led services, 2-4 monthly ART refills and annual nurse checks; clinic-based services are nurse-/doctor-driven with 2-monthly ART refills and 4-monthly clinical appointments. Using study follow-up visits conducted separately from routine care in either arm, we evaluated the primary trial outcome of VL<400 copies/mL at 12 months on ART (8 months after randomisation).

Results: Between Jan 2017 and Apr 2018, 220 consecutive non-pregnant adults who met local criteria for referral to ACs were enrolled and randomised (mean age 35y; 67% female; 24% previous ART; median nadir CD4 366 cells/mm_3; median time on ART 18w). 88% of patients randomised to ACs attended the club visit on schedule. VL measures for the primary outcome were available on 214 participants (97%) with no differences between those retained versus lost to follow-up, overall and by arm. By 12m on ART, VL<400 cps/mL was observed in 89% of participants randomised to be referred to ACs versus 93% of participants randomised to be retained in the clinic (risk difference, -4.3%; 95% CI, -11.9% to 3.2%). The finding for similar outcomes between AC and clinic-based care was consistent across subgroups of age, gender, previous ART use and nadir CD4 cell count; in a binomial model adjusted for the same factors; and when the outcome was examined at cutpoints of VL<50 and <1000 cps/mL.
Conclusion: These novel data suggest that referral of stable ART patients to community-based DSD may take place as early as 4 months after ART initiation in this setting with comparable virologic outcomes achieved at 12 months on ART versus clinic-based services.

1111 DIFFERENTIATED SERVICE DELIVERY FOR HIV CARE: THE FAST-TRACK EXPERIENCE FROM ZAMBIA

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Background: Differentiated service delivery (DSD) models are designed to lower barriers to HIV care for people living with HIV (PLWH). In 2017, we implemented a DSD model known as "Fast Track" (FT) within Zambia's HIV program that provided PLWH "stable" on ART (defined as WHO stage I/II disease, on ART ≥ 6 months, and CD4+ >350 or viral load suppression [VLS]) with expedited clinical services. We report clinical outcomes for FT patients during the first 2 years of implementation.
Methods: We reviewed individual-level PLWH data from Zambia's electronic health record, SmartCare. Patients 15–59 years were included in our analysis if they started ART any time from January 1, 2010 at any of 14 high-volume (>3,000 patients on ART) clinics in Lusaka. All patients in FT from its inception (January 1, 2017) through September 30, 2018 had their data reviewed to ascertain 6- and 12-month retention (i.e. any visit within 90 days of their 6- and 12-month post-ART initiation anniversaries) and VLS. To enable comparison, we reviewed records for all FT eligible patients who did not participate in FT during the same period at the same clinics. Using random-effects log binomial regression modeling, we estimated relative risk of retention in care for FT versus non-FT patients.
Results: During the review period, 3,671 patients participated in FT and 83,764 did not. FT participants were more likely to be female (64.9% vs 62.3%), ≥35 years (70.9% vs 60.2%), and on ART ≥24 months (77.6% vs 73.6%) (all p<0.01); there was no difference in the proportion with WHO I/II disease (72.6% vs 72.4%). FT patients were more likely to be retained at 6- and 12-months and to achieve VLS at 6-months compared to non-FT patients (p<0.001) (Figure). After adjusting for clinic, age, sex, WHO stage, and time on ART, FT patients were 1.23 and 1.49 times as likely to be retained in care as non-FT patients at 6- and 12-months, respectively (p<0.001).
Conclusion: We observed superior retention in care and VLS, and higher risk of care retention in adjusted analyses, among patients receiving FT versus non-FT services at ART clinics in Lusaka, Zambia. Due to limitations with routine data, we could not control for baseline CD4 and other unmeasured confounders. New DSD models, such as FT, hold promise for increasing care retention and VLS among stable ART patients in routine HIV treatment programs.



1112 DIFFERENTIATED CARE: TIME SPENT IN DIFFERENT ART DELIVERY MODELS IN RURAL ZIMBABWE

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Background: Differentiated service delivery (DSD) may contribute to reaching the UNAIDS 90-90-90 targets as the number of people living with HIV (PLWH) on antiretroviral therapy (ART) increases. The implementation of differentiated ART delivery is part of the national DSD guideline in Zimbabwe, with the aim to meet the diverse needs of PLWH, to reduce the time spent at health facilities (HFs) and to decongest the health system.
Methods: We assessed 26 rural HFs in Bikita District, Zimbabwe, in 2019. At each HF, one or two nurses involved in HIV service delivery, and consecutive PLWH attending the HF on the day of data collection were recruited. We collected data on the availability of various ART delivery models and the time that PLWH spend at the HF using standardized electronic data collection forms. We used descriptive statistics and linear regression analysis on log transformed time data.
Results: We assessed 22 rural health centers, 2 rural hospitals and 2 district hospitals. Median numbers of staff and patients registered were 4 and 346 (rural health centers), 13 and 994 (rural hospitals) and 24 and 1152 (district hospitals), respectively. Twenty HFs (77%) had at least one or more differentiated ART delivery model in place. The most common model was the community-based ART refill group (CARG; 13 HFs), followed by facility-based fast track (8 HFs), family refill group (6 HFs) and facility-based club refill (1 HF). Time spent at the HF was assessed for 203 PLWH (68% female, 12% pregnant or breastfeeding, median age 43 years [interquartile range: 34-52]). Fifty-seven (28%) were enrolled in a differentiated ART delivery model (34 in a facility- and 23 in a community-based or family model). Table 1 shows mean times spent at the HFs and results from multivariable regression. There was no evidence that PLWH enrolled in a facility-based model spent less time than those on standard care, while PLWH in community-based models spent 54% more time at the HF during their visit. Time spent was overall longer at rural health centers compared to hospitals, and shorter at HFs with a patient-to-staff ratio >100.
Conclusion: Differentiated ART delivery models are available in most of the assessed HFs in rural Zimbabwe, and a considerable proportion of PLWH on ART are enrolled in a differentiated ART delivery model. However, the type of HF and patient-to-staff ratios were more important determinants of the time spent at the HF than the ART delivery model.

Table 1: Predictors for time spent at the HF (N=203)

	n	Mean time spent, minutes (SD)	Coefficients from linear regression model* (95% CI)	P value
Model of care				
Standard care	146	46 (40)	1	
Facility-based model[&]	34	24 (15)	0.98 (0.70-1.38)	0.029
Community-based model[#]	23	75 (62)	1.54 (1.10-2.16)	
Type of health facility				
Rural Health Center	165	49 (45)	1	
Rural Hospital	20	26 (23)	0.66 (0.45-0.95)	0.017
District Hospital	18	33 (25)	0.69 (0.46-1.02)	
Staff-to-patient ratio				
1-50	54	50 (47)	1	
51-100	83	58 (47)	1.11 (0.84-1.47)	<0.0001
>100	66	26 (19)	0.54 (0.38-0.75)	

n=Number of observations, SD=Standard deviation, CI=Confidence interval
*Adjusted for all variables listed, pregnancy-breastfeeding-status and number of services received during the visit
[&]Fast track refill or club refill
[#]Community-based ART refill group (CARG) or family refill group

1113 PROSPECTIVE STUDY ON IMPACT OF DIFFERENTIATED CARE ON HIV RETENTION IN KEY POPULATION

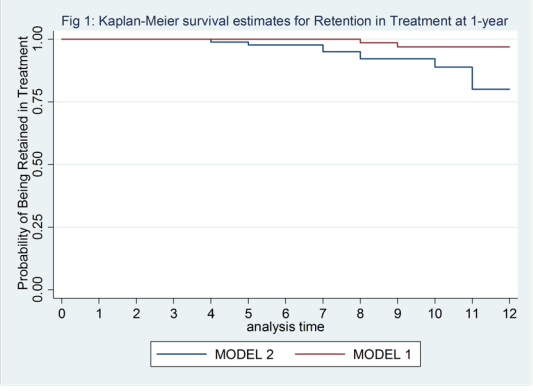
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Background: MSM and FSWs are prone to stigma and discrimination which may affect their retention in treatment. Key population (KP) designated facilities, termed One-stop shops (OSS) have shown promise in providing culturally appropriate care and treatment to KPs. We assessed the effect of different models of OSS on linkage to and retention in treatment in Nigeria.

Methods: Between December 2017 and June 2018, newly diagnosed MSM and FSW were enrolled into treatment at two OSS models and followed prospectively for one year. Model 1 was a fully integrated OSS with all clinical services while Model 2 was a prevention site with treatment needs supported by a different implementing partner in the state. Retention was estimated from drug pick records and was defined as being on treatment within 90 days one-year post ART initiation. Cox regression was used to identify the independent effect of the OSS models on retention while probability of being retained in treatment at 1-year was estimated with Kaplan-Meier product limit.

Results: A total of 605 newly diagnosed clients were enrolled into the study (340 in Model 1 and 265 in Model 1; 342 were FSW, while 263 were MSM). Median age was 26 years for MSM and 30 years for FSW. A majority of MSM had completed secondary level education in both M1 and M2 (54% vs. 67%) while most of FSW had completed primary level education (49% vs. 45%). Linkage to treatment was similar in both models (67%). Among those linked to treatment, retention was higher in M1 than in M2 (65% vs. 52%; p=0.007). Among those not retained, mean days to be lost-to-follow up (LFTU) was 60 days. Controlling for educational level, population type and age, clients who received treatment in M2 were 6 times more likely not to be retained in treatment at the end of 1 year (Hazard ratio 5.89; 95% CI: 1.04 – 33.16). The Kaplan Meier estimates of the probability of being retained in 6 months, 9 months and 12 months was 0.97, 0.92, 0.80 and 1.00, 0.96, 0.91 for M2 and M1 respectively.

Conclusion: Linkage to treatment was suboptimal across both models with less than 90% of newly identified positives initiated on treatment. Retention was higher and more likely among those who received care at model 1 compared to model 2. Mean time to be lost was two months requiring intensive monitoring within this period. This has implications for programs and policies that support one stop shops for HIV care and treatment.



1114 COMMUNITY PRIVATE PHARMACY ANTIRETROVIRAL THERAPY REFILL IN KAMPALA, UGANDA

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Background: Of the 1,000,000 (72%) persons living with HIV (PLHIV) on antiretroviral therapy (ART) in Uganda, 20% received care in Kampala, the capital, and its surrounding areas between April and June, 2019. The number of PLHIV attending Kampala's mid-level public health facilities has grown four times in the last 10 years, resulting in high patient-provider ratios, congestion, and long waiting times. The Kampala private community pharmacy ART refill model is a differentiated care approach that was introduced in 2017 for stable clients to address these challenges. Here, we describe the model and evaluate its effectiveness

Methods: The Infectious Diseases Institute in partnership with the Kampala Capital City Authority selected 6 private pharmacies to serve as community ART refill points for stable PLHIV from 4 high-volume public health facilities (8000–13,000 PLHIV on ART at each site). Virally suppressed adults on first-line ART were enrolled in this model by their primary care providers. They received ART refills at the pharmacy and attended semi-annual follow-up appointments at the primary health facility per national guidelines. A nurse-dispenser per pharmacy supported free ART refills, symptomatic opportunistic infection screening, patient referrals, tracking and follow-up, ART inventory management, and reporting. Program data from pharmacy and facility records has been summarized and analysed.

Results: Over a 30-month period (Jan 17 - June 19), 9921 (29% men) PLHIV enrolled in the pharmacy refill model, representing 30% of clients at the 4 facilities. Of these, 96% had received ART refills as scheduled, and the average waiting time at the pharmacy was <10 minutes. The 12-month retention in care rate was 98%, and >99% of enrolled clients remained virally suppressed.

Conclusion: Rapid enrolment and good retention rates indicate high acceptability of this model among urban PLHIV in Uganda. Structured public-private partnerships present opportunity for delivery of simplified ART refill services for PLHIV in resource-limited settings.

1115 COMMUNITY-BASED SERVICE DELIVERY OF HIV TREATMENT IN ZAMBIA: COSTS AND OUTCOMES

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Background: There are 1 million Zambians receiving antiretroviral treatment (ART) for HIV, severely straining existing healthcare infrastructure and human resources. To address this challenge, community-based differentiated service delivery (DSD) models of care have been implemented to reduce provider workload and improve quality of care. The costs and impact of these DSD models have not yet been evaluated in routine settings.

Methods: We conducted a cost and outcomes analysis of ART patients whom entered into DSD models in Zambia between 2015-2017 to estimate the average cost per patient per year. We evaluated the former standard of care (SOC), in which stable patients received care and medication refills at healthcare facilities every 3 months, and four out-of-facility models of care (which, per country guidelines, require two clinical facility-based visits per year): community adherence groups (CAGs), urban adherence groups (UAGs), home ART delivery, and mobile ART services. Using patient-level data, we captured individual resource utilization in each model over the first 12 months of model participation, then estimated the cost/patient by assigning unit costs to each resource. Retention in care at 12 months was defined as attending a clinic visit at 12 months +/- 3 months. We then used percentage of patients retained in care after 12 months to estimate an average cost/outcome for each model. To account for missing patient-level data in the number of DSD visits for three of the models, we also considered high and low visit utilization scenarios. Costs are reported in 2018 USD.

Results: Differentiated models of service delivery cost more per patient/year than the standard of care for all models assessed, as illustrated in Table 1. Costs ranged from as little as an annual $116 to $199 for the DSD models, compared

to an annual $100 for SOC. CAGs and UAGs increased retention by 2% and 14%, respectively. All DSD models also cost more per patient retained at 12 months than the standard of care. The CAG had the lowest cost/patient retained for DSD models ($140-157) followed by the UAG ($155-$169).

Conclusion: Though they achieve equal or improved retention in care, out-of-facility models of ART delivery should be expected to be more expensive than traditional, facility-based care. Future studies should focus on comparison of these models of care to newer facility-based models of care currently implemented in Zambia, such as fast-track ART refills and 6-month ART scripting and dispensing.

Table 1. Total provider cost, cost per patient retained, by model of care

	Models of service delivery				
Outcome	Standard of care	Community adherence groups	Urban adherence groups	Home ART Delivery	Mobile ART Services*
12 month retention in ART care	948/1174 (81%)	627/754 (83%)	183/193 (95%)	134/169 (79%)	148/216 (69%)
Annual cost per person treated	$100	$116-$130**	$147-$160**	$139-$188**	$199
Annual cost per person retained at 12 months	$124	$140-$157**	$155-$169**	$176-$237**	$291

*Includes stable and unstable patients; the only facility-based appointments are through mobile ART services
**Range reflects the low and high DSD utilization estimates

1116 HIV+ PATIENTS RECEIVING ANTIRETROVIRAL DRUGS THROUGH HOME DELIVERY: A CAUSAL ANALYSIS

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Background: Differentiated service delivery (DSD) models, which focus more on individual patient preferences and the needs of vulnerable subpopulations, are key to meeting the UNAIDS 90-90-90 goals for 2020 and beyond. Courier delivery of chronic medication by to a patient's home (home refill) is an attractive and scalable intervention to potentially improve antiretroviral therapy (ART) adherence and viral suppression; data, however, remains limited and is found predominantly in real-world settings with electronic health record (EHR).

Methods:

Building on a previous study, we conducted a retrospective analysis of ART naïve HIV-infected adults in Aid for AIDS (AFA) cohort, an HIV health management scheme for the private sector in South Africa who initiated first line NNRTI based ART between January 2002 and July 2013. The primary endpoint was all-cause mortality; secondary endpoints included CD4 and viral load (VL) response, loss to follow-up (LTFU), and switching to home-refill. Statistical analyses included descriptive, baseline (propensity-score) model, and time-updated (marginal structural) models (MSM).

Results: 40,939 patients, contributing over follow-up 66,000 years were evaluated. In a baseline analysis only, courier was associated with improved survival (adjusted hazard ratio = 0.90 [95% CI: 0.84-0.96], p-value for log-rank test < 0.001) after adjusting for baseline differences. Within an MSM framework, which addresses time-varying aspects, courier was associated with higher benefit (adjusted hazard ratio = 0.66 [95% CI: 0.55-0.78]). LTFU and switching were positively associated with lower CD4 and higher VL, explaining the improvement in the adjusted hazard ratio; CD4 response and VL suppression rates were superior for home-refill (including cases in which patients switched to home-refill). Finally, hospitalisation days and average costs, and CD4/VL monitoring were higher in home-refill compared to the self-refill groups ($p<0.00.1$) despite improved survival, CD4 and VL responses (see figure 1), which suggests that that home-refill promotes better health-seeking behaviour and better outcomes.

Conclusion: Our findings support the adoption of home-refill (courier) within the DSD models to facilitate the UNAIDS 90-90-90 targets, for HIV programs in both resource-poor and -rich settings. Further research is needed on the potential impact of home-refill in vulnerable groups with known transportation barriers such as postpartum woman and adolescents.

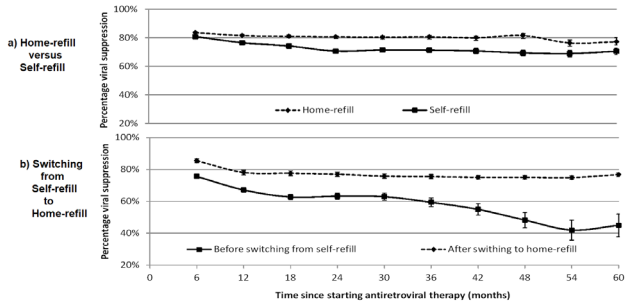


Figure 1: Comparing HIV viral load response (% suppression) from baseline to 60 months on antiretroviral therapy with 95% confidence ranges for home-refill by courier with (a) self-refill and (b) switching from self-refill to home-refill by courier

1117 OUTCOMES OF COMMUNITY-BASED ANTIRETROVIRAL TREATMENT PROGRAM IN NAMIBIA

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Background: Namibia is a sparsely populated country of 2.5 million people, with an HIV prevalence 12.6% (persons aged 15-64 years). About 52.1% of the population lives in rural areas, having to travel, on average, 25-59 km for HIV care. During 2007–2014, communities and health care facilities (HCF) in two high HIV burden districts in northern Namibia collaborated to establish Community-Based Antiretroviral Treatment (C-BART) services. Community members constructed basic structures close to their homes where healthcare workers visited quarterly to provide HIV clinical assessment, viral load (VL) and CD4 specimen collection, and antiretroviral (ARV) refills. We evaluated clinical outcomes at these C-BART sites to inform program expansion.

Methods: We conducted a retrospective cohort review of patients who were down-referred from HCFs to C-BART sites for continued HIV care during January 01, 2007–July 31, 2017, in Okongo (16 sites) and Eenhana (18 sites) Districts. We abstracted data on demographics, clinical encounters, ARV dispensation, and VL results from electronic and paper records. We measured C-BART retention (3-60 months), defined as being alive and on ART with a documented visit within 90 days of appointment date, and viral suppression (VS) (<1000 copies/ml) on a VL test at least 3 months after down-referral and closest to data abstraction date (November 30, 2017).

Results: Of the 1031 patients (909 adults and 122 children) included in the analysis, 100% of patients were retained in C-BART at 3 months and 99% of adults (n=522) and children (n= 71) were retained at 12 months (Table). In Okongo District, 91% of adults (n=141) and 96% of children (n=28) were retained at 60 months. Overall, 98% of adults (n=568) and 87% of children (n=77) retained at CBART sites for ≥3 months had viral suppression; 98% of adults (n=427) and 84% (n=58) of children in CBART ≥12 months, and 98% of adults (n=121) and 83% (n=23) of children in CBART ≥60 months (Okongo) had VS. VS did not differ by the time on ART in CBART (range: 3 months–10 years) (p=0.49 and p=0.81, respectively).

Conclusion: The C-BART program demonstrates high retention and VS among patients and alleviates concerns about providing community-based ART to children. High retention rates were sustained up to 60 months after down-referral to C-BART, demonstrating the utility of C-BART as a long-term model for managing patients on ART, particularly in rural settings.

Table. Retention in C-BART care following down-referral from healthcare facilities in two districts in Namibia, 2007-2017

Retention Time Point	Adults (=15 years) Number of patients followed (% retained) [a]			Children (<15 years) Number of patients followed (% retained) [a]		
	All patients N=909	Okongo N=504	Eenhana[b] N=405	All patients N=122	Okongo N=62	Eenhana[b] N=60
3 months	907 (99.7%)	503 (99.8%)	404 (99.5%)	122 (100%)	62 (100%)	60 (100%)
6 months	816 (99.1%)	461 (99.1%)	355 (99.2%)	110 (100%)	57 (100%)	53 (100%)
12 months	522 (99.0%)	364 (98.6%)	158 (100.0%)	71 (98.6%)	53 (100%)	18 (94.4%)
24 months	297 (96.0%)	297 (96.0%)	-	47 (97.9%)	47 (97.9%)	-
36 months	216 (94.0%)	216 (94.0%)	-	38 (97.4%)	38 (97.4%)	-
48 months	187 (93.0%)	187 (93.0%)	-	32 (96.9%)	32 (96.9%)	-
60 months	141 (90.8%)	141 (90.8%)	-	28 (96.4%)	28 (96.4%)	-

[a] Percentage retained is the number of patients alive and on ART at the retention time point divided by the total number of patients down-referred to C-BART and expected to be alive and on ART in C-BART at the retention time point, including those who died, were LTFU, and stopped ART, but excluding those who transferred out of the health district.

[b] Because C-BART sites in Eenhana District were opened in 2016, C-BART patients were followed for less than 24 months.

1118 PATIENTS EXPERIENCING VIRAEMIA IN ADHERENCE CLUBS: IS BACK-TO-CLINIC ALWAYS BEST?

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Background: ART adherence clubs have proven a successful model for many stable patients to receive peer support and convenient ART refills while utilizing fewer clinic resources. In the Western Cape, South Africa, patients are eligible to join a club after 6 months on ART, provided they are clinically stable, with a suppressed viral load (VL) and are not pregnant. Current guidelines, requiring viraemic patients to leave clubs and return to clinic care, are not strictly implemented. We describe the implementation of guidelines and 12-month outcomes of club patients who experience viraemia.

Methods: We included data on all patients ever in a club at three large primary healthcare clinics in Khayelitsha, a high HIV-prevalence, low-income, peri-urban area in Cape Town, South Africa. We identified patients with viraemia (VL>1000 copies/mL) that occurred after joining the club, before they first exited the club (<3 months after last club visit), and before 1 October 2017. We describe characteristics of these patients at the time of the unsuppressed VL test result, subsequent 12-month outcomes, and we performed multivariate logistic regression to identify predictors of 12-month VL resuppression.

Results: Of 8680 total club patients with a median time of 29.8 months in clubs (IQR:20-51) and VL testing data available, 503 (6%) experienced viraemia. Of the 494 patients who had any ART visits >2 months after viraemia, 345 (70%) returned to clinic care. Those who remained in clubs had the same chance of remaining in ART care 12 months later (93%), higher resuppression rates, similar VL completion rates, and a similar yet slightly lower median first high VL, compared to those returning to clinic (Table 1). A multivariate logistic regression showed 12-month VL resuppression was associated with remaining in clubs after one high VL result, compared to returning to clinic (OR:1.39; 95%CI:0.93-2.06), and the log of the first high VL (OR:0.84; 95%CI:0.75-0.93).

Conclusion: Inconsistent application of guidelines may result from clinical oversight or deliberate decisions based on patient-specific factors. Regardless, promising resuppression rates among those remaining in clubs suggest that there is scope to adapt adherence club guidelines to give patients and providers more flexibility, while providing safe clinical management of viraemic patients.
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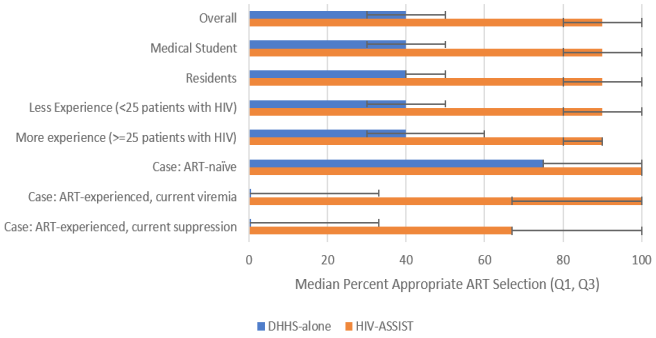
1119 RANDOMIZED TRIAL OF HIV-ASSIST VERSUS GUIDELINES FOR ART SELECTION BY TRAINEES

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Background:
Support for primary care clinicians in HIV medicine is critical in light of national HIV-provider shortages. Department of Health and Human Services (DHHS) guidelines are comprehensive but complex to apply for antiretroviral therapy (ART) selection. HIV-ASSIST (www.hivassist.com) is a free, online tool providing individualized ART decision-support. We hypothesized that trainees with access to HIV-ASSIST would be more likely to select appropriate ART for diverse HIV patient scenairios, compared to those using DHHS HIV guidelines alone.
Methods:
We conducted a randomized study of medical students and residents at Johns Hopkins University, in which participants were asked to select an ART regimen for 10 HIV case scenarios through an electronic survey. Participants were randomized to receive either DHHS guidelines alone (with a video tutorial), or DHHS guidelines and HIV-ASSIST (with a video tutorial) to support their decision-making. ART selections were graded 'appropriate' if consistent with DHHS guidelines, or concordant with ART regimens selected by HIV experts at three major academic institutions.
Results:
Among 118 trainees, participants randomized to receive HIV-ASSIST had significantly higher percentage of appropriate ART selections compared to those receiving DHHS alone(% appropriate responses in DHHS vs HIV-ASSIST arms: median 40% [Q1, Q3: 30%, 50%] vs 90% [80%, 100%], p<0.001). This difference was consistent among both medical students (median 40% vs 90%, p<0.001) and residents (median 40% vs 90%, p<0.001). The effect was seen for all case-types, but most pronounced for complex cases involving ART-experienced patients with ongoing viremia (DHHS vs HIV-ASSIST: median 0% [0%, 33%] vs 100% [66%, 100%]). In qualitative feedback, 61% commented on difficulty navigating or interpreting DHHS guidelines; by contrast 82% commented that HIV-ASSIST was user friendly, with 85 and 98% agreeing or strongly-agreeing that HIV-ASSIST was useful for making ART selections for ART-naive and experienced patients, respectively.
Conclusion:
Trainees using HIV-ASSIST were significantly more likely to choose appropriate ART regimens compared to those using guidelines alone. Interactive decision-support tools may be important and necessary to ensure appropriate interpretation and implementation of HIV clinical practice guidelines.

Figure: Appropriate ART selection comparing study arms



1120 TRANSITION TO DOLUTEGRAVIR-BASED REGIMEN: NIGERIAN EXPERIENCE AMONG KEY POPULATIONS

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Background: Following the release of the preliminary results of the largest ever HIV/AIDS indicator and Impact survey in Nigeria, the government of Nigeria and PEPFAR launched an aggressive effort towards improving virologic supression among PLHIV. We transitioned clients from efavirenz to dolutegravir based regimen. We examined the viral load among key population groups transitioned from TLE to TLD in three high burden states.

Methods: A descriptive observational study that compared the routine viral load result of 3,327 key population (KP) clients from three high burden states who were transitioned from Tenofovir-Lamivudine-Efavirenz (TLE) to Tenofovir-Lamivudine-Dolutegravir (TLD). We carried out a repeat viral load tests on clients 1 to 3 months after transitioning to TLD using the Roche (C6800 & C8800) and Abbott PCR analyzers. We analyzed data using SPSS version 21. Paired sample t-test was used to compare the means of the viral load test results

and Chi-square to compare the proportion of respondents with <1000 copies/ml and those that achieved untransmitable viral load level of < 200 copies/ml before and after start of TLD. We used ANOVA to determine difference in means between the different KP groups. We set P-value at P < 0.05, being statistically significant.

Results: 64.7% (n=2153) females and 35.3% (n=1174) males were enrolled (FSW 55.9% (n=1861); MSM 24% (n=797); PWID 14.3% (n=476); sexual partners of key population 5.6%; (n=190); People in prisons 0.1%; (n=3)). Mean age of clients is 31.19 ±2.82. Lower viral load achieved when on TLD (mean= 6924.71, SD = 65687.079) than when on TLE (mean= 17059.85, SD= 118859.603). Paired sample t-test found this difference to be significant (t = 4.572, p<0.005). Chi square reveals more clients achieved viral load <1000copies and <200 copies/ml while on TLD than while on TLE (X2 = 217.491, p< .005; X2 = 175.722, p< .005 respectively). ANOVA showed no significant difference in the mean of the viral load between the groups before and after start of TLD (f (4) = 1.113, p=0.35 for viral load results before start of TLD: f (4) = 0.665, p=0.62. for viral load results after start of TLD).

Conclusion: DTG-based regimen significantly suppressed viral load of KP PLHIV following transition from Efavirenz based regimen. Virologic suppression and untransmitable viral levels achieved were superior with the use of TLD.

1121 POOR LINKAGE TO CARE AMONG HIV+ PERSONS IN EMERGENCY DEPARTMENTS IN SOUTH AFRICA

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Background: Despite efforts to extend HIV services cross South Africa a significant number of persons living with HIV in the Eastern Cape remain either untested or unengaged. Even though Emergency Departments (EDs) were designed to address acute medical issues, they may also represent an under-utilized gateway for identification and engagement of HIV positive individuals at high risk for disease progression as well as onward transmission. We therefore sought to examine the feasibility and acceptability of universal HIV testing in the ED and subsequent linkage to treatment.

Methods: We conducted a prospective cohort study across four EDs in the Eastern Cape province of South Africa, for a period of six weeks each, from July 2016 to July 2018. All adult (over 18yrs) non-critical patients presenting were systematically offered HIV testing. HIV+ patients were further consented to participate in a follow up study to ascertain linkage to care (LTC) via; 1) Telephone follow-up and/or; 2) Tracking in the National Health Laboratory System (NHLS) database. LTC at one-year was defined as self-reporting linkage (telephonic) or evidence of repeated CD4/viral load testing (NHLS). All patients followed the usual down referral care pathway (follow up in local clinic near their home after receiving a letter stating their results).

Results: Over the study period 5900 patients were enrolled, of which 4846 (82.1%) accepted testing, of which 1172 (24.2%) were HIV positive of which 949 consented to participate in a LTC follow up study. Of these 633 (66.7%) had a known diagnosis of HIV and 316 (33.3%) had a new diagnosis of HIV infection. Of the known HIV positive patients, 30.9% had evidence of LTC via NHLS (72/233) and 48.6% confirmed via phone (71/146). Among newly diagnosed patients, 27.6% (40/145) had evidence of LTC in the NHLS database, and 38.4% confirmed via phone (28/73). There was no significant difference in linkage to care between those with known HIV versus those with HIV diagnosed in the ED.

Conclusion: ED-based HIV testing in South Africa identified individuals with new HIV diagnoses and those out of HIV care. Overall LTC in this population was extremely poor. While the ED is a critical venue to identify HIV individuals not on ART there is a need to deploy novel, targeted LTC interventions in the ED.

1122 LINKAGE TO CARE AND VIRAL SUPPRESSION FASTER OVER TIME AMONG NEW HIV DIAGNOSES IN DC

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Background: Treatment for all people with HIV and improved antiretroviral therapy and care infrastructure are expected to have improved health outcomes in the US. We aimed to describe changes in initial care outcomes for people diagnosed with HIV in the District of Columbia (DC) over time.

Methods: We used DC HIV surveillance data for people ages 13 and older diagnosed with HIV in DC in 2009-2017 to calculate linkage to care (LTC, presence of CD4 or viral load after HIV diagnosis) and viral suppression (VS, HIV RNA <200 copies/ml) as continuous variables (time from diagnosis to outcome) and dichotomous variables (LTC-30, or LTC within 30 days, and VS-90, or VS within 90 days of diagnosis). Chi square tests were used to compare demographics and CD4 at diagnosis between those diagnosed in 2009-2012 (DX09-12) vs. 2013-2017 (DX13-17). For DX13-17, multivariable (MV) logistic regression was used to calculate adjusted prevalence ratios (aPR) for LTC-30 and VS-90, adjusted for age at diagnosis, gender, race/ethnicity, mode of transmission, year of diagnosis, and CD4 at diagnosis.

Results: Compared to DX09-12 (n=3124), DX13-17 (n=2119) were more likely to be men (75.2% vs. 71.3%), Latino (10.9% vs. 7.5%), MSM (50.1% vs. 43.0%), and younger (all p<0.001). There were no differences by LTC-30 between the groups. The proportion never virally suppressed declined (22.7% DX09-12 vs. 19.8% DX13-17, p<0.0001). Median time from HIV diagnosis to initial VS declined from 250 days (DX09-12) to 137 days (DX13-17) (p<0.0001); among those with CD4>350 cells/µl at HIV diagnosis, median time from HIV diagnosis to initial VS declined from 235 days (DX09-12) to 129 days (DX13-17) (p<0.0001). Among DX13-17, achievement of VS was lowest among transgender people (TG, 67.9%), PWID (58.6%), and adolescents 13-18 (69.2%). MV analysis (Table) demonstrated that non-White races, MSM/PWID, ages 25-39, dx year 2014, and CD4>500 were less likely to achieve LTC-30. Black race and MSM/PWID (aPR 0.45, 95% CI 0.22-0.91) were less likely to achieve VS-90, and women, TG, dx years 2015-2017, and those with CD4>500 (aPR 1.47, 95% CI 1.13-1.90) were more likely to achieve VS-90.

Conclusion: Time from HIV diagnosis to LTC and VS have significantly improved from 2009 to 2017 for people diagnosed in DC, but gender, race, and risk factor-based disparities were found. Results can guide interventions for focus populations, including men, MSM/PWID, Black individuals, and those with lower CD4 counts. Future research may elucidate reasons for delays.

Correlates† of linkage to care within 30 days of HIV diagnosis and viral suppression (HIV RNA <200 copies/ml) within 90 days of HIV diagnosis

	Linked to care within 30 days of HIV diagnosis	Virally suppressed within 90 days of HIV diagnosis
	aPR (95% CI)	*aPR (95% CI)*
Gender		
Men	Reference	Reference
Women	0.94 (0.69-1.28)	1.35 (1.02-1.79)*
Transgender or non-binary	1.09 (0.57-2.06)	2.31 (1.28-4.17)*
Race/ethnicity		
Black	0.56 (0.40-0.78)**	0.73 (0.55-0.97)*
White	Reference	Reference
Latino	0.57 (0.37-0.97)*	0.71 (0.49-1.03)
Other or Unknown	0.39 (0.23-0.65)**	0.66 (0.41-1.06)
Year of Diagnosis		
2013	Reference	Reference
2014	0.56 (0.42-0.74)***	1.07 (0.81-1.42)
2015	1.65 (1.21-2.27)*	1.58 (1.19-2.08)*
2016	1.72 (1.24-2.37)*	2.64 (1.99-3.50)***
2017	2.0 (1.43-2.78)***	2.34 (1.75-3.12)***

* P<0.05, ** P<0.001, ***P<0.0001

†Multivariable models were adjusted for age at HIV diagnosis, race/ethnicity, gender, year of HIV diagnosis, mode of transmission, and CD4 cell count within 90 days of HIV diagnosis. Adjusted PR and 95% CI for age at diagnosis and mode of transmission not shown.

1123 TRENDS IN LINKAGE INTO CARE AFTER "TEST AND START" AMONG ADOLESCENTS AND YOUNG ADULTS

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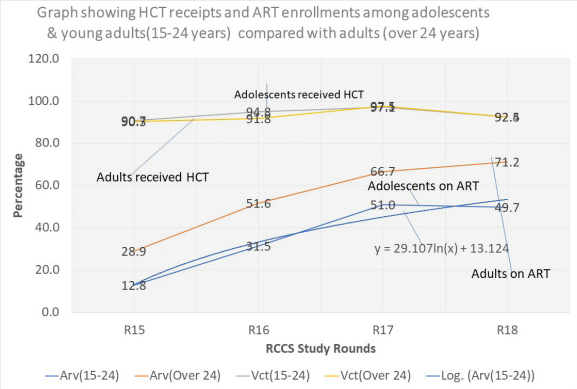
Background: There is underutilization of anti-retroviral Therapy (ART) among HIV positive adolescent and young adults (AYA: 15–24 years) compared to adults (25-49 years). We examined trends and factors associated with ART uptake after the test and start program in a community-based cohort in Rakai, Uganda.

Methods: We analyzed data from the Rakai Community Cohort Study (RCCS) for 10,827 HIV positive participants collected between 2013 and 2018 and compared 1,669 AYA (15-24 years) to 9,158 adults (25-49years). Covariates included: gender, marital status, religion, occupation, alcohol consumption, family size, education and number of sexual partners. In addition, we used

bivariate analysis to test the associations between hypothesized correlates and uptake of ART and the Generalized Linear Model (GLM) to estimate the risk ratios associated with ART uptake

Results: The average difference in proportions of ART use between AYA and adults was 18.4% (CI; 13.7, 22.9; P<0.01). In 2013, 12.8% of the AYA were on ART compared to 28.9.1% for adults, and by 2018, the proportions were 49.7% and 71.2%, respectively. In multivariate models, risks of not being on ART among AYA were increased in males (RR: 1.21; CI 1.01- 1.44), never married compared to married (1.19; CI 0.99, 1.41), and one and 2+ sexual partners compared to those with none (RR: 1.39; CI 1.00- 1.95); (RR: 1.50; CI 1.07- 2.11, respectively).

Conclusion: There is an increase in ART uptake among AYA over time, but still remains lower than the UNAIDS 95-95-95 goals. AYA with multiple sexual partners and fishing occupations were less likely to use ART. We recommend targeted efforts to promote ART initiation and retention among adolescents in order to achieve epidemic control.



1124 ENGAGEMENT IN CARE AND VIRAL SUPPRESSION AMONG NEWLY DIAGNOSED HIV-INFECTED PERSONS

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Background: Achieving and maintaining viral suppression (VS) in persons living with human immunodeficiency virus (HIV) protects their own health and prevents new infections. An important step to achieving and maintaining VS is being engaged in care. This study describes how newly diagnosed HIV-infected persons are engaging with their provider and achieving VS over a 24-month period.

Methods: Persons newly diagnosed with HIV infection from June 30, 2012-December 31, 2014 who presented at one of six HIV clinics (Birmingham, AL; Boston, MA; Houston, TX; Miami, FL; San Diego, CA; Seattle, WA) were included in the cohort. All participants had an unsuppressed viral load on their first viral load (VL) test at the clinic and observed for up to 24 months from the date of their first VL test. We examined patterns of VS (<200 copies/mL) across time and the percentage of persons who had VS on their latest VL test during the 24-month follow up period. We used chi-squared statistics to compare persons with VS and not virally suppressed (nVS) by proportion of kept HIV care visits and by clinic, age, sex, race/ethnicity, and insurance.

Results: Overall, 76% (1111/1469) of all newly diagnosed HIV-infected patients were VS at their latest VL test with an average of 149 days to achieve VS. Examining the cohort across time revealed that after achieving VS, 69% remained VS on all subsequent VL tests and 19% were nVS on any of their tests. The percentage VS varied by clinic, race/ethnicity, age, insurance, and proportion of kept visits with their provider (Table). Notably, as the proportion of clinic visits increase, the proportion of VS patients increase with 90% of those who kept >50% of their clinic visits being VS on their latest test. We also see differences in distribution of VS by race/ethnicity, with Non-Hispanic Blacks having significantly smaller proportion being VS.

Conclusion: A large proportion of newly diagnosed HIV-infected patients achieved and maintained VS however nearly 20% never achieved suppression. There is a need for close clinical monitoring and identification of barriers impacting some newly diagnosed patients, particularly the unmet needs of minorities to increase the number who achieve stable suppression.

Table: Characteristics of viral suppression among newly diagnosed HIV-infected patients

Variable**	Viral Suppression^				p-value~
	Never VS N=283	Ultimately nVS N=75	Remained VS N=1,018	Ultimately VS N=93	
	No		Yes		
	N=358	Row %	N=1,111	Row %	
Site					<0.01
Boston	7	9.6	66	90.4	
San Diego	61	28.0	157	72.0	
Miami	16	35.6	29	64.4	
Seattle	38	19.9	153	80.1	
Birmingham	46	21.9	164	78.1	
Houston	190	26.0	542	74.0	
Gender					0.47
Male	264	23.8	844	76.2	
Female	90	25.7	260	74.3	
Age at start of study					<0.01
17-39	232	26.6	641	73.4	
40-49	78	25.2	231	74.8	
50+	48	16.7	239	83.3	
Race/Ethnicity					<0.01
Hispanic	91	22.0	322	78.0	
Non-Hispanic Black	187	28.0	482	72.0	
Non-Hispanic White	50	17.7	233	82.3	
Non-Hispanic Other	7	14.3	42	85.7	
Risk					<0.05
MSM	127	20.6	490	79.4	
MSM+IDU	17	29.8	40	70.2	
IDU	15	31.9	32	68.1	
Heterosexual	150	26.0	428	74.1	
Insurance					<0.01
Private	27	11.5	208	88.5	
Medicare/Medical	11	13.3	72	86.8	
Medicaid	42	18.0	192	0	
Ryan White	201	27.1	541	72.9	
Proportion of Kept Visits (quartiles)#					<0.01
>75%	28	7.9	325	92.1	
>50% and ≤75%	49	10.3	428	89.7	
>25% and ≤50%	148	35.7	267	64.34	
≤25%	109	64.5	60	35.5	

*Due to small cell sizes, comparisons could not be done with persons who remained VS, ultimately VS, never VS, and ultimately nVS.
Remained VS=after achieving VS, persons remained VS on all subsequent VL tests in the 24-month period <200 copies/mL;
Ultimately VS=fluctuation in VLs however the person's last VL test <200 copies/mL in the 24-month period;
Never VS=all the person's VL tests in the 24-month period >200 copies/mL;
Ultimately nVS=fluctuation in VLs however the person's last VL test >200 copies/mL in the 24-month period
**Missing were excluded from the tables, includes 11 gender, 55 race/ethnicity, 170 risk, 175 insurance, 55 kept visits.
^Viral suppression is at the latest viral load test in the 24-month period
Stratified by quartiles for proportion of kept visits.
~Chi-square test

1125 FREQUENT DETECTION OF UNDIAGNOSED HIV WITHIN EMERGENCY DEPARTMENTS IN BOTSWANA

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Background: Botswana has a severe generalized HIV epidemic (23% adult HIV prevalence) with a high annual HIV incidence (1.3%). In 2004, Botswana became Africa's first country to routinize "opt out" provider-initiated HIV testing and counseling (PITC) at health facilities, though it is rarely implemented in Emergency Departments (EDs). EDs provide episodic, unplanned care to large volumes of undifferentiated patients. Thus, EDs provide an opportunity to capture patients with undiagnosed HIV infection missed by other facility-based HIV testing.

Methods: We evaluated the frequency of detecting undiagnosed HIV infection in the ED using data from a national HIV testing program in Botswana. From January 2018 to September 2019, HIV testing was conducted by program counselors at 149 facilities in 16 districts, including 55 EDs. Electronic data captured demographic information (age, sex, citizenship) and testing date, location and result. Data were included from individuals' first HIV test during the program within ED, voluntary counseling and testing (VCT), or other PITC settings. We excluded data from risk-based testing strategies (e.g., index testing, STI or TB clinics) and antenatal clinics. Observations were excluded if test results were unavailable or if the individual previously tested HIV-positive.

Results: In total, 130,161 individuals were tested in ED (9,695; 7%), VCT (12,760; 10%), or other PITC (107,706; 83%) and were included in the analysis; median age was 30 years (IQR 24-30), 29% were <25 years, 53% were male, and 57% were tested in urban centers. Compared to individuals who tested in VCT or other PITC, individuals who tested in the ED differed in age, sex, and urbanicity (Table 1). Overall, frequency of detecting undiagnosed HIV infection was 3.4%; 2.2% in VCT, 3.4% in other PITC, and 4.7%, in ED, respectively. Frequency of HIV detection in EDs was 2-fold higher than in VCT (prevalence ratio[PR]=2.2, 95% CI 1.4-3.3, p<0.001) and 1.4-fold higher than in other PITC (OR=1.4, 95%

CI 1.1-1.9, p=0.03). Among individuals with ART information (3,505), those who tested HIV-positive in EDs less frequently initiated same-day ART compared to VCT/other PITC (71% vs 82%, PR=0.9, 95% CI 0.8-1.0, p=0.003).
Conclusion: HIV testing was successful within EDs in Botswana and yielded higher frequency of detecting undiagnosed HIV infections than VCT or other PITC; however, immediate ART initiation was less frequent. ED HIV testing programs should strengthen linkage to care for those who test positive.

Table 1. Characteristics of HIV testers in Botswana from January 2018 to September 2019, by HIV testing department

	N (%) or Median (IQR)				
		HIV testing department[1]			
Individual characteristics	Overall (N= 130,161)	VCT (n=12,760)	Other PITC (n= 107,706)	ED (n=9,695)	p-value[2]
Age (years)	30 (24-39)	29 (23-38)	30 (24-39)	30 (23-41)	0.039
Male sex	68433 (53%)	7009 (55%)	56465 (52%)	4959 (51%)	0.003
Urban setting[3]	74288 (57.1%)	6110 (47.9%)	61200 (56.8%)	6978 (72.0%)	<0.001
Newly detected HIV-positivity[4]	4387 (3.4%)	276 (2.2%)	3656 (3.4%)	455 (4.7%)	<0.001
ART initiation[5,6]	2848 (81.3%)	177 (78.7%)	2433 (82.6%)	238 (71.0%)	<0.001

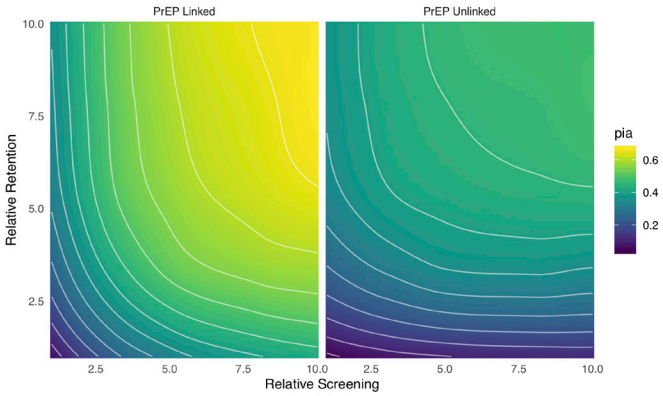
VCT=voluntary HIV counseling and testing; PITC=provider-initiated HIV counseling and testing; ED=emergency department; ART=antiretroviral therapy

[1] We excluded records from antenatal care clinics and risk-based testing strategies (e.g., index testing, STI clinics, TB clinics, etc) and records without HIV test results available. Only observations from first HIV tests were included.
[2] Kruskal –Wallis tests for continuous measures and Chi-squared tests for proportions comparing ED versus VCT/Other PITC
[3] Urban settings included the districts of Gaborone, Greater Francistown, Lobatse, Mahalapye, Serowe/Palapye, and Maun
[4] Newly detected HIV-positivity defined as no previous HIV positive test result
[5] Among individuals with HIV-positive test results
[6] Among n=3505 individuals with ART initiation information; 882/4387 (20%) of individuals were missing ART initiation information as this variable was implemented are the program was initiated.

1126 COMBINATION HIV PREVENTION STRATEGIES TO MEET THE 2030 ENDING THE HIV EPIDEMIC GOALS

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Background: The goal of the US Ending the HIV Epidemic (EHE) plan is to reduce HIV incidence by 90% over the next decade. This initiative will direct a major scale-up of prevention and care activities in high-burden areas like the Southeast US. It is unknown what interventions, alone or in combination, will have the greatest impact towards meeting the EHE 2030 targets.
Methods: We developed a stochastic network-based HIV transmission model for men who have sex with men (MSM) stratified by race. Our model was calibrated to current surveillance-based estimates of HIV prevalence, PrEP utilization, and HIV care continuum levels in the Atlanta area. Counterfactual model scenarios varied HIV screening rates relative to empirical levels, under assumptions that HIV-negative screens are linked to PrEP initiation versus no PrEP linkage, and also relative improvements to HIV care linkage and care retention for those testing HIV-positive.
Results: Compared to current HIV screening rates, a ten-fold relative increase (to approximately biannual screening for black and Hispanic MSM and quarterly for white MSM) would lead to 41.2% of infections averted under the assumption of PrEP linkage, with prevention through both increased PrEP coverage (from 14.9% to 67.0%) and increased HIV viral suppression (from 48.9% to 55.8% of all infected). At the same relative increase in screening but under the assumption of no PrEP linkage, 9.9% of infections would be averted, with prevention only through increased viral suppression. HIV care linkage, even if immediate upon screening HIV-positive, would have a negligible effect on infections averted (0.2%). Improvements to HIV care retention could avert 33.5% of infections if retention rates were improved 10-fold, through increased viral suppression (from 48.9% to 79.6% of all infected). If both screening and retention were jointly improved up to 10-fold (Figure), 66.6% and 47.9% of infections would be averted under assumptions of PrEP linkage and no-linkage, respectively.
Conclusion: Interventions to improve HIV screening linked with PrEP for those screening negative and HIV care retention would have the largest impact on HIV incidence. Additional interventions beyond these improvements to HIV screening, PrEP coverage, and HIV care retention will be necessary to reach the EHE targets.



1127 COMMUNITY HIV-PREVENTION SERVICES IMPROVE THE HIV TREATMENT CASCADE IN 5 COUNTRIES

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Background: The effect of using HIV prevention services on using HIV treatment services has not been well documented in southern Africa. Using nationally representative data from household surveys conducted in Eswatini, Lesotho, Malawi, Zambia, and Zimbabwe (2015–2017), we examined the correlation of self-reported voluntary medical male circumcision (VMMC) and condom use among HIV-negative adults with use of treatment services by people living with HIV (PLHIV), represented by the UNAIDS 90-90-90 targets, at the community level.
Methods: Among HIV-negative adults in the surveys, we estimated the prevalence of self-reported VMMC status and condom use (during last sexual act in the prior 12 months) at the smallest geographic sampling unit (enumeration area [EA]). We used multilevel mixed-effects logistic regression, adjusted for demographic and risk behavior variables at individual level to estimate the correlation between VMMC and condom use at the EA level with the likelihood of PLHIV being aware of their status, currently on ART, or virologically suppressed (VS).
Results: Among 10,861 PLHIV aged 15–64 years (62% women) residing in 1,734 EAs across surveys, 76% had a previous HIV diagnosis, 68% were receiving ART, and 60% were VS. Median EA-level prevalence of HIV infection, VMMC, and condom use was 16% (interquartile range [IQR], 10%–24%), 16% (IQR, 6%–32%), and 72% (IQR, 55%–88%), respectively.
On multilevel analysis, the odds of knowing HIV-positive status, receiving ART, or being VS were significantly higher for PLHIV residing in an EA where ≥75% of the adults reported condom use (adjusted odds ratio [AOR], 1.3 [95% confidence interval (CI), 1.2–1.5]; 1.3 [95% CI, 1.1–1.4]; 1.2 [95% CI, 1.1–1.3], respectively). The odds of knowing HIV-positive status, receiving ART, or being VS were significantly higher for PLHIV residing in an EA where ≥15% of men reported VMMC (AOR, 1.2 [95% CI, 1.1–1.3]; 1.1 [95% CI, 1.0–1.3]; and 1.1 [95% CI, 1.0–1.2], respectively).
Conclusion: In these five countries, community utilization of prevention services was positively correlated with the individual use of treatment services, suggesting that combination prevention services can play a synergistic role in epidemic control.

Table. Results of the multi-level mixed-effects logistic regression model to examine the relationship between two proxies for utilization of HIV prevention services (i.e. the prevalence of VMMC and condom use) and the odds of HIV positive adults being aware of their status, currently on ART or virologically suppressed.

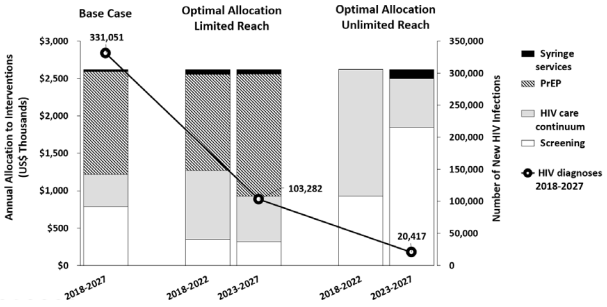
Outcome / Covariates	Aware of HIV+ status	95% CI	On ART	95% CI	Virologically suppressed	95% CI
Individual-level variables						
Female	-	-	-	-	-	-
Male	0.48***	(0.43-0.54)	0.54***	(0.49-0.60)	0.57***	(0.51-0.62)
15-24 years	-	-	-	-	-	-
25-34 years	2.42***	(2.04-2.86)	1.88***	(1.61-2.20)	2.01***	(1.72-2.36)
35-44 years	5.13***	(4.27-6.16)	3.78***	(3.20-4.47)	3.76***	(3.19-4.43)
45-54 years	5.94***	(4.82-7.31)	5.14***	(4.25-6.21)	5.51***	(4.59-6.61)
55-64 years	6.23***	(4.64-8.37)	6.21***	(4.74-8.13)	6.77***	(5.26-8.72)
Never married	-	-	-	-	-	-
Married or living together	1.20*	(1.03-1.40)	1.16*	(1.01-1.33)	1.15*	(1.01-1.32)
Divorced or separated	0.93	(0.77-1.13)	0.92	(0.77-1.10)	0.91	(0.77-1.08)
Widowed	1.36**	(1.08-1.71)	1.22*	(1.00-1.48)	1.21*	(1.01-1.45)
None or one partner	-	-	-	-	-	-
Multiple partners	0.81**	(0.69-0.94)	0.80**	(0.70-0.92)	0.91	(0.80-1.04)
First sex 15 + years	-	-	-	-	-	-
First sex before 15	1.19	(0.99-1.45)	1.13	(0.96-1.34)	1.06	(0.91-1.24)
EA-Level variables						
Less affluent EA (below average)	-	-	-	-	-	-
More affluent EA (above average)	0.88*	(0.78-0.98)	0.84***	(0.76-0.93)	0.87**	(0.80-0.96)
HIV prevalence <15%	-	-	-	-	-	-
HIV prevalence >=15%	1.41***	(1.24-1.59)	1.31***	(1.17-1.46)	1.28***	(1.15-1.42)
Condom use prevalence <75%	-	-	-	-	-	-
Condom use prevalence >=75%	1.30***	(1.16-1.46)	1.26***	(1.14-1.40)	1.21***	(1.10-1.33)
VMMC prevalence <15%	-	-	-	-	-	-
VMMC prevalence >=15%	1.19**	(1.06-1.34)	1.14*	(1.02-1.26)	1.13*	(1.02-1.24)
Observations	10861		10861		10861	

* p<0.05, ** p<0.01, *** p<0.001

1128 OPTIMIZING HIV PREVENTION EFFORTS WITHOUT NEW INVESTMENT CAN REDUCE INCIDENCE

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Background: We optimized current societal spending on HIV prevention to assess how best to achieve large reductions in HIV incidence.
Methods: We used a national model of HIV transmission to estimate the potential maximum 10-year reduction in new infections from 2018 to 2027. The model applied current estimated public and private HIV prevention spending ($2.6 billion for 2018) each year to the following intervention categories: HIV screening (high- and low-risk MSM and heterosexuals, PWID), HIV care continuum (linkage to care at and after diagnosis, prescription of ART, retention in care, viral suppression), PrEP, and SSPs. The model optimized expenditures for two consecutive 5-year periods. We compared the base case (no optimization) to two optimization scenarios: a limited-reach scenario, in which estimates of the maximum number of persons who can be reached by each intervention generally reflect current conditions; and an ideal, unlimited-reach scenario, where all eligible persons can be reached by each intervention.
Results: In the base case in which 30.0% and 16.7% of societal investments are applied to HIV screening and care-continuum interventions, there were 331,000 new cases over the next 10 years. Optimization in the limited-reach scenario in the first 5 years decreased the allocation to HIV screening to 13.4% and increased the allocation to care-continuum interventions to 35.1%. In the unlimited-reach scenario, allocations to both HIV screening and care-continuum interventions increased (to 35.4% and 64.6%, respectively). The 10-year reduction in incidence was 69% in the limited-reach scenario and 94% in the unlimited-reach scenario. Investment in HIV screening decreased in the limited-reach scenario to focus on groups other than low-risk heterosexuals, whereas in the unlimited-reach scenario, screening investments increased to cover all eligible persons. In the unlimited-reach scenario, investment in PrEP was minimized because that scenario included extensive diagnosis and effective viral suppression through the increased funding of ART adherence interventions. However, under the more realistic conditions of the limited-reach scenario, continued investment in PrEP was required.
Conclusion: Optimal allocation of current societal investments in HIV prevention can achieve substantial reductions in new infections. Achieving reductions over 90% is theoretically possible, but implausible with current resources.



1129 IMPACT OF COMBINATION HIV PREVENTION IN ZIMBABWE: A MULTIDISTRICT TRANSMISSION MODEL

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Background: The Zimbabwean HIV epidemic is generalized, and heterogeneous at the district level. Combination HIV prevention (CHP) has been rolled out in Zimbabwe over the past decades, including antiretroviral therapy (ART), voluntary male medical circumcision (VMMC), prevention of mother to child transmission, behavior change programmes, and condom distribution. Evaluating the impact of these programs on the HIV epidemic is important to improve intervention planning.
Methods: Together with local policy makers and stakeholders, we developed a multidistrict, individual based HIV transmission model that simulates dynamic interactions between districts to accurately represent transmission dynamics, and quantified it using Zimbabwean demographic, epidemiological, and behavioral data. We used this model to evaluate the impact and cost-effectiveness of CHP in Zimbabwe over the period 2011 – 2015. This period was chosen as it encapsulates the national HIV strategic plan, and because the two large-scale population based surveys were conducted at the end of that period. We also estimate the future impact of alternative strategies.
Results: We simulated the Zimbabwean HIV epidemic over 4 different districts, representative of rural, urban, mining, and commercial farming districts, and were able to reproduce district specific and national census data, sexual behavior in key and general populations, and HIV prevalence and incidence. We show that CHP in Zimbabwe over the period 2011 – 2015 prevented an estimated total of 90 thousand new infections, at 2259 US$ per infection averted (table). Interventions were most cost-effective in urban districts, and least cost-effective in rural districts. Importantly, our model closely reproduced national HIV incidence estimates in 2015 without specifically tuning to these data, serving as an important validation of our unique approach, and shows that we managed to closely reproduce the effects of CHP on incidence.
Conclusion: We have shown that CHP in 2011-2015 in Zimbabwe was highly cost-effective, even over the short period of implementation. Our approach in modeling a geospatially dynamic representation of the Zimbabwean HIV epidemic proved successful, and could be a valuable to further understand underlying transmission dynamics, and in turn optimize location specific resource allocation, allowing for the dynamic spillover effects of these interventions to other areas. Further expanding these tools could help policy makers in Zimbabwe and other countries to develop efficient and effective strategies to end AIDS by 2030.

Table. Cost-effectiveness of combination HIV prevention in Zimbabwe as implemented over the period 2011-2015, national and by district type.

	National	By district			
		Rural	*Urban*	*Mining*	*Farming*
Total costs (million US$)	204.0	81.6	71.4	22.5	28.6
Infections averted					
Vertical	12041	4335	4696	1204	1806
Horizontal	78295	28186	30535	7830	11744
Total	90335	34100	36941	9472	14208
Cost per infection averted (US$)	2259	2394	1934	2370	2011

1130 IMPLEMENTATION OF U=U IN REAL LIFE IN ITALY: RESULTS FROM THE ICONA COHORT

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Background: Zero risk of linked HIV transmission in sero-discordant couples when the HIV-infected partner had viral load (VL)<200 copies/mL (U=U status) was observed in large observational studies. We aimed at estimating the proportion of time in which this status was maintained and identifying factors associated to the risk of losing it among people living with HIV (PLWH) enrolled in a clinical cohort.

Methods: We included participants in the ICONA cohort who had reached an established U=U status (VL<=200 copies/mL for >6 months) as of December 2010. The outcome was the number of person days of follow up (PDFU) with a VL>200 copies/ml (cp/ml), relative to the total number of PDFU observed in follow-up. Logistic regression model was used to identify factors independently associated to the risk of losing U=U status. For this analysis, a participant was defined as losing his/her U=U status if he/she spent <90% of his/her PDFU on observation with a VL <=200 cp/mL. The median of VL measurements was 9 (IQR: 4-15).

Results: 8,241 PLWH were included in the analysis and contributed 12,670,888 PDFU. Of these, 1,648 (20%) were female, 768 (9%) were people who inject drugs (PWID), 3,786 (46%) men who have sex with men and 3,176 (39%) heterosexuals. Overall, during the entire follow-up, 96.9% of PDFU observed were with a VL<=200 cp/ml. Thus, only 3.1% of PDFU were observed when VL was >200 cp/mL with some evidence for a decrease after 2016. The median time with VL>200 cp/ml was 47.3 days (IQR: 46.3-47.9). Of note, the proportion of PDFU with VL>200 cp/ml was higher than average in females (5.3%), unemployed (5.4%), PWID (4.7%) and in people with>3 previous virological failures (6.3%). At individual level, 617 participants (7.5%) spent <90% of PDFU with a VL<=200 cp/mL and were classified as losing their initial U=U status. Unadjusted and adjusted OR of losing U=U status from fitting the logistic regression model are shown in Table 1.

Conclusion: In our population of PLWH meeting the definition of U=U this status was maintained for 97% of the following 10 years of observation with a trend towards an increase in recent years. These findings reinforce the validity of the U=U message in real world settings. However, we identified subsets of our population, including females and foreign-born, at higher risk of not maintaining the U=U status, for whom greater efforts are needed to reduce these infrequent periods of VL>200 cp/ml.

Table. 1. Logistic regression estimates of factors associated with losing U=U status

	Unadjusted		Adjusted*		
Factor	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**	**Type III p-value**
Gender					
Female vs. Male	2.26 (1.89, 2.69)	<.001	1.55 (1.20, 2.00)	<.001	
Mode of HIV Transmission					<.001
PWID vs. MSM	3.68 (2.86, 4.72)	<.001	2.50 (1.80, 3.46)	<.001	
PWID vs. Heterosexual	2.09 (1.72, 2.54)	<.001	1.43 (1.10, 1.87)	0.009	
PWID vs. Other/Unknown	1.77 (1.24, 2.53)	0.002	1.67 (1.07, 2.60)	0.017	
Nationality					
Foreign-born vs. Italian	1.36 (1.14, 1.63)	<.001	1.42 (1.12, 1.80)	0.004	
Employment, n (%)					<.001
Unemployed vs. Employed	2.14 (1.70, 2.70)	<.001	1.46 (1.13, 1.89)	0.004	
Occasional vs. Employed	2.00 (1.33, 3.02)	<.001	1.17 (0.75, 1.82)	0.496	
House work vs. Employed	2.52 (1.70, 3.74)	<.001	1.8 (0.88, 2.17)	0.141	
CD4 count, cells/mmc					
per 100 lower	1.05 (1.02, 1.08)	0.002	1.04 (1.00, 1.08)	0.042	
CD8 count, cells/mmc					
per 100 higher	1.01 (1.00, 1.03)	0.161	1.03 (1.01, 1.05)	<.001	
Previous virological failure, n					<.001
1-3 vs. 0	2.02 (1.50, 2.73)	<.001	1.84 (1.22, 2.76)	0.003	
>3 vs. 0	3.52 (2.64, 4.69)	<.001	2.85 (1.84, 4.44)	<.001	

*Multivariable model includes all variables selected by backward selection that were retained with a p-value less than 0.3 level. Also adjusted for age, AIDS diagnosis, HBsAg/HCV status, duration of ART, anchor drug used, geographical region, diabetes, smoking, use of statins/lowering blood pressure drugs, glucose and prior STDs. PWID: people who inject drugs; MSM: men who have sex with men.

1131 IMPACT OF PrEP AND TasP ON INCIDENCE OF HIV DIAGNOSES IN 48 HIGHEST-BURDEN US AREAS

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Background: Use of Tenofovir Disoproxil/Emtricitabine (TVD) for Pre-Exposure Prophylaxis (PrEP) has significantly reduced the HIV diagnosis rate in many US states, independent of the effect of treatment as prevention (TasP).

Methods: Using publicly available HIV surveillance data on HIV diagnoses from 105 US metropolitan statistical areas (MSAs) (2012-2017), virologic suppression data from 38 US states and DC as a proxy for Treatment as Prevention (TasP), and TVD for PrEP drug utilization obtained from a national pharmacy and medical claims database, we evaluated the independent impact of PrEP and TasP on HIV diagnosis rates in 48 counties and localities in the End the Epidemic Initiative (48-ETE). We calculated the person time at risk of HIV infection excluding time of those taking PrEP as well as those who became HIV positive. Incidence rates, rate ratios and 95% confidence intervals were assessed using a multilevel Poisson regression model for the 48-ETE and overall after adjusting for the effect of PrEP and TasP.

Results: Over this 6-year analysis, the US rate of HIV diagnoses in the 48-ETE locations decreased at a rate of 7.1% (95%CI –6.9 to –7.3%) per year while PrEP use in those with a CDC-defined PrEP indication increased 9.9-fold in the same locations from a mean 1.31/100 individuals (95% CI 0.3-2.3) in 2012 to 13.1/100 (95% CI 12.1-14.1) in 2017. HIV viral suppression (viral load <200 c/mL) increased by 1.4% per year (95% CI 1.1 to 1.7%) during the same time among HIV treated subjects. A multivariate poisson model showed that PrEP use was significantly associated with the decline in the rate of new HIV cases in the 48-ETE localities, independent of a significant TasP effect. 48-ETE localities with an average PrEP use rate of 17.4 per 100 subjects at risk could expect a decline of 15.5% in the rate of new HIV diagnoses. 48-ETE localities had significantly higher new HIV diagnosis rate than the rest of the US MSAs (IRR 2.0, 95% 1.61 – 2.58), but had a significantly lower PrEP use (-2.1 per 100 subjects at risk, 95% CI -0.93 to -3.2), and TasP proportion (-1.30 %, 95% CI -0.41 to -2.2%) than those MSAs not selected for intervention.

Conclusion: From 2012-2017, HIV diagnoses declined significantly in the 48 counties and localities selected for intervention where PrEP use was the highest. The effect of PrEP use was significantly associated with this decline and was independent of treatment as prevention. Improvements in PrEP and TasP coverage in these localities could yield important declines in the rate of new HIV diagnoses.

1132 IMPACT OF FOOD INSECURITY ON THE HIV EPIDEMIC IN SUB-SAHARAN AFRICA (2015–2017)

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Background: To assess associations between food insufficiency (FI) and HIV-related outcomes, including infection, we used data from nationally representative population-based HIV impact assessment (PHIA) surveys in Zambia, Eswatini, Lesotho, Uganda, Tanzania, and Namibia (2015–2017).

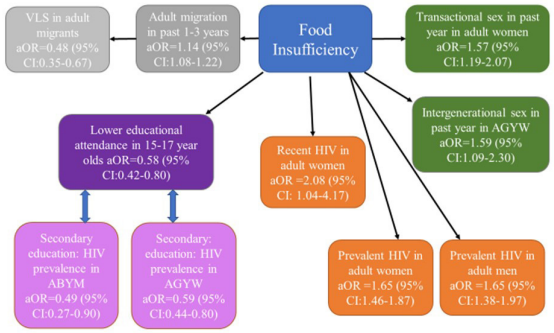
Methods: We collected FI data, defined as having any time with no food in the house in the past 4 weeks, from the household head. We also offered household-based HIV testing. Recent infection (<130 days) was measured using the HIV-1 Limiting Antigen (LAg) Avidity assay combined with lack of viral load suppression (VLS, <1000 copies/mL) and antiretroviral (ARV) testing data. Recent infection indications were those with LAg<1.5 normalized Optical Density (ODn), VL>1000 copies/mL, and no detectable ARVs. We performed pooled analyses to determine the association between FI and several HIV-related outcomes on weighted data on adults aged 15–59 years using logistic regression adjusted for age, sex, urban/rural residence, wealth quintile, and education, fitting an interaction term between country and FI. We stratified by sex for transactional

and intergenerational sex and for recent HIV as outcomes. As part of the analytic framework, we also assessed whether secondary or greater education was associated with HIV infection in young adults (aged 15-24).

Results: Of the 112,964 enrolled adults aged 15–59 years, 23% lived in households reporting FI. FI was associated with migration (away for >1 month in past 1–3 years), and in older adolescents (aged 15–17 years), lower odds of current school enrolment (Figure). Higher educational attainment was associated with lower odds of prevalent HIV in men and women aged 15–24 years. FI was associated with intergenerational sex in women aged 15–24 years and, in all women, with transactional sex, and with a two-fold increase in recent HIV infection (adjusted odds ratio [aOR], 2.08; 95% confidence interval [CI]: 1.04–4.17). FI was not associated with lower odds of VLS, but migrants were less likely to be suppressed (aOR, 0.48; 95% CI: 0.35–0.67).

Conclusion: FI could negatively impact the HIV epidemic both in the short-term, by increasing high-risk sexual behaviors and HIV infection rates in women, and in the long-term, by impeding educational attainment and increasing migration.

Figure. Food insufficiency and its association with HIV-related outcomes in sub-Saharan Africa (2015–2017). Migration was defined as being away from home for more than 1 month in the past 1 year (3 in Namibia). Secondary education was defined as having attended at least secondary school, compared to only attending primary school or no formal education. Abbreviations: VLS, viral load suppression; aOR, adjusted odds ratio; CI: confidence intervals; AGYW, adolescent girls and young women, aged 15-24 years; ABYM, adolescent boys and young men aged 15-24 years; adults: participants aged 15-59 years.



1133 GEOGRAPHIC ESTIMATE OF SEXUAL HIV TRANSMISSION BURDEN IN ERA OF U=U: DC COHORT DATA

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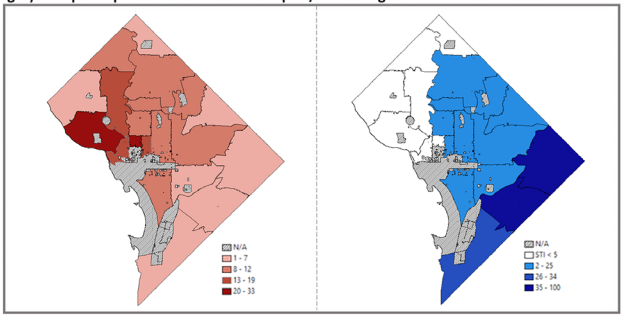
Background: Washington, DC (DC) has the highest jurisdictional prevalence of HIV in the US. Sexual transmission is the primary driver of the HIV epidemic in DC, the US, and globally. The Undetectable = Untransmittable (U=U) campaign advances the goal of ending the HIV epidemic by promoting durable viral suppression and reducing sexual transmission. On the other hand, insights into geographic areas of high HIV transmission burden allow for focused and impactful interventions. We aimed to assess HIV transmission by zip code of residence in the DC Cohort, a city-wide cohort of persons with HIV infection (PWH). We define HIV transmission burden as the number of PWH with high-risk sexual behaviors as identified by an incident STI who also are at risk for transmitting HIV.

Methods: We conducted an analysis of DC Cohort participants, ages ≥13 from April 1, 2016 to March 31, 2018. We assessed by zip code of residence, HIV transmission burden: the number of those with incident STIs (gonorrhea, chlamydia, and syphilis) and any HIV VL ≥200 copies/mL from the nine months prior to the day of STI diagnosis to 3 months post STI diagnosis (to approximate the U=U criteria for undetectable).

Results: Of 3,467 participants, 270 (7.8%) had at least one incident STI. Compared to those without any STIs, those with ≥1 STI were younger (mean age 41.1 with vs. 54.1 years without STIs), male (91.5% vs. 64.5%) and MSM (79.6% vs. 31.9%). White race was more frequently represented among those with STIs (23.3%) compared to those without STIs (8.6%) and blacks were less frequently represented (66.7% with vs. 83.2% of those without STIs). Homelessness or temporary housing was more common among those with STIs, 18.9% vs. 9.1% without. (P <0.0001 for all comparisons.) Ten or more DC Cohort participants lived in 20 Washington DC zip codes. Of the 270 PWH with incident STIs, 85.6% lived in 10 zip codes (See figure). Of the 270 participants with incident STI, at least one HIV VL was available for 254 (94.1%). Overall, 69 (27.2%) of individuals with incident STIs had an HIV VL ≥200 copies/ml. Of these 69, 72.5% resided in 6 of the 20 Washington DC zip codes.

Conclusion: In Washington DC, 6 zip codes of residence accounted for 72.5% of the estimated HIV transmission burden among participants in the DC Cohort. Estimates of HIV transmission burden by zip code of residence allow for targeted, neighborhood-level interventions that may strengthen efforts to end the HIV epidemic.

Figure. Washington, DC zip code maps showing (left) number with at least one incident STI, and (right) % of participant with HIV VL ≥200 copies/mL among those with an incident STI



1134 LATE PRESENTATION PERSISTS UNDER UTT IN SOUTH AFRICA: A NATIONAL COHORT STUDY

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Background: South Africa implemented Universal Test-and-Treat (UTT) in Sept 2016, extending eligibility for antiretroviral therapy (ART) to all people with HIV, regardless of CD4 count. However, the impact of UTT will be limited if people do not seek care early in infection.

Methods: We constructed a national HIV cohort by linking the complete historical laboratory records of South Africa's public sector HIV program, Apr 2004 – Mar 2018, enabling all patients to be tracked longitudinally. For each patient, we defined "CD4 at presentation" as first CD4 count in the database and "CD4 at ART start" as the first CD4 count within 90 days of ART workup (ALT/HG/CRT) taken in advance of starting ART. (The same CD4 count would apply for each if a patient started ART at presentation.) We assessed the distribution of CD4 counts at presentation and at ART start in 2015 (pre-UTT) and 2017 (post-UTT) and assessed features of these distributions (e.g. median) over time, 2004-2018. We also estimated trends in numbers of patients entering care and starting ART (as proxied by a VL or ART workup) at different CD4 counts, and evaluated the impact of ART eligibility expansions (from <200 to <350, to <500, and to UTT) on these trends.

Results: 12M patients had a first CD4 count through March 2018. In 2017, 48.2% of patients presented with CD4 >=350 cells/mm$_3$, and just 29.3% presented with CD4 counts >=500 (newly-eligible with UTT) (Fig 1a). The shares were nearly identical in 2015 (pre-UTT): 48.3% >=350 and 28.8% >=500. Median CD4 at presentation increased from 229 cells/mm$_3$ in 2005 to 338 in 2015, but plateaued thereafter, reaching only 337 in 2017 (Fig 1b). Median CD4 at ART start increased from 173 cells/mm$_3$ in 2005 to 327 in 2015, with a marginal increase to 332 in 2017. With each ART eligibility expansion, the gap between median CD4 at presentation and ART start narrowed, disappearing under UTT (Fig 1b). Numbers seeking care did not increase with UTT. Although ART eligibility expansions led to short-run increases in numbers starting ART, each successive change in CD4 criteria affected a smaller share of patients, and as a result, the numbers starting ART have plateaued since 2011 (Fig 1c).

Conclusion: UTT has not led to an increase in early care-seeking, with most patients still presenting with CD4<350. The impact of UTT on numbers starting ART has been limited by late presentation in South Africa.

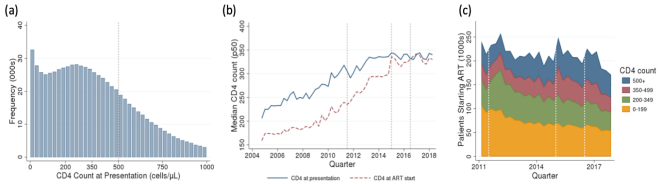


Fig 1. Figure shows (a) distribution of CD4 counts among patients presenting in 2017; (b) median CD4 at presentation (solid blue) and ART start (dashed red) 2004-2018; and (c) estimated number of patients starting ART by CD4 count, 2011-2018. In (b) and (c), vertical lines denote ART eligibility expansions to CD4<350 (Aug 2011), CD4<500 (Jan 2015) and UTT (Sept 2016). Source: Data are from National Health Laboratory Service and reflect the complete lab records of the national HIV program except for labs conducted in KwaZulu-Natal prior to 2010.

1135 CD4 COUNT AT ART INITIATION IN THE UTT ERA: AN INTERRUPTED TIME SERIES ANALYSIS

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Background: South Africa implemented universal test and treat (UTT) in September 2016 in an effort to encourage earlier initiation of antiretroviral therapy (ART). We conducted an interrupted time series (ITS) analysis to assess the impact of UTT on median CD4 count at ART initiation among adults attending public sector primary care services in rural South Africa.

Methods: We analysed data from individuals >=16 years old initiating ART between 2014 and 2019 at 17 clinics in northern KwaZulu-Natal and registered on TIER.net, the national ART clinical database. Our outcome of interest was CD4 count at ART initiation, defined as the value closest to ART start date in a window from 6 months prior to 3 months after ART initiation. Our primary exposure of interest was calendar period, based on CD4 eligibility expansions: (i) <January 2015, (ii) Option B+/pre-UTT era (January 2015 - August 2016) and (iii) post-UTT era (>=September 2016). We used a segmented linear regression model with a continuous time variable, binary exposure variables for each policy change, and time-by-policy interaction terms. To distinguish between short- and longer-term effects of eligibility expansions, we allowed a change in trend 12 months after policy rollout. We fitted separate regression models for men and women.

Results: Between July 2014 and March 2019, 20,603 (54% under UTT) individuals (69% female) aged >=16 years commenced ART. Median age at ART initiation was 30 (interquartile range 25-38) years. CD4 counts within window were available for 74% individuals. In January 2015 median CD4 at ART initiation was 381 cells/μL among women and 282 cells/μL among men. After UTT implementation, there was an immediate increase in median CD4 at ART initiation of 123 cells/μL (95% CI 81.7 to 164.3, p<0.001) among women, and 98.3 cells/μL (95% CI 75.6 to 121.0, p<0.001) among men (Figure 1). However, there was a significant downward monthly trend in CD4 count at ART initiation in both women (-12.5 cells/μL, 95%CI -18.1 to -6.9, p<0.001) and men (-7.0 cells/μL, 95%CI -11.2 to -2.7, p=0.002) for 12 months after UTT implementation. The trends stabilised thereafter (Figure 1).

Conclusion: UTT led to an immediate boost in earlier initiation of ART in this rural community. However, the effect declined over time before stabilising. More efforts are needed to increase early ART initiation, particularly among men.

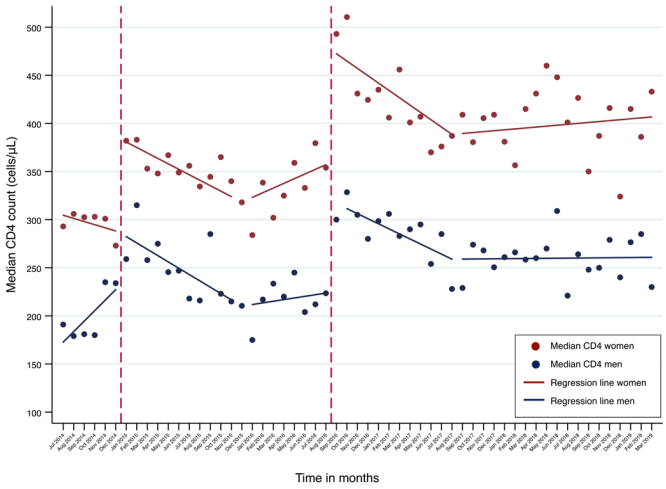


Figure 1. Median CD4 count at ART initiation among women and men.
Dashed vertical lines depict policy changes in January 2015 and September 2016.

1136 USING SOCIAL NETWORKS TO REACH INDIVIDUALS WITH LOW CD4 AT HIGH RISK OF DEATH

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Background: HIV+ persons with low CD4 (<200 cells/mm$_3$) are at high risk of death without effective treatment. We evaluated the potential for a social network strategy based on outreach to social contacts of HIV+ persons in care to identify HIV+ individuals who had CD4<200 and were out of care.

Methods: Adult (≥15 years) residents enumerated during a 2013-2014 census in 32 rural Kenyan and Ugandan communities in the SEARCH Study (NCT01864603) named social contacts in five domains: health, money, emotional support, food, and free time. Named contacts were matched to enumerated residents to build social networks among 150,395 adult residents; 135,484 (90%) were tested for HIV; 117,593 had at least one contact and were included in analyses. The target population was defined as HIV+ adults with CD4<200 and out of care. We evaluated strategies for reaching this target population based on outreach to 1st degree contacts of two index populations: 1) all HIV+ adults in care, 2) HIV+ adults in care with CD4<350. For each strategy we calculated coverage (% of the target population potentially identified), number needed to screen (NNS, # of persons outreached to per target individual identified), and ratio of coverage and NNS of each index population relative to the other. Clustering was quantified with an assortative mixing coefficient; p-values were based on randomly permuting node labels.

Results Among 10,285 adults known to be HIV+ at baseline with at least one contact, 8,168 had a record of HIV care, of whom 1,904 had CD4<350; 394 HIV+ adults had CD<200 and were out of care. HIV+ persons in care had an average of 4.3 1st degree network members; HIV+ persons in care with CD4<350 had an average of 4.4 1st degree network members. An outreach strategy to 1st degree contacts of all HIV+ adults in care would have reached 40% of target persons (p<0.001) and required outreach to 52 contacts per target individual identified (p<0.001). Outreach to 1st degree contacts of HIV+ in care with CD4<350 would have reached 15% of target persons (p<0.001) and required 31 contacts per target individual identified (p<0.001)[Table]. The assortative mixing coefficient was 0.009 for persons with CD4<200 out of care, 0.02 for HIV+ in care with CD4<350, 0.10 for all HIV+ persons.

Conclusion: HIV+ persons with low CD4 who are out of care are socially connected to HIV+ individuals engaged in care. An outreach strategy through the social networks of HIV+ persons in care may be an effective way to reach this high-risk population.

Table. Coverage, Coverage Ratio, Number needed to screen (NNS), and NNS Ratio for 1) a strategy of outreach to 1st degree contacts of HIV+ with CD4<350; and 2) a strategy of outreach to 1st degree contacts of all HIV+ persons, to reach the target population of HIV+ individuals with CD4<200 not on ART.

	Coverage	Coverage ratio (vs. index= CD4<350)	Coverage ratio (vs. index=all HIV+)	Number needed to screen (NNS)	NNS ratio (vs. index= CD4<350)	NNS ratio (vs. index=all HIV+)
Index population						
CD4<350 in care (n = 1688)	15%	--	0.35	31	--	0.60
All HIV+ in care (n = 6988)	40%	2.85	--	52	1.68	--

1137 IMPROVING HIV CASE-FINDING WITH MACHINE LEARNING

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Background: Alliance for Public Health implements social network strategy for HIV case-finding among key populations. We developed a model to improve recruitment of undiagnosed HIV-positives in the network using machine learning (ML) algorithm.

Methods: Since 2016, 130,095 people who inject drugs and their extended risk network peers were recruited in 12 regions of Ukraine. Recruitment starts from HIV positive cases with following criteria: 14+ years, inject drugs. Participants provided with 3 coupons to invite their peers defined as an injecting or sexual partner or somebody from the social network who can be also at risk of HIV. Recruitment stops if there are two HIV-negative cases next to each other in a chain. Data on recruitment chains and participants' characteristics collected in mobile application. Additional coupons are provided to participants with certain characteristics, such as "over 10 years of injecting drugs", "history of incarceration", "positive HIV test result". We implemented a ML algorithm to predict in real-time the probability of recruiting an undiagnosed HIV-positive person within onestep from the participant who receives coupons. Considering the estimated probability, recommendations on a number of additional coupons are provided.

Results: Among participants who received coupons, 75.9%(n=35,965/47,404) recruited at least one peer and 15%(n=7,146/47,404) recruited at least one HIV-positive participant within onestep. In comparison with current recruitment algorithm ML model is 1.5-2.5 times more efficient (based on GINI index) in predicting chances of undiagnosed positive case (Fig.1). ML model with 42predictors yielded a GINI index of 34%for classification of HIV-positives and negatives. The most informative predictors of recruitment of HIV-positives included "HIV test result", "Region", "Years of injecting drugs", while "Age" and "Marital Status"had the lowest contribution to prediction.

Conclusion: Higher level of discriminatory power (an ability to distinguish between successful and not successful recruitment)of ML model suggests that application of ML algorithm during recruitment could improve HIV-positive yield and guide HIV testing to address gap in locating undiagnosed cases. Further steps include piloting of ML algorithm with randomizing recruiters to evaluate effectiveness of ML in improving case-finding in groups connected in risk networks with high prevalence of HIV.

Fig.1.

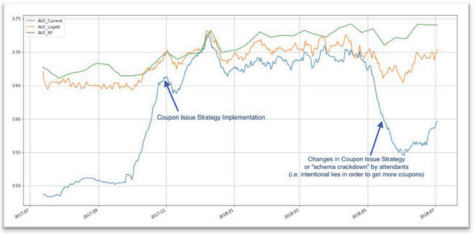


Figure abbreviations: AUC – area under the receiver operating characteristic curve; AUC_current – AUC for the Standard of Care (Coupon Issue Strategy); AUC_logit – AUC for logistic regression classification; AUC_RF – AUC for random forest classification. GINI=AUC*2-1

1138 HIV SCREENING IN EMERGENCY DEPARTMENTS: LINKAGE WORKS, BUT WHAT ABOUT RETENTION?

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Background: Universal opt-out HIV screening programs in emergency department (ED) settings have been successful in linking newly-diagnosed and out-of-care known HIV-positive persons into care. However, most of these programs report linkage to care but not retention rates and so the actual impact of these programs on the HIV care cascade remains unknown. The objective of this analysis was to evaluate rates of linkage to care and subsequent retention in care associated with an ED-based universal opt-out HIV screening program in San Diego.

Methods: All newly HIV diagnosed and known HIV-positive out-of-care (i.e. >12 months without a clinic visit) individuals were identified through EMR-based universal opt-out HIV screening for persons aged 13-64 years at the University of California San Diego EDs between July 2017 and September 2019. Case managers dedicated to the program focused on (re)linking these individuals to care and stopped case management at the time of (re)linkage. Retention in care was assessed at 6 and 12 months following initial (re)linkage to care. Univariate and multivariable binary logistic regression models assessed medical, and social variables (derived from existing literature) as predictors of successful linkage and retention in care (Table).

Results: A total of 47 newly diagnosed and 92 known HIV-positive out-of-care persons were identified. 40 of 47 (85%) newly diagnosed individuals were linked to care, and 48 of 92 (52%) known HIV+ out of care individuals were re-linked to care. At 6 months follow-up, 23/33 (70%) of the newly diagnosed individuals were still in care, 5 (15%) were confirmed to be out of care, and 5 (15%) were unable to be contacted. At 6 months follow-up, 14/26 (54%) of the known HIV-positive persons were still retained in care, 11 (42.3%) were confirmed to be out of care, and 1 (4%) was unable to be contacted (p=0.04 vs new diagnoses). Methamphetamine use (within six months of ED screening; 43% of Meth users confirmed out of care) was significantly associated with falling out of care in the multivariable model (p=0.033; Table).

Conclusion: While our universal opt-out ED HIV screening program achieved high rates of (re)linkage to care, 37% had (again) fallen out of care within 6 months. In particular, persons using methamphetamine may benefit from continuous case management that goes beyond initial linkage in order to achieve higher rates of retention in care and increase the impact of ED HIV screening programs.

Table 1 Univariate and Multivariable Binary Logistic Regression Models for Predicting Follow Up in 6 Months (p-values <0.2 are italic and those <0.05 bold)

Model	Descriptive Statistics (n = 55)	OR	95% CI	p value	aOR	95% CI	p value
		Univariate Model			Multivariable Model*		
Age (per year)	40.45 ± 12.244	1.035	0.986 – 1.087	*0.164*	n.s.		
Female Sex at Birth	11 (20%)	1.000	0.253 – 3.949	1.000			
Female Gender Identity	15 (27%)	0.808	0.238 – 2.737	0.732			
Hispanic Ethnicity	23 (42%)	1.046	0.782 – 1.399	0.761			
If male, sex with men (MSM)	26 (47.3%)	0.865	0.772 – 1.038	*0.119*	n.s.		
Transperson who has sex with men	5 (9.1%)	0.932	0.742 – 1.171	0.545			
Injection Drug Use	12 (21.8%)	0.858	0.737 – 0.999	***0.049***	n.s.		
Methamphetamine use	21 (47.2%)	0.822	0.686 – 0.984	***0.033***	0.822	0.686 - 0.984	***0.033***
Other Substance Use (excluding alcohol and marijuana)	19 (34.5%)	0.853	0.722 – 1.006	*0.060*	n.s.		
Psychiatric Illness	29 (52.7%)	0.873	0.720 – 1.058	*0.165*	n.s.		
Unstable Housing	1 (63.6%)	0.862	0.686 – 1.083	0.653			
Imprisonment	7 (12.7%)	0.911	0.786 – 1.055	0.213			

*x2 = 1.937; P = 0.164 Hosmer–Lemeshow; forward Wald binary logistic regression.
Abbreviation: OR=odds ratio; aOR=adjusted odds ratio

1139 EXPERIENCE FROM THE LARGEST WESTERN US EMERGENCY DEPARTMENT ON ENDING THE EPIDEMIC

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Background: Emergency Departments (ED) account for 135 million healthcare visits annually. HIV positive patients are 3 times more likely to visit an ED, be a racial minority and lack insurance than their non HIV counter parts. EDs are a safety net for HIV infected individuals, and it is often their sole and only point of entry into the healthcare system. The role out of HIV testing in US emergency departments has paralleled the decline in undiagnosed HIV in the US, potentially contributing substantially to curbing the epidemic. However,

a recent systemic review of 37 ED programs across the US showed that linkage to care (LTC) from EDs is suboptimal. The Los Angeles County plus University of Southern California (LACUSC) ED is the largest ED in the western US sitting in the heart of the epidemic in LAC with 50% of the PLWHIV in it's catchment area. 170,000 patient visits annually, 65% by Hispanics, 15% blacks, 5% Asians, 42% women and 80% of the patients claim a household income of <$20,000 annually. We describe LACUSC EDs HIV testing program and its uniquely successful LTC programs for newly diagnosed and return to care patients.

Methods: Results In March of 2011, the LACUSC ED implemented routine HIV screening via a parallel program with a designated tester and POC tests. In June of 2013, it implemented HIV 1-2 antigen antibody immune assay testing and offered provider initiated routine screens to all patients getting labs, in 2015 adding an EMR pop-up window. In Dec 2014, we began Rapid ART for first for acutely infected individuals then newly diagnosed and return to care patients.

Results: To date we have tested 116,116 patients, 71420 (61.5%) male, 44672 (38.5%) female, 22 (0.0%) trans including Hispanic 61.6%, Black 15.6%, White 10.3% the majority over the age of 30. See Table 1 and 2. 2479 positive tests (males 2110 (85.1%), females 365 (14.7%) and transgender 1(0.0%). 609 (24.5%) newly diagnosed (Hispanic (44%), Blacks (21.1%) and whites 10.3%) and 61 (10%) acutely infected with HIV (Hispanic (70.5%), White (30%) and Blacks (11.5%). And 1870 (75%) were previously known positives. Of newly diagnosed patients 574 (94%) successfully LTC. For return to care patients 51% seen in ED and 48% LTC <60days.

Conclusion: HIV screening programs in ED's reach into the heart of the US epidemic and ensures some of the most difficult to reach individuals access testing and rapid treatment. Scale up will contribute substantially to ending the US epidemic.

1140 BUPRENORPHINE VS METHADONE AND ART PRESCRIBING IN VIETNAM: A RANDOMIZED TRIAL

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Background: Integrating methadone or buprenorphine treatment of opioid use disorder (OUD) into HIV care is a recommended strategy for achieving UNAIDS 90-90-90 targets, and associated with improved antiretroviral therapy [ART] uptake in observational studies and a single-site U.S. trial, but adoption of HIV clinic-based buprenorphine has been limited in many countries. We hypothesized that HIV-infected persons with OUD in Vietnam randomized to HIV clinic-based buprenorphine versus methadone would experience comparable 12-month uptake of ART.

Methods: We conducted a non-blinded, multi-center non-inferiority trial randomizing people with HIV and DSM-5 moderate-to-severe OUD to HIV clinic-based buprenorphine versus referral for methadone for treatment of OUD in 6 Vietnam HIV clinics. The primary outcome was medical record documentation of ART prescription. Secondary outcomes included retention on OUD treatment and positive urine drug screen (UDS) for opiates, assessed at baseline, 3, 6, 9, and 12 months. Generalized linear mixed models assessed buprenorphine versus methadone and change in outcomes over time in intention-to-treat analyses.

Results: Participants (n=281) were randomized to receive buprenorphine (n=141) or methadone (n=140). At baseline, 96.8% of participants were male, 45.9% employed, with mean age 38.3 (SD 6.1) years and 7.4 (SD 5.7) years since HIV diagnosis. Mean CD4 count was 405 (SD 224). At baseline, 100% tested positive for heroin and 18.7% for methamphetamines. Retention in treatment at 12 months was 75.9% for buprenorphine and 82.1% for methadone and did not differ by treatment group (p=0.92). Heroin use at 12 months decreased to 46.8% for buprenorphine and 51.4% for methadone and did not differ by treatment assignment at 12 months (p=0.58). ART receipt increased from 68.0% to 73.8% for buprenorphine and 67.9% to 80.7% for methadone, and was higher for participants on methadone versus buprenorphine at 12 months (p=0.009).

Conclusion: Both buprenorphine and methadone improved ART receipt despite modest decreases in heroin use, comparable to those achieved in U.S. practice. Opioid agonist treatment can help achieve UNAIDS 90-90-90 goals for ART uptake.

1141 HRSA'S RYAN WHITE HIV/AIDS PROGRAM RESPONSE TO THE OPIOID EPIDEMIC

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Background: The U.S. is in the midst of an unprecedented opioid crisis with injection drug use (IDU)-related HIV outbreaks increasing, particularly in rural areas. The Health Resources and Services Administration's Ryan White HIV/AIDS Program (HRSA RWHAP) is well positioned to integrate treatment for IDU-associated HIV infections with treatment for drug use disorders. The purpose of this study was to evaluate the sociodemographic characteristics and substance use service utilization of RWHAP clients with HIV attributed to IDU nationwide compared to seven southern states identified with large rural HIV epidemics. These activities will be crucial for the "Ending the HIV Epidemic: A Plan for America" initiative.

Methods: Data from the 2017 RWHAP Services Report were used to assess the sociodemographic characteristics of RWHAP clients aged 13 and older with HIV attributed to IDU ("IDU clients"). We also examined the proportion of RWHAP-funded providers who delivered substance use services and the characteristics of RWHAP clients who accessed these services. Data were examined nationally and in seven states with significant rural HIV epidemics. HRSA convened a technical expert panel to explore how the RWHAP can best respond to the opioid crisis; we identified key themes.

Results: In 2017, RWHAP 6.7% of clients served (31,683) had HIV attributed to IDU. When compared with IDU clients served by the RWHAP nationwide, IDU clients in the seven rural states were younger (27.2% aged <45 years vs. 17.0% nationally), White (52.8% vs. 30.7% nationally), and stably housed (84.7% vs. 80.1% nationally). Nationwide, 17.5% (269) of RWHAP providers delivered substance use services, but only 3.3% (17,716) of RWHAP clients accessed substance use services. Key themes from the panel included the impact of stigma on service availability and access, workforce challenges, and social determinants of health.

Conclusion: A significant proportion of RWHAP clients are impacted by substance use disorder and the opioid crisis with sociodemographic differences observed in rural areas as compared to national trends. RWHAP data and input from experts highlight the RWHAP's unique position to respond to the growing opioid crisis, nationally and in rural areas, and can inform the RWHAP's approach to care delivery in areas at the intersection of the HIV and opioid crises.

Table 1. Ryan White HIV/AIDS Program clients (non–ADAP) with HIV infection attributed to injection drug use, by selected characteristics, 2017—United States and 7 States with Rural Epidemics

	National		7 States with Rural Epidemics	
	No.	%	No.	%
Age group (yr)				
13-24	162	0.5	21	1.2
25-34	1,619	5.1	150	8.8
35-44	3,620	11.4	293	17.2
45-54	9,531	30.1	547	32.0
55-64	13,162	41.5	571	33.4
≥65	3,589	11.3	126	7.4
Subtotal	31,683	100.0	1,708	100.0
Race/ethnicity				
American Indian/Alaska Native	259	0.8	19	1.1
Asian	204	0.6	8	0.5
Black/African American	12,977	41.0	692	40.6
Hispanic/Latino[a]	8,057	25.4	57	3.3
Native Hawaiian/Pacific Islander	39	0.1	0	0.0
White	9,722	30.7	901	52.8
Multiple races	362	1.1	29	1.7
Subtotal	31,620	100.0	1,706	100.0
Gender				
Male	20,755	65.5	1,153	67.5
Female	10,790	34.1	553	32.4
Transgender	138	0.4	2	0.1
Subtotal	31,683	100.0	1,708	100.0
Federal poverty level				
0–100%	24,533	79.6	1,315	78.2
101–138%	2,840	9.2	132	7.9
139–250%	2,440	7.9	173	10.3
251–400%	775	2.5	53	3.2
>400%	227	0.7	8	0.5
Subtotal	30,815	100.0	1,681	100.0
Health care coverage				
Private employer	1,059	3.4	140	8.3
Private individual	1,007	3.2	209	12.4
Medicare	3,760	12.0	277	16.4
Medicaid	15,381	49.2	490	29.0
Medicare and Medicaid	3,920	12.5	147	8.7
Veterans Administration	100	0.3	7	0.4
Indian Health Service	20	0.1	2	0.1
Other plan	364	1.2	5	0.3
No coverage	2,930	9.4	234	13.8
Multiple coverages	2,726	8.7	180	10.6
Subtotal	31,267	100.0	1,691	100.0
Housing status				
Stable	24,936	80.1	1,429	84.7
Temporary	3,397	10.9	154	9.1
Unstable	2,793	9.0	104	6.2
Subtotal	31,126	100.0	1,687	100.0
Total[b]	31,683	—	1,708	—

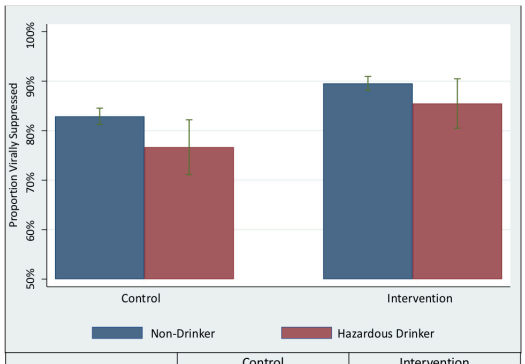
[a]Hispanics/Latinos can be of any race.
[b]Subtotals for each subpopulation are displayed to reflect the denominator used for the percentage calculation of each subpopulation; due to missing data, the values in each column may not sum to the column total.

1142 SEARCH TEST & TREAT INTERVENTION IMPROVES VIRAL SUPPRESSION AMONG HAZARDOUS DRINKERS

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Background: Hazardous alcohol use has been associated with poor HIV care cascade outcomes. We previously reported that hazardous drinkers had lower baseline viral suppression (VS) than non-drinkers in the SEARCH universal test and treat (UTT) trial. In this analysis, we sought to assess if gaps in VS persisted between hazardous drinkers and non-drinkers by arm in intervention and control communities after 3 years and to determine if the intervention improved VS compared to control among hazardous drinkers.
Methods: SEARCH randomized 32 communities in Kenya and Uganda to a UTT intervention of annual testing and universal ART eligibility via streamlined care designed to decrease barriers to engagement in care and VS, or a control of baseline universal testing with ART eligibility and delivery by evolving country standards over 3 years (2013-17). We evaluated VS at year 3 in baseline HIV+ adults. We assessed baseline alcohol use by Alcohol Use Disorders Identification Test-Concise (AUDIT-C) score: hazardous drinking was defined as a score 3 for women and 4 for men and non-drinking as a score of 0. Within each arm, associations between baseline alcohol use and year 3 VS were estimated using individual-level Targeted Maximum Likelihood Estimation (TMLE) to adjust for sociodemographic factors, mobility and clustering by community. Comparisons of year 3 VS between arms among hazardous drinkers were based on cluster-level TMLE.
Results: Of 9,936 HIV+ adults with baseline AUDIT-C measures, 871 (9%) reported hazardous alcohol use. Men accounted for 75% of hazardous drinkers (655/871) and 29% (2655/9065) of non-drinkers. After adjustment for confounders, year 3 VS in the control arm was lower among hazardous drinkers (77%) compared to non-drinkers (83%, aRR: 0.93, 95%CI:0.86-0.99, p=0.04). In contrast, in the intervention arm, year 3 VS among hazardous drinkers (86%) was not significantly different than among non-drinkers (90%, aRR: 0.96, 95%CI:0.9-1.01, p=0.11). Hazardous drinkers in intervention communities were more likely to achieve VS than hazardous drinkers in control communities (RR 1.21, 95%CI: 1.1-1.3, p<0.001).
Conclusion: The SEARCH intervention reduced the gap in VS between baseline hazardous drinkers and non-drinkers, achieving high prevalence of VS regardless of alcohol use, whereas a disparity in VS by alcohol use persisted in the control arm. These data suggest that the SEARCH intervention may have decreased barriers to HIV care and VS for hazardous drinkers.

Figure: Proportion achieving viral suppression at year 3, by SEARCH trial arm and baseline hazardous drinking among persons with HIV*



	Control % (95% CI)	Intervention % (95% CI)
Non-Drinkers	83 (81-85)	90 (88-91)
Hazardous Drinkers	77 (71-82)	86 (81-91)

*Adjustment set included: sex, age, mobility, marital status, education level, occupation, and wealth quintile

1143 END OF HIV EPIDEMIC AMONG PWID IN A LOW-MIDDLE INCOME COUNTRY: THE HAI PHONG CASE

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Background: The HIV epidemic among people who inject drugs (PWID) has been ended in many high-income countries, but no such achievement has been reported from the low-middle income countries (LMIC) where the epidemic has flared. In Vietnam, despite a persistent repressive policy regarding drug use, directly-observed methadone therapy and universal ART have been implemented, along with community-based organizations (CBO) to deliver harm reduction and assist PWID in accessing care. In this context, we assessed whether the HIV epidemic could be ended in this high-risk group, taking the case of Haiphong, a 2 million inhabitant city.
Methods: After a feasibility phase which estimated the active PWID population size to 5500 in Haiphong, we implemented 3 community-based respondent driven sampling surveys (RDS) in October 2016, 2017 and 2018. We enrolled active PWID with recent injection skin marks and heroin detected in urine, recorded drug use behaviors, and tested them for HIV and plasma viral load. From each RDS, all HIV-positives and 200 to 400 HIV-negative PWID entered in two open cohorts with bi-annual follow-up. HIV incidence was calculated using follow-up accumulated from both the cohort (bi-annual HIV testing) and recaptured PWID between RDS. We also estimated the HIV cascade of care, recent infections and HIV viremia prevalence.
Results: The 3 RDS recruited 1380, 1451 and 1443 PWID, representing 3146 distinct individuals; all of them were injecting heroin, 23% for less than 5 years, and 11.8%, 32.4% and 41.5% reported being in the methadone program, respectively. Their mean age was 39 years, and 94.9% were male. Reported needles/syringes sharing was low at 3.9%, 3.2% and 3.6%, respectively. The HIV prevalence was 26.5%, similar across RDS. Overall, 1497 person-years of follow-up were accumulated with 1 HIV seroconversion, yielding a HIV incidence of 0.7/1000 person-years (95%CI: 0.02-4). At RDS1, the cascade of care was 87-93-97, improving to 91-92-95 and 95-93-95 at RDS2 and RDS3. There was no recent infection among all HIV-positives. The viremia prevalence (threshold of 1000 copies/mL) decreased from 7.2% at RDS1, to 5.4% at RDS2 and 3.1% at RDS3.
Conclusion: Ending the HIV epidemic among PWID in a LMIC setting can be reached, thanks to low sharing rate and high success of the HIV care program, much facilitated by an active CBO network.

1144 ENDING THE HIV EPIDEMIC AMONG PEOPLE WHO INJECT DRUGS: A COST-EFFECTIVENESS ANALYSIS

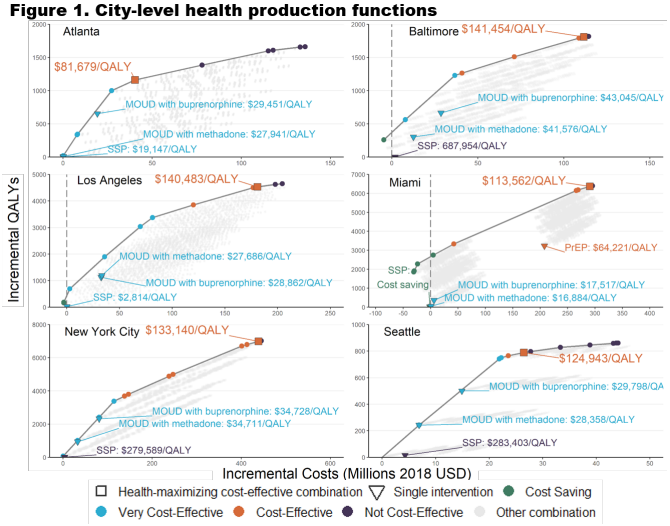
Emanuel Krebs[1], Xiao Zang[1], Benjamin Enns[1], Jeong E. Min[1], Bohdan Nosyk[1], for the Localized Economic Modeling Study Group
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Background: In the United States, people who inject drugs (PWID) continue to be disproportionately at risk of HIV infection. We aimed to determine the cost-effectiveness of expanded access to evidence-based prevention and care interventions for PWID and to identify the highest-valued combination implementation strategies to reduce the burden of HIV among PWID in six US cities with diverse HIV microepidemics.
Methods: We identified and estimated costs, effectiveness and previously-documented scale of delivery for 14 evidence-based interventions from the US CDC's Compendium of Evidence-Based Interventions and Best Practices for HIV Prevention and from the published literature. Using a dynamic, compartmental HIV transmission model calibrated for Atlanta, Baltimore, Los Angeles, Miami, New York City and Seattle, we assessed combinations of evidence-based interventions implemented at either previously-documented, optimistic or ideal scale. We estimated averted HIV infections among PWID, quality-adjusted life-years (QALYs), total costs and incremental cost-effectiveness ratios (ICERs) for each combination and city compared to the status quo over a 20-year time horizon (healthcare perspective; 3% annual discount rate, 2018$US). Interventions were implemented for a 10-year period. In addition, we estimated health production functions, representing combination implementation strategies providing the greatest health benefits for incremental investment levels.
Results: Strategies that maximized health benefits while remaining cost-effective according to international standards contained between six (Atlanta and Seattle) and twelve (Miami) interventions. The ICER values for these

strategies ranged from $81,679/QALY for Atlanta to $141,454/QALY for Baltimore (Figure 1). Implemented at documented scale, these would result in 1.7% (Seattle) to 27.0% (Miami) reductions in new HIV infections among PWID across cities by 2030. PrEP for PWID was found to be cost-effective in Miami ($64,221/QALY). Incidence reduction reached 11.8% (New York City) to 81.9% (Miami) when strategies were implemented at ideal scale.

Conclusion: Evidence-based interventions targeted to PWID can deliver considerable value, however ending the HIV epidemic among PWID will require innovative implementation strategies and supporting programs to reduce social and structural barriers to care.

Figure 1. City-level health production functions



1145 INTEGRATING ANTIRETROVIRAL TREATMENT AND HARM REDUCTION SERVICES ON HIV AND OVERDOSE

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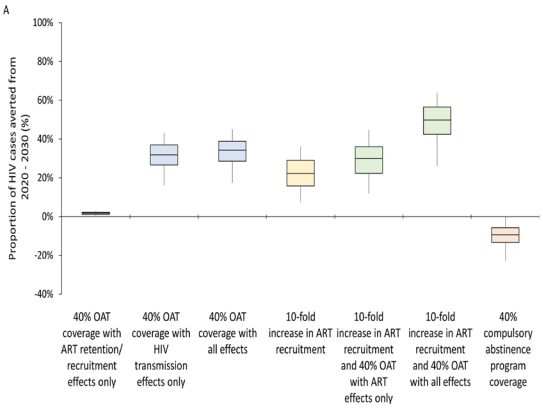
Background: The HIV epidemic in Tijuana, Mexico is concentrated in key populations, including people who inject drugs (PWID). Mexico's drug law reform included referral to drug treatment, yet funding was provided for non-evidence based compulsory abstinence programs (CAP) associated with elevated HIV and overdose risk. However, evidence-based opioid agonist therapy (OAT) reduces overdose, HIV transmission, and reincarceration, while improving antiretroviral therapy (ART) outcomes. We assessed the potential impact of integrated ART and drug treatment (OAT or CAP) on HIV and fatal overdose among PWID in Tijuana.

Methods: We developed a dynamic model of HIV transmission, incarceration, and fatal overdose among PWID in Tijuana. We incorporated synergistic benefits of OAT on reducing injecting-related HIV transmission, increased ART recruitment and retention, reducing reincarceration, and averting fatal overdose. We also modeled harms associated with CAP on HIV and overdose. We assessed HIV incidence and fatal overdose over the next decade with the following scenarios: 1) status quo (10% ART among HIV-positive PWID and no drug treatment), 2) OAT scale-up to 40%, 3) ART scale-up (10-fold recruitment) among HIV-positive PWID, 4) scale-up OAT to 40% and ART (10-fold recruitment), 5) scale-up CAP to 40% (no ART scale-up).

Results: OAT scale-up to 40% coverage could avert 32% (95%CI: 19–45%) and 19% (95%CI: 8-26%) of new HIV infections and fatal overdoses, respectively, over the next decade (see figure). Due to low ART coverage, OAT had marginal impact on averting HIV through its effect on ART recruitment/retention. However, with integrated OAT and ART scale-up synergistic benefits were observed, with the OAT effect on ART recruitment/retention averting 10% more new infections compared to ART scale-up alone. Scaling-up OAT and ART could avert 50% (95%CI: 28-67%)) of new HIV infections and one-fifth of fatal overdoses over the next decade. Conversely, scaling-up ART and CAP could increase HIV and overdoses.

Conclusion: Integrating ART with OAT scale-up could provide synergistic benefits on ART recruitment/retention, and prevent new HIV infections and fatal overdoses among PWID in Tijuana. Conversely, non-evidence based CAP could contribute major harms. Policymakers should consider the synergistic benefits of integrated OAT and HIV services on HIV and overdose among PWID.

Proportion of HIV cases averted from 2020-2030 among PWID in Tijuana compared to the base case scenario. Blue bloxplots represent OAT scale-up to 40% coverage only; yellow boxplot represents 10-fold increase in ART recruitment only; green bloxplots represent OAT scale-up to 40% coverage plus increase ART recruitment by 10-fold. Red boxplots represent scale-up of compulsory abstinence programs to 40% coverage (instead of OAT).



1146 SMARTPHONE INTERVENTION TO REDUCE HEAVY DRINKING IN HIV CARE: EFFECT ON ART ADHERENCE

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Background: Heavy drinking among People Living With HIV (PLWH) reduces antiretroviral adherence and worsens health outcomes. Brief interventions to reduce heavy drinking in primary care patients are effective, but in heavy-drinking PLWH, more extensive intervention may be needed. Lengthy interventions are not feasible in most HIV primary care settings, and patients seldom follow referrals to outside treatment. Utilizing visual and video features of smartphone technology, we developed and tested HealthCall as an electronic (smartphone) means of increasing patient involvement in brief intervention to reduce drinking and improve medication adherence without making unfeasible demands on providers.

Methods: Alcohol-dependent patients at a large urban HIV clinic were randomized to receive 1 of 2 brief (~25 min) baseline drinking-reduction interventions plus ART adherence education, and then HealthCall (daily use on the smartphone, ~4-5 min/day) or standard care for 60 days. All patients had 2 brief (15-min) check-in sessions at 30 and 60 days. Baseline interventions: NIAAA Clinician's Guide (CG) or Motivational Interviewing (MI). HealthCall included coverage of drinking and ART adherence. Patients were randomly assigned to CG+standard care (n=37), CG+HealthCall (n=38) or MI+HealthCall (39). Outcomes assessed at 30, 60, 90 days, 6 and 12 months: drinks per drinking day; ART adherence (unannounced phone pill-count method; possible adherence scores: 0%-100%). Analysis: generalized linear mixed models with pre-planned contrasts.

Results: Study retention was excellent (85%-94% across timepoints) and unrelated to treatment arm or patient characteristics. Drinking decreased overall during treatment, with continued declines at 6 and 12 months in the CG+HealthCall arm. During treatment, patients in MI+HealthCall drank less than others (p=0.07-0.003). However, at 6 and 12 months, drinking was lower among patients in CG+HealthCall (p=0.04-0.06). Overall ART adherence declined slightly by 12 months. However, at 60 days, 90 days and 6 months, ART adherence was significantly better among patients in CG+HealthCall than CG+standard care (p=0.03-0.09).

Conclusion: HealthCall paired with CG resulted in better ART adherence than the other treatment conditions. Given the importance of ART adherence and the low costs and time required for HealthCall, pairing HealthCall with brief interventions within HIV clinics merits widespread consideration.

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